Laparoscopic Anti-reflux Surgery

Indications, Techniques and Physiological Effects

J.A.J.L. Broeders

Laparoscopic Anti-reflux Surgery
Indications, Techniques and Physiological Effects
Broeders, Joris Adrianus Josephus Leonardus

Thesis, Utrecht University, the Netherlands

ISBN/EAN 978-90-393-5548-0
Printed by Gildeprint Drukkerijen, the Netherlands
Illustrations I.G.J. Janssen

Laparoscopic Anti-reflux Surgery

Indications, Techniques and Physiological Effects

Laparoscopische Antirefluxchirurgie

Indicaties, Technieken en Fysiologische Effecten

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op donderdag 26 mei 2011
des middags te 2.30 uur

door

Joris Adrianus Josephus Leonardus Broeders

geboren op 30 maart 1984 te Tilburg

Promotoren:	Prof.dr. H.G. Gooszen
	Prof.dr. A.J.P.M. Smout
Co-promotoren:	Dr. E.J. Hazebroek
	Dr. W.A. Draaisma

Publication of this thesis was financially supported by:

A clinical research trainee grant from Nycomed BV, Medical Measurement Systems BV, Chirurgisch Fonds Heelkunde UMC Utrecht, Nauta holding BV, J.E. Jurriaanse Stichting, Nederlandse Vereniging van Gastroenterologie, Hoogland Medical BV, Sectie Neurogastroenterologie en Motiliteit van de Nederlandse Vereniging voor Gastroenterologie, Covidien Nederland BV, Sigma Medical BV, Stöpler Instrumenten & Apparaten BV, Chipsoft BV, Ruijs Visual Computing BV, Erbe Nederland BV, Olympus Nederland BV, Pentax Nederland BV, Unisensor Switzerland AG, Karl Storz Germany GmbH & Co. KG and MD Solutions Australasia Pty Ltd.

Aan mijn ouders
Voor Holly

Contents

1

Introduction

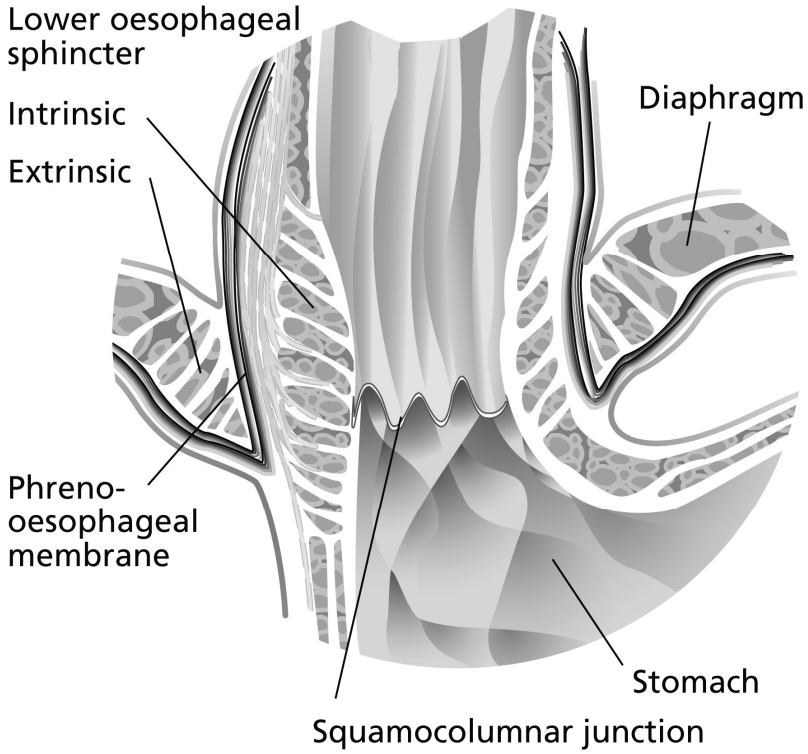
Physiology of the gastro-oesophageal junction

The gastro-oesophageal junction (GOJ) is a functional valve that separates the gastric and oesophageal cavities. The GOJ consists of an intrinsic and an extrinsic sphincter.[1] The intrinsic sphincter is formed by a specialised part of the circular muscle layer of the distal oesophagus, the lower oesophageal sphincter (LOS). The crural diaphragm forms the extrinsic sphincter and is anchored to the distal oesophagus via the phreno-oesophageal membrane. Normally, the LOS and crural diaphragm show an anatomic overlap at the level of the GOJ (figure 1) to form a functional valve with three functions. The first is to allow solids and liquids to pass from the oesophagus to the stomach during swallow-induced relaxations of the LOS. The second is to allow ventilation of gas from the stomach to the mouth (i.e. belching) during transient LOS relaxations (TLOSRs) that are not associated with swallows.[2] The third function of the GOJ is to compensate for the positive abdomen-to-thorax pressure gradient by preventing backward flow of liquid gastric contents into the oesophagus (i.e. gastro-oesophageal reflux). These three functions seem to be mutually exclusive and are delicately balanced in normal physiology. At one side of the spectrum, an incompetent GOJ results in excessive gastro-oesophageal reflux (i.e. gastro-oesophageal reflux disease). At the other side a supracompetent GOJ gives rise to difficulty in swallowing (i.e. dysphagia) and inability to allow ventilation of gas from the stomach (i.e. inability to belch).

Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease (GORD) is a highly prevalent chronic disorder in which troublesome symptoms or lesions occur as a result of retrograde flow of gastric contents into the oesophagus.[3] Cardinal symptoms for GORD are heartburn and regurgitation. Atypical manifestations are nausea, dysphagia and extra-oesophageal symptoms (chronic cough, hoarseness, dental erosions and gastric asthma). GORD is the most common upper gastrointestinal disorder in the Western world. Between 10 and 20 per cent of the general population of Western countries suffer at least weekly from heartburn or acid regurgitation.[4] GORD severely impairs quality of life compared with control populations[5;6] and patients with other chronic disease.[7-9] Apart from the discomfort caused by chronic symptoms, GORD often results in an inflammation of the distal mucosa of the oesophagus (i.e. oesophagitis).[10]

Figure 1 Anatomy of the gastro-oesophageal junction
N Engl J Med 1997;**336**(13):924-32 (with permission)



Pathophysiology

The squamous mucosa of the oesophagus has inferior defence mechanisms against the noxicity of gastric contents compared with the columnar mucosa that lines the stomach. As a result, excessive reflux of gastric contents into the oesophagus causes reflux complaints and oesophagitis. There are three pathophysiological mechanisms causing gastro-oesophageal reflux. The first is incompetence of the intrinsic sphincter, reflected by a low pressure of the LOS. The second is a migration of the GOJ into the thorax due to circumferential laxity of the phreno-oesophageal membrane (i.e. sliding hiatal hernia). A sliding hiatal hernia abolishes positive intra-abdominal pressure on the anti-reflux barrier and disturbs the overlap of the intrinsic LOS and extrinsic crural diaphragm. LOS incompetence and sliding hiatal hernias are the two most important mechanisms causing reflux in patients with severe GORD.[11] The third mechanism is constituted by TLOSRs, which cause 90 per cent of reflux episodes in patients with mild GORD.[12-14]

Diagnosis

In most patients GORD is diagnosed based on the combination of the presence of typical symptoms and a favourable response to pharmacological therapy. In such cases diagnostic tests are unnecessary. Response to empirical pharmacological therapy has a sensitivity of 78 per cent and a specificity of 54 per cent. Upper gastrointestinal endoscopy, 24-h pH monitoring and 24-h combined oesophageal impedance-pH monitoring can be used to confirm the diagnosis in case of an atypical clinical history, insufficient response to pharmacological therapy or as part of the preoperative work-up for anti-reflux surgery.

Based on the presence of oesophagitis during upper gastrointestinal endoscopy, GORD patients can be subdivided into those with erosive (ERD) and non-erosive reflux disease (NERD). Endoscopy is highly specific (90-95 per cent) for GORD,[15] but has a low sensitivity since only 50 per cent of patients has endoscopic evidence of oesophagitis.[16] The presence and size of a hiatal hernia can also be assessed endoscopically. In addition, endoscopy is indicated in patients with weight loss or progressive dysphagia to evaluate complications of the disease such as strictures and adenocarcinoma of the distal oesophagus. Metaplasia of the oesophagus (i.e. Barrett's oesophagus) is another complication of GORD that can be assessed using endoscopy.

Ambulatory 24-h oesophageal pH monitoring enables physicians to diagnose reflux disease in both NERD and ERD patients by quantifying total oesophageal acid exposure time and symptom-reflux correlation.[17] A catheter with a pH sensor is used to record reflux of acid gastric contents at 5 cm above the GOJ. Based on the percentage of time the oesophageal pH is below 4, patients can be classified as having pathological or physiological acid exposure time. Ambulatory 24-h pH monitoring divides GORD patients into three reflux patterns according to the body position in which pathological reflux occurs: isolated upright, isolated supine and bipositional reflux.[18] The presence of pathological acid exposure has a 90 per cent sensitivity and 95 per cent specificity in separating controls and patients with oesophagitis.[19] The sensitivity drops to 60 per cent with a specificity of 95 per cent in segregating controls and patients with reflux symptoms but no oesophagitis.[19] In addition, this investigation provides the possibility to evaluate the temporal relationship between symptoms and acid reflux episodes. In absence of oesophagitis, the gold standard objective test to investigate whether a patient's symptoms are caused by gastro-oesophageal reflux is ambulatory 24-hour pH monitoring with symptom association analysis.[19]

Recently, ambulatory 24-h combined oesophageal impedance-pH monitoring has been introduced.[20] This technique uses a catheter that combines a pH sensor at 5

cm above the GOJ with six impedance segments across the length of the oesophagus. Intraluminal impedance monitoring evaluates changes in electrical resistance and detects reflux independently of the acidity of the refluxate. It therefore enables one to evaluate not only acid reflux, but also weakly acidic reflux.[21] In addition, the six impedance segments allow quantification of the proximal extent of reflux episodes.[22]

Conventional manometry enables physicians to evaluate oesophageal peristalsis, LOS resting pressure and LOS relaxation pressure. Manometry is not used to diagnose reflux disease in patients with GORD symptoms and candidates for anti-reflux surgery This investigation is mainly performed to exclude oesophageal motility disorders such as achalasia, oesophageal spasm and scleroderma as the underlying cause of the patient's symptoms.[23]

Anti-reflux surgery

Pharmacological management is the standard initial therapy for GORD and the majority of the patients are treated by general practitioners with proton pump inhibitors (PPIs), often lifelong. Combined impedance-pH monitoring has demonstrated that PPIs do not reduce gastro-oesophageal reflux, but minimises its noxicity by reducing gastric acid secretion.[24] PPI therapy provides long-term control of GORD symptoms in 95 per cent of the patients.[25] The remaining 5 per cent of GORD patients had an incomplete response to PPIs (i.e. PPI-refractory GORD). Patients with PPI-refractory GORD,[26-28] patients unwilling to take lifelong medication,[26-28] or patients with extra-oesophageal manifestations[29-32] are candidates for anti-reflux surgery. Candidates for anti-reflux surgery with erosive reflux disease on endoscopy and/or pathological supine or bipositional reflux with a positive symptom-reflux association during 24-h pH metry, have a classic indication for anti-reflux surgery. Fundoplication is the surgical treatment of choice for GORD.

Part I - Indications

Traditionally, patients with pathological supine and bipositional reflux are considered good candidates for fundoplication.[18;33] In **chapter 2** the long-term outcome of patients with isolated upright reflux is compared with patients with supine and bipositional reflux. In addition, classic candidates for fundoplication have both pathological acid exposure time and a positive correlation between symptoms and reflux episodes during 24-h pH monitoring. Based on these two criteria there are two subgroups of patients that do not have a classic indication for fundoplication.

The first subgroup consists of patients with physiological acid exposure time but a positive relationship between symptoms and acid reflux episodes (i.e. oesophageal acid hypersensitivity).[34] **Chapter 3** describes a study that compares the outcome of fundoplication in patients with oesophageal acid hypersensitivity and patients with both pathological acid exposure and a positive symptom-reflux association. The second subgroup of patients suffers from pathological acid exposure, but do not have a positive symptom-reflux correlation on pH metry. In **chapter 4** the outcome of fundoplication in these patients is compared with patients with both pathological acid exposure and a positive symptom-reflux association.
Until recently, NERD was considered a milder form of GORD and physicians were reluctant to refer these patients for fundoplication. To test this hypothesis **chapter 5** compares preoperative reflux parameters as well as long-term outcome of fundoplication in NERD and ERD.
Recurrent reflux disease and dysphagia are the main indications for reintervention after fundoplication. Recurrent reflux disease due to failed anti-reflux surgery requires patients to resume PPI therapy or to undergo revisional surgery. Postfundoplication dysphagia necessitates endoscopic dilation or surgical reintervention. **Chapter 6** describes a study that identifies objective predictors for recurrent reflux disease after fundoplication. In **chapter 7** the results of the largest cohort study evaluating the impact of preoperative oesophageal peristalsis on the incidence of postfundoplication dysphagia are reported.

Part II - Techniques

Laparoscopic Nissen (posterior total) fundoplication

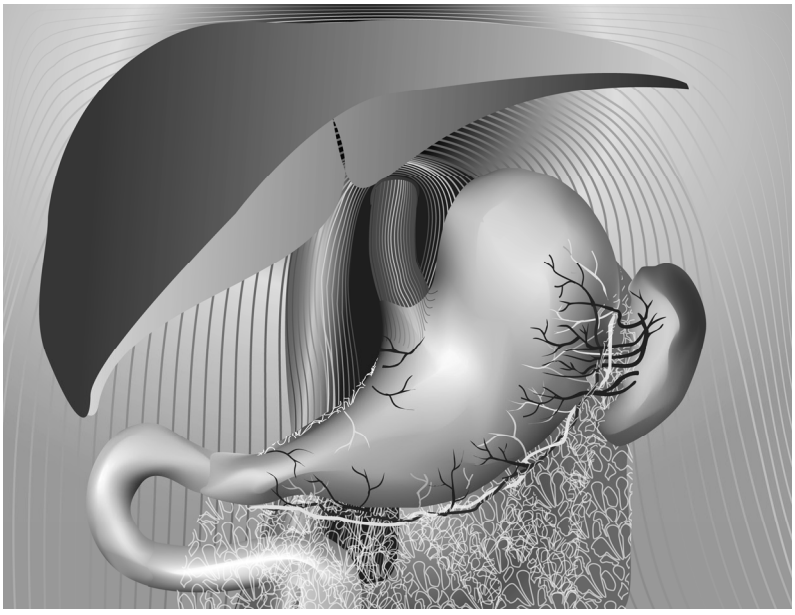
In 1956, Rudolph Nissen performed the first fundoplication for GORD[35] after the serendipitous discovery of the anti-reflux effect of wrapping the fundus of the stomach around the distal oesophagus.[36] The original publication described a fundoplication of the posterior wall of the stomach.[37] In an article published in 1964, Nissen discusses the Nissen-Rossetti fundoplication, which was developed to be employed in obese patients.[38] After modifications, total fundoplication according to Nissen has become the most frequently performed operation for GORD. The procedure includes mobilisation of the distal oesophagus (figure 2a), division of the short gastric vessels (figure 2b), posterior repair of the crural diaphragm (figure 2b) and wrapping the fundus of the stomach posteriorly around the oesophagus with a 360° circumference. The modified Nissen wrap is a fundoplication using both the anterior and the posterior wall of the stomach.[37] It is fixated to the anterior wall of the stomach with three sutures and one suture to the right crus (figure 3). The Nissen-Rossetti variation has also been modified and includes mobilisation of the

distal oesophagus (figure 2a) and posterior crural repair (figure 2b). The only differences between the two operations are that the short gastric vessels are not divided and that a fundoplication is created using the anterior wall of the stomach only.[37] A meta-analysis has demonstrated that there are no differences in short and long-term outcome after Nissen and Nissen-Rossetti fundoplication.[39]

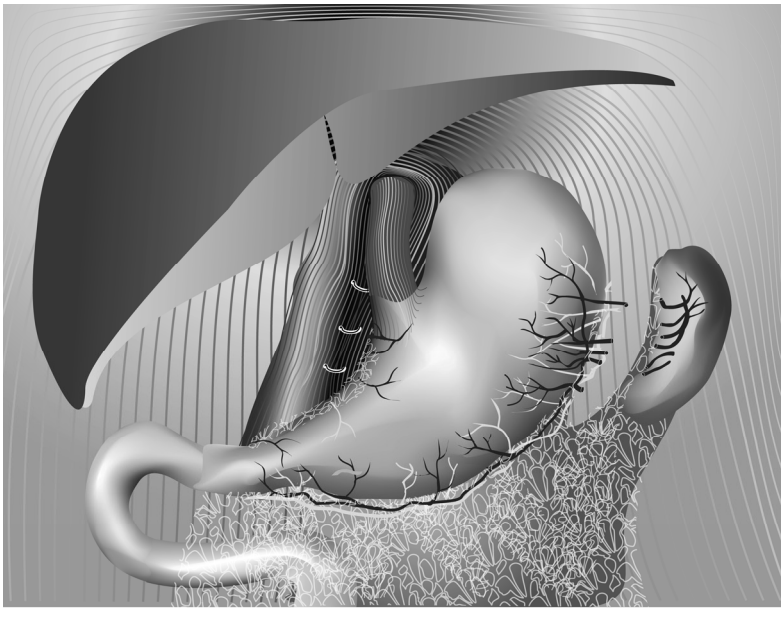
Laparoscopic Nissen fundoplication (LNF) rapidly replaced conventional Nissen fundoplication (CNF) after its first report in 1991.[40] The hypothesis at the time of its introduction was that LNF would reduce morbidity with similar long-term effectiveness. This hypothesis was tested in **chapter 8** using the 10-year outcome of a randomised clinical trial (RCT) comparing LNF and CNF. The short-term results of this RCT[41] raised questions about the effect of operator experience on the outcome of laparoscopic anti-reflux surgery.[42-47] **Chapter 9** evaluates the impact of surgeon experience on long-term outcome after LNF. The purpose of this prospective study was thus to determine the isolated effect of surgeon experience on intra-operative and in-hospital characteristics, short-term objective reflux control and the five-year outcome of LNF. In 1999, robot-assisted laparoscopic fundoplication was first reported.[48] A recent meta-analysis, however, does not justify the use of this surgical approach since clinical outcome is similar with higher costs compared with laparoscopic fundoplication.[49]

LNF restores the anti-reflux barrier with excellent 5-year reflux control.[50] However, the procedure results in a supracompetent valve, which tends to impair the two other functions of the GOJ. Consequently, the main side-effects of LNF are difficulty in swallowing solids and liquids (i.e. dysphagia) and gas-related symptoms caused by an inability to allow ventilation of gas from the stomach (i.e. inability to belch). As many as 19 per cent of LNF patients develop postfundoplication dysphagia[39] and it is commonly assumed that impairment of the ventilation of swallowed air from the stomach causes gas bloating and flatulence.[51-57] As a result, 19 per cent of the patients suffer from gas bloating[39] and 59 per cent report flatulence after LNF.[58]

Figure 2 Laparoscopic fundoplication techniques

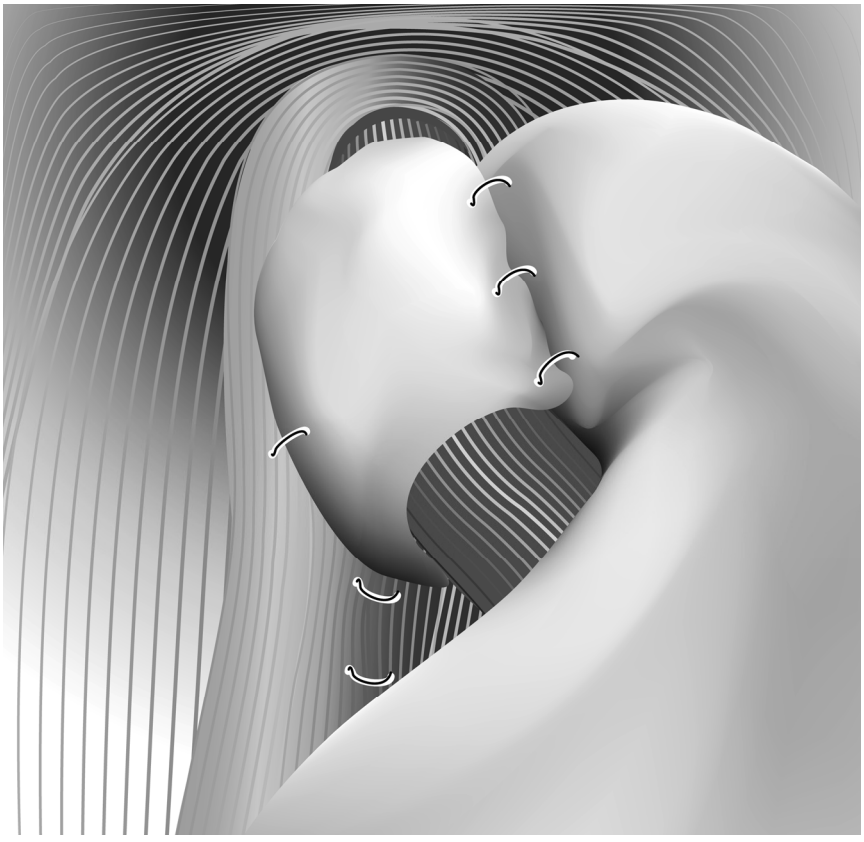


2a Short gastric vessels and hiatal hernia after mobilisation of distal oesophagus



2b Division of short gastric vessels between the stomach and the spleen, repair of crural diaphragm

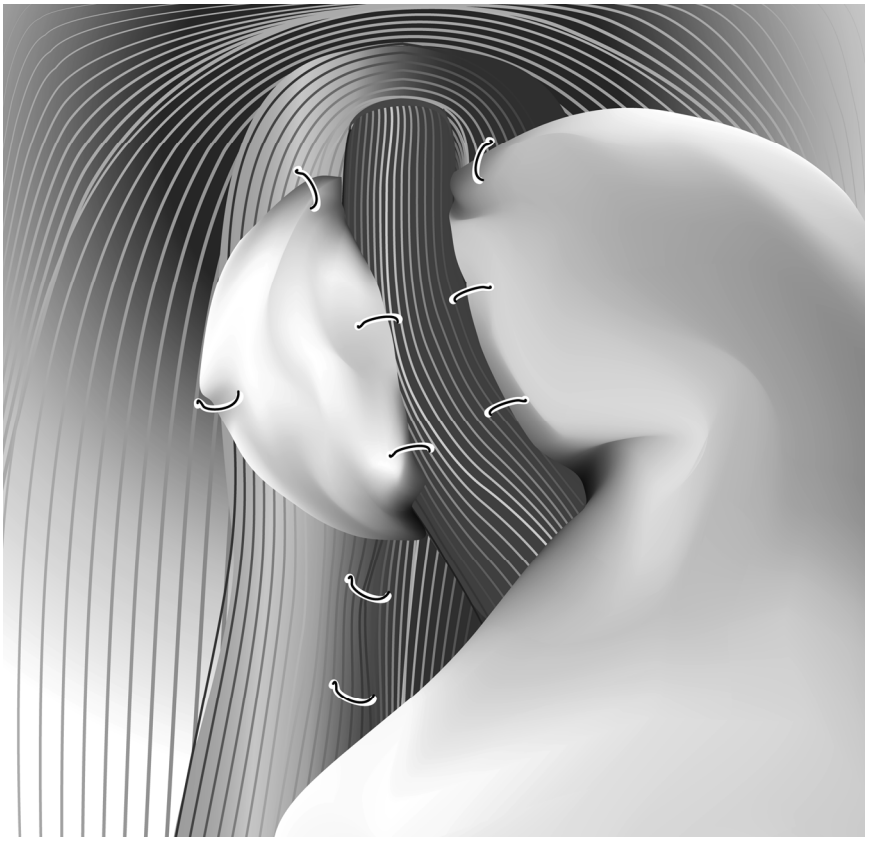
Figure 3 Nissen (posterior total) fundoplication



Laparoscopic Toupet (posterior partial) fundoplication

In 1963, André Toupet proposed partial posterior fundoplication as an alternative operation for GORD.[59] This procedure aims to reduce dysphagia and gas-related symptoms after surgery. A modified laparoscopic Toupet fundoplication includes the same steps as Nissen fundoplication (figure 2a and 2b), the only difference being the creation of a partial posterior wrap with a circumference of 270° degrees. Both margins of the fundoplication are fixated to the oesophagus with four sutures and the wrap is anchored to the crus using three sutures (figure 4). **Chapter 10** describes a systematic review and meta-analysis comparing laparoscopic Nissen and Toupet fundoplication.

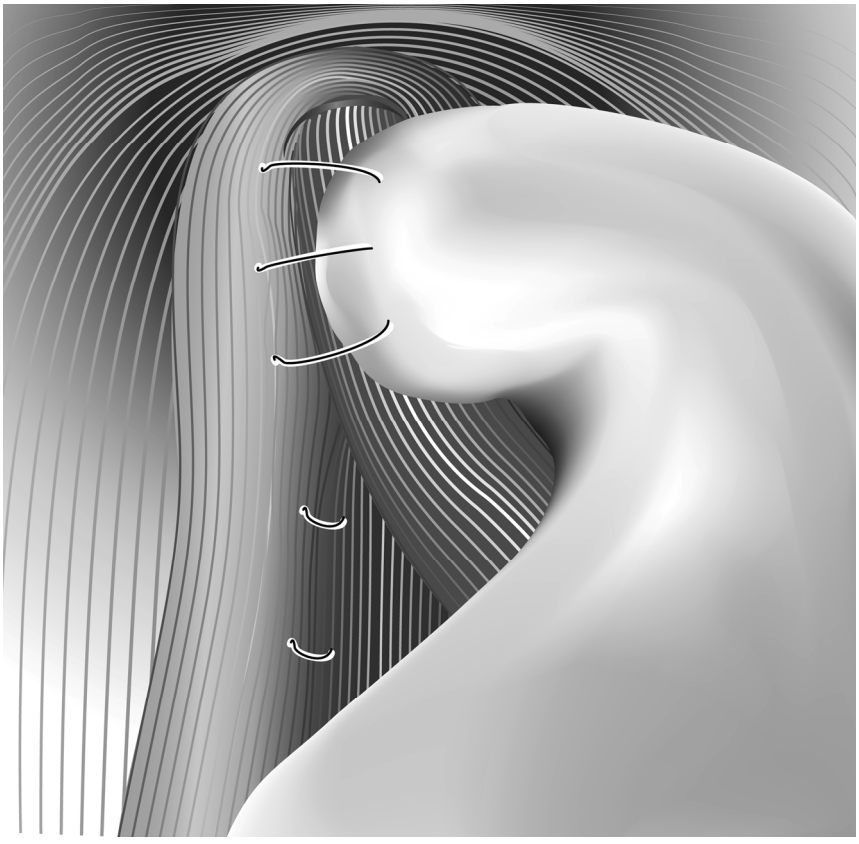
Figure 4 Toupet (posterior partial) fundoplication



Laparoscopic Dor (anterior partial) fundoplication

In 1967, Jacques Dor introduced anterior partial fundoplication.[60] This anti-reflux procedure involves wrapping the fundus of the stomach anteriorly around the oesophagus. The technique was also designed to reduce postoperative dysphagia and gas-related symptoms. The modifications of this procedure that are currently used in clinical practice are laparoscopic 90°[61] and 180°[62] anterior fundoplication. The modified Dor fundoplication includes mobilisation of the oesophagus (figure 2a) and posterior crural repair (figure 2b), without division of the short gastric vessels. An anterior partial wrap with a circumference of either 90° or 180° is then created (figure 5). The margin of the fundoplication is fixated to the oesophagus with four sutures and to the crus using three sutures. The results of a systematical review and meta-analysis comparing laparoscopic anterior and posterior fundoplication are given in **chapter 11**. In addition, **chapter 12** reports the 5-year results of four RCTs comparing laparoscopic anterior and Nissen fundoplication.

Figure 5 Dor (anterior partial) fundoplication



Endoluminal EsophyX® fundoplication

Recently, endoluminal fundoplication using the EsophyX® device has been introduced as an endoscopic alternative for laparoscopic fundoplication. Endoluminal fundoplication creates a 270° wrap from within the stomach. The procedure is performed trans-orally and therefore no incisions are required. The procedure aims to reduce hospital stay, sick leave, in-hospital complications and long-term morbidity related to laparoscopic fundoplication, such as the formation of (obstructive) adhesions and incisional hernias. The outcome of laparoscopic fundoplication after previous endoluminal fundoplication is described in **chapter 13**.

Part III - Physiological effects

Fundoplication corrects the three pathophysiological mechanisms causing GORD. Firstly, fundoplication reinforces the intrinsic sphincter by increasing the resting pressure and the relaxation pressure of the LOS.[63] Secondly, reduction of a sliding hiatal hernia by mobilisation of the distal oesophagus and repair of the crural diaphragm re-establish positive intra-abdominal pressure on the anti-reflux barrier and the overlap of the intrinsic and extrinsic sphincter.[64] Thirdly, fundoplication reduces the number of TLOSRs and the percentage of TLOSRs associated with reflux.[64]

It has previously been demonstrated that weakly acidic reflux can induce reflux symptoms[24] and that proximal extent of the refluxate determines whether a reflux episode is perceived as a symptom by the patient.[65] Therefore, 24-h combined oesophageal impedance-pH monitoring has a distinct role in the evaluation of symptoms that persist or recur after fundoplication. Furthermore, intraluminal impedance-pH monitoring has made it possible to detect the passage of air through the oesophagus, either in aboral or oral direction.[66;67] This enables physicians to evaluate the effect of fundoplication on air swallowing and belching. As a result, this technique is a valuable tool to evaluate the mechanism that causes inability to belch, gas bloating and flatulence after fundoplication.

Chapter 14 evaluates the effect of laparoscopic Nissen fundoplication on weakly acidic reflux and belching. Impedance-pH monitoring also enables physicians to compare the effect of different fundoplication types. **Chapter 15** describes an impedance study that aims to investigate differences in effects of laparoscopic Toupet and Nissen fundoplication on weakly acidic reflux, proximal reflux extent and belching.

References

(1) Mittal RK, Balaban DH. The esophagogastric junction. *N Engl J Med* 1997; **336**(13):924-932.

(2) Wyman JB, Dent J, Heddle R, Dodds WJ, Toouli J, Downton J. Control of belching by the lower oesophageal sphincter. *Gut* 1990; **31**(6):639-646.

(3) Dent J, Armstrong D, Delaney B, Moayyedi P, Talley NJ, Vakil N. Symptom evaluation in reflux disease: workshop background, processes, terminology, recommendations, and discussion outputs. *Gut* 2004; **53 Suppl 4**:iv1-24.

(4) Dent J, El Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005; **54**(5):710-717.

(5) McDougall NI, Johnston BT, Kee F, Collins JS, McFarland RJ, Love AH. Natural history of reflux oesophagitis: a 10 year follow up of its effect on patient symptomatology and quality of life. *Gut* 1996; **38**(4):481-486.

(6) Revicki DA, Wood M, Wiklund I, Crawley J. Reliability and validity of the Gastrointestinal Symptom Rating Scale in patients with gastroesophageal reflux disease. *Qual Life Res* 1998; **7**(1):75-83.

(7) Dimenas E. Methodological aspects of evaluation of Quality of Life in upper gastrointestinal diseases. *Scand J Gastroenterol Suppl* 1993; **199**:18-21.

(8) Revicki DA, Wood M, Maton PN, Sorensen S. The impact of gastroesophageal reflux disease on health-related quality of life. *Am J Med* 1998; **104**(3):252-258.

(9) Stewart AL, Greenfield S, Hays RD, Wells K, Rogers WH, Berry SD et al. Functional status and well-being of patients with chronic conditions. Results from the Medical Outcomes Study. *JAMA* 1989; **262**(7):907-913.

(10) Ronkainen J, Aro P, Storskrubb T, Johansson SE, Lind T, Bolling-Sternevald E et al. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. *Scand J Gastroenterol* 2005; **40**(3):275-285.

(11) Murray JA, Camilleri M. The fall and rise of the hiatal hernia. *Gastroenterology* 2000; **119**(6):1779-1781.

(12) van Herwaarden MA, Samsom M, Smout AJ. Excess gastroesophageal reflux in patients with hiatus hernia is caused by mechanisms other than transient LES relaxations. *Gastroenterology* 2000; **119**(6):1439-1446.

(13) Schoeman MN, Tippett MD, Akkermans LM, Dent J, Holloway RH. Mechanisms of gastroesophageal reflux in ambulant healthy human subjects. *Gastroenterology* 1995; **108**(1):83-91.

(14) Dent J, Dodds WJ, Friedman RH, Sekiguchi T, Hogan WJ, Arndorfer RC et al. Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects. *J Clin Invest* 1980; **65**(2):256-267.

(15) Richter JE. Diagnostic tests for gastroesophageal reflux disease. *Am J Med Sci* 2003; **326**(5):300-308.

(16) Anon. An evidence-based appraisal of reflux disease management: the Genval Workshop Report. *Gut* 1999; **44 (suppl 2)**:s1-s16.

(17) Johnson LF, DeMeester TR. Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. *Am J Gastroenterol* 1974; **62**(4):325-332.

(18) DeMeester TR, Johnson LF, Joseph GJ, Toscano MS, Hall AW, Skinner DB. Patterns of gastroesophageal reflux in health and disease. *Ann Surg* 1976; **184**(4):459-470.

(19) Kahrilas PJ, Quigley EM. Clinical esophageal pH recording: a technical review for practice guideline development. *Gastroenterology* 1996; **110**(6):1982-1996.

(20) Silny J. Intraluminal multiple electric impedance procedure for measurement of gastrointestinal motility. *J Gastrointest Motil* 1991; **3**:151-162.

(21) Sifrim D, Castell D, Dent J, Kahrilas PJ. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. *Gut* 2004; **53**(7):1024-1031.

(22) Castell DO, Vela M. Combined multichannel intraluminal impedance and pH-metry: an evolving technique to measure type and proximal extent of gastroesophageal reflux. *Am J Med* 2001; **111 Suppl 8A**:157S-159S.

(23) Castell DO. Esophageal manometry prior to antireflux surgery: required, preferred, or even needed? *Gastroenterology* 2001; **121**(1):214-216.

(24) Vela MF, Camacho-Lobato L, Srinivasan R, Tutuian R, Katz PO, Castell DO. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. *Gastroenterology* 2001; **120**(7):1599-1606.

(25) Klinkenberg-Knol EC, Nelis F, Dent J, Snel P, Mitchell B, Prichard P et al. Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety, and influence on gastric mucosa. *Gastroenterology* 2000; **118**(4):661-669.

(26) Bredenoord AJ, Dent J. Proton pump inhibitor-therapy refractory gastro-oesophageal reflux disease patients, who are they? *Gut* 2007; **56**(4):593-594.

(27) Spechler SJ, Lee E, Ahnen D, Goyal RK, Hirano I, Ramirez F et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. *JAMA* 2001; **285**(18):2331-2338.

(28) Vakil N. Review article: the role of surgery in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2007; **25**(12):1365-1372.

(29) Oelschlager BK, Eubanks TR, Oleynikov D, Pope C, Pellegrini CA. Symptomatic and physiologic outcomes after operative treatment for extraesophageal reflux. *Surg Endosc* 2002; **16**(7):1032-1036.

(30) Lindstrom DR, Wallace J, Loehrl TA, Merati AL, Toohill RJ. Nissen fundoplication surgery for extraesophageal manifestations of gastroesophageal reflux (EER). *Laryngoscope* 2002; **112**(10):1762-1765.

(31) Meyer TK, Olsen E, Merati A. Contemporary diagnostic and management techniques for extraesophageal reflux disease. *Curr Opin Otolaryngol Head Neck Surg* 2004; **12**(6):519-524.

(32) Rakita S, Villadolid D, Thomas A, Bloomston M, Albrink M, Goldin S et al. Laparoscopic Nissen fundoplication offers high patient satisfaction with relief of extraesophageal symptoms of gastroesophageal reflux disease. *Am Surg* 2006; **72**(3):207-212.

(33) DeMeester TR, Bonavina L, Albertucci M. Nissen fundoplication for gastroesophageal reflux disease. Evaluation of primary repair in 100 consecutive patients. *Ann Surg* 1986; **204**(1):9-20.

(34) Galmiche JP, Clouse RE, Balint A, Cook IJ, Kahrilas PJ, Paterson WG et al. Functional esophageal disorders. *Gastroenterology* 2006; **130**(5):1459-1465.

(35) NISSEN R. [A simple operation for control of reflux esophagitis.]. *Schweiz Med Wochenschr* 1956; **86**(Suppl 20):590-592.

(36) NISSEN R. Die transpleurael resektion der kardia. *Dtsch Chir* 1937; **249**:311-316.

(37) Jamieson GG, Duranceau A. What is a Nissen fundoplication? *Surg Gynecol Obstet* 1984; **159**(6):591-593.

(38) Rossetti ME, Liebermann-Meffert D, Brauer RB. Nissen fundoplication for gastroesophageal reflux disease: the Rossetti modification of the Nissen fundoplication – technique and results. *Dis Esophagus* 1996; **9**:251-257.

(39) Catarci M, Gentileschi P, Papi C, Carrara A, Marrese R, Gaspari AL et al. Evidence-based appraisal of antireflux fundoplication. *Ann Surg* 2004; **239**(3):325-337.

(40) Dallemagne B, Weerts JM, Jehaes C, Markiewicz S, Lombard R. Laparoscopic Nissen fundoplication: preliminary report. *Surg Laparosc Endosc* 1991; **1**(3):138-143.

(41) Bais JE, Bartelsman JF, Bonjer HJ, Cuesta MA, Go PM, Klinkenberg-Knol EC et al. Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. *Lancet* 2000; **355**(9199):170-174.

(42) Bloechle C, Mann O, Gawad KA, Izbicki JR. Gastro-oesophageal reflux disease. *Lancet* 2000; **356**(9223):69-3.

(43) Booth M, Dehn TC. Gastro-oesophageal reflux disease. *Lancet* 2000; **356**(9223):70-71.

(44) de Beaux AC, Watson DI, Jamieson GG. Gastro-oesophageal reflux disease. *Lancet* 2000; **356**(9223):71-72.

(45) de Brauw LM, Beets GL. Gastro-oesophageal reflux disease. *Lancet* 2000; **356**(9223):69-70.

(46) Gorecki PJ, Hinder RA. Gastro-oesophageal reflux disease. *Lancet* 2000; **356**(9223):70-73.

(47) Pellegrini CA. Gastro-oesophageal reflux disease. *Lancet* 2000; **356**(9223):71-73.

(48) Cadiere GB, Himpens J, Vertruyen M, Bruyns J, Fourtanier G. [Nissen fundoplication done by remotely controlled robotic technique]. *Ann Chir* 1999; **53**(2):137-141.

(49) Maeso S, Reza M, Mayol JA, Blasco JA, Guerra M, Andradas E et al. Efficacy of the Da Vinci surgical system in abdominal surgery compared with that of laparoscopy: a systematic review and meta-analysis. *Ann Surg* 2010; **252**(2):254-262.

(50) Draaisma WA, Rijnhart-de Jong HG, Broeders IA, Smout AJ, Furnee EJ, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. *Ann Surg* 2006; **244**(1):34-41.

(51) Camilleri M, Dubois D, Coulie B, Jones M, Kahrilas PJ, Rentz AM et al. Prevalence and socioeconomic impact of upper gastrointestinal disorders in the United States: results of the US Upper Gastrointestinal Study. *Clin Gastroenterol Hepatol* 2005; **3**(6):543-552.

(52) Johnsson F, Holloway RH, Ireland AC, Jamieson GG, Dent J. Effect of fundoplication on transient lower oesophageal sphincter relaxation and gas reflux. *Br J Surg* 1997; **84**(5):686-689.

(53) Low DE, Mercer CD, James EC, Hill LD. Post Nissen syndrome. *Surg Gynecol Obstet* 1988; **167**(1):1-5.

(54) McNally EF, Kelly JE, Ingelfinger FJ. Mechanism of belching: effects of gastric distension with air. *Gastroenterology* 1964; **46**:254-259.

(55) Pouderoux P, Ergun GA, Lin S, Kahrilas PJ. Esophageal bolus transit imaged by ultrafast computerized tomography. *Gastroenterology* 1996; **110**(5):1422-1428.

(56) Smith D, King NA, Waldron B, Cullen PT, Millar B, Fenwick M et al. Study of belching ability in antireflux surgery patients and normal volunteers. *Br J Surg* 1991; **78**(1):32-35.

(57) Woodward ER, Thomas HF, McAlhany JC. Comparison of crural repair and Nissen fundoplication in the treatment of esophageal hiatus hernia with peptic esophagitis. *Ann Surg* 1971; **173**(5):782-792.

(58) Varin O, Velstra B, De SS, Ceelen W. Total vs partial fundoplication in the treatment of gastroesophageal reflux disease: a meta-analysis. *Arch Surg* 2009; **144**(3):273-278.

(59) TOUPET A. [Technic of esophago-gastroplasty with phrenogastropexy used in radical treatment of hiatal hernias as a supplement to Heller's operation in cardiospasms.]. *Mem Acad Chir (Paris)* 1963; **89**:384-389.

(60) Dor J, Humbert P, Paoli JM, Miorclerc M, Aubert J. [Treatment of reflux by the so-called modified Heller-Nissen technic]. *Presse Med* 1967; **75**(50):2563-2565.

(61) Krysztopik RJ, Jamieson GG, Devitt PG, Watson DI. A further modification of fundoplication. 90 degrees anterior fundoplication. *Surg Endosc* 2002; **16**(10):1446-1451.

(62) Watson DI, Jamieson GG, Pike GK, Davies N, Richardson M, Devitt PG. Prospective randomized double-blind trial between laparoscopic Nissen fundoplication and anterior partial fundoplication. *Br J Surg* 1999; **86**(1):123-130.

(63) Mathew G, Watson DI, Myers JC, Holloway RH, Jamieson GG. Oesophageal motility before and after laparoscopic Nissen fundoplication. *Br J Surg* 1997; **84**(10):1465-1469.

(64) Bredenoord AJ, Draaisma WA, Weusten BL, Gooszen HG, Smout AJ. Mechanisms of acid, weakly acidic and gas reflux after anti-reflux surgery. *Gut* 2008; **57**(2):161-166.

(65) Bredenoord AJ, Weusten BL, Curvers WL, Timmer R, Smout AJ. Determinants of perception of heartburn and regurgitation. *Gut* 2006; **55**(3):313-318.

(66) Fass J, Silny J, Braun J, Heindrichs U, Dreuw B, Schumpelick V et al. Measuring esophageal motility with a new intraluminal impedance device. First clinical results in reflux patients. *Scand J Gastroenterol* 1994; **29**(8):693-702.

(67) Sifrim D, Silny J, Holloway RH, Janssens JJ. Patterns of gas and liquid reflux during transient lower oesophageal sphincter relaxation: a study using intraluminal electrical impedance. *Gut* 1999; **44**(1):47-54.

Part I

Indications

2

The preoperative reflux pattern as prognostic indicator for long-term outcome after Nissen fundoplication

J.A.J.L. Broeders[1]
W.A. Draaisma[1]
D.R. de Vries[2]
A.J. Bredenoord[3]
A.J.P.M. Smout[2]
H.G. Gooszen[1]

[1]Dep. of Surgery, University Medical Center Utrecht
[2]Dep. of Gastroenterology, University Medical Center Utrecht
[3]Dep. of Gastroenterology, St. Antonius Hospital, Nieuwegein

14th annual meeting of the European Surgical Association
Dublin, Ireland, April 2007

American Journal of Gastroenterology 2009; 104:1922-30.

Abstract

Objective: To investigate the impact of the preoperative reflux pattern on long-term outcome after Nissen fundoplication.

Background: Recent studies disagree on whether patients with pathological upright reflux should be discouraged to undergo surgery.

Methods: A total of 338 patients underwent Nissen fundoplication. Of these, 234 out of 289 patients had pathological acid exposure on preoperative 24-hour esophageal pH monitoring and were classified as pathological upright (*n*=81), supine (*n*=55) or bipositional (*n*=98) reflux. Clinical outcome and results of endoscopy, manometry and 24-hour pH monitoring were compared preoperatively, after 3 months and after 5 years postoperatively.

Results: Patients with pathological upright and supine reflux had similar preoperative reflux parameters. In patients with pathological bipositional reflux however, preoperative total acid exposure was higher than in patients with upright and supine reflux (18.3% *vs* 10.7% and 7.5%; *P*<0.001 and *P*<0.001). Prevalence of esophagitis was higher in patients with bipositional reflux than in upright reflux, both before (64.0% *vs* 45.6%; *P*=0.035) and 3 months after surgery (16.0% *vs* 3.5%; *P*=0.018). Before surgery mean LES pressure was lower compared to the upright and supine reflux group (1.0 *vs* 1.5 and 1.6 kPa; *P*=0.007 and *P*=0.005). The increase in quality of life and reduction of symptoms, acid suppressing drug use, total acid exposure and esophagitis was independent of reflux pattern at three months and five years (all *P*<0.05). Prevalence of recurrent pathological acid exposure was higher in the bipositional group than in upright group (40.9% *vs* 10.7%; *P*=0.013). Surgical reintervention was significantly more common in bipositional reflux patients (20.0% *vs* upright=8.9% *vs* supine=4.1%).

Conclusion: All three pathological reflux patterns respond favorably to Nissen fundoplication on the long-term. Patients with pathological bipositional reflux, however, suffer from more severe disease with higher chance of recurrence and reoperation.

Introduction

Gastroesophageal reflux disease (GERD) is the most common upper gastrointestinal tract disorder in the Western world.[1] GERD refractory to acid suppression and a documented relation between symptoms and reflux is a well-accepted indication for antireflux surgery. Currently, the gold standard for diagnosis of GERD is 24-hour ambulatory esophageal pH monitoring.[2] This analysis classifies patients with GERD into three reflux patterns according to the body position in which pathological reflux occurs; isolated upright, isolated supine and bipositional reflux.[3] Persistent pathological supine and bipositional reflux are classic indications for surgical intervention.[3,4] Traditionally, isolated upright reflux has been considered to be associated with less severe manifestations of the disease and it is reported that these patients suffer from higher rates of postoperative gas bloating and flatus.[3,4] Therefore, surgery tends to be withheld from these patients.[3,4]

In contrast, new studies have shown that patients with pathological upright reflux have a symptomatic outcome that is similar to that in patients operated for isolated supine or bipositional reflux.[5-10] The only two studies in which the result of the fundoplication was evaluated objectively support the view that patients with isolated upright reflux do well after surgery.[10-11] Other authors have recently reopened the debate and it has been reported that poorer symptomatic improvement occurs after surgery in patients with pathological upright reflux.[12-15] Thus, at present, it remains controversial whether isolated upright reflux should be regarded as a relative contraindication for antireflux surgery, because studies comparing long-term objective and subjective parameters are lacking.

In an era of growing demand for preoperative counseling, differentiated information on a patient's individual risk for recurrence and reoperation seems indispensable. This prospective study, aims to fill part of that gap and to provide risk profiles for the three reflux patterns, based on objective and subjective long-term evaluation of data obtained before, three months and five years after Nissen fundoplication.

Methods

Study design and participants

A consecutive cohort of 338 patients with GERD symptoms refractory to acid suppression were operated between January 1997 and October 2005 and prospectively followed for five years. PPI-refractory GERD was defined as reflux symptoms persisting over six months despite double dose PPI use (>40 mg omeprazole / 24 hours or comparable therapy), with a pathological esophageal acid exposure time during 24-h pH monitoring. The indication for surgery,

preoperative work-up, surgical technique, patient management and follow-up were identical for all patients. In all patients a standardized 360° degree Nissen fundoplication of 3.0 to 3.5 cm was constructed after ligation and division of the short gastric vessels, full mobilization of the esophagus and posterior crural repair. Results have been published in different parts earlier.[16-18] The patients included in this study were asked to fill out a questionnaire on quality of life and use of acid suppressing drugs before surgery, at three months and five years after surgery. Three months and five years after surgery, all patients were asked to rate the change in their reflux symptoms compared to the preoperative state. Surgical reinterventions and indications for reintervention were recorded up to six years after initial surgery. For objective analyses, all patients were asked to undergo stationary esophageal manometry and 24-hour pH monitoring both preoperatively and after three months and additional stationary esophageal manometry and 24-hour pH testing five years after surgery. Patients were included in the present study if preoperative 24-hour pH monitoring demonstrated pathological reflux and subjective or objective outcome was registered after surgery.

Clinical outcome

The Visick score was applied to monitor the subjective effect of surgery as it correlates well to the most prominent symptom of GERD (heartburn)[19] and gives an over-all impression of how the effect of antireflux surgery is appreciated. Patients were asked to rate the effect of surgery on their reflux symptoms by modified Visick grading as follows: complete resolution (Visick I), improvement (Visick II), no effect of surgery (Visick III) or deterioration (Visick IV), always in comparison with their preoperative state. A visual analogue scale (VAS), validated for quality of life assessment after esophageal surgery, was used to measure the impact on quality of life.[20] The scale ranged from 0 to 100, where zero represented worst possible health and 100 represented perfect health.[21] Subjective outcome and results of upper endoscopy, manometry, 24-hour pH monitoring, use of acid suppressing drugs and surgical reintervention were collected prospectively in consecutive patients.

Upper GI-endoscopy

During endoscopy, the presence of esophagitis and hiatal hernia size were determined by experienced gastroenterologists. Initially, esophagitis was graded according to the Savary-Miller classification.[22] Later, patients were graded according to the Los Angeles classification for esophagitis.[23]

Stationary esophageal manometry

All studies were performed after suspending medication that could affect esophageal motility 48 hours in advance. Manometric recordings were performed using a water-perfused system with a multiple-lumen catheter with an incorporated sleeve sensor (Dentsleeve Pty Ltd, Adelaide, Australia). In order to determine the distal and proximal border of the lower esophageal sphincter (LES), the catheter was introduced transnasally and subsequently retracted. Then, the sleeve sensor was positioned at the level of the LES. At 5, 10 and 15 cm above the proximal border of the LES the intraluminal esophageal pressures were recorded. The manometric response to ten standardized wet swallows (5-ml water bolus) was recorded. The gastric baseline pressure (registered 2 cm below the distal margin of the sleeve sensor) was used as the zero reference point.

24-hour esophageal pH monitoring

Ambulatory 24-hour pH testing was performed with the patient at least seven days free of medication that could affect results. A pH glass electrode (model LOT440, Medical Instruments Corporation, Solothurn, Switzerland) was introduced transnasally and positioned 5 cm above the manometrically determined upper margin of the LES. The tracings were recorded in a digital data logger (Medical Measurements Systems BV, Enschede, The Netherlands) and patients were instructed to register body position and reflux symptoms in a diary. In addition, they were asked to press a button on the digital data logger at the beginning of each symptom episode. After 24 hours, the recordings were analyzed automatically using a software program (MMS, Enschede, The Netherlands). If the patients experienced symptoms during the measurement, the symptom index (SI) and symptom association probability (SAP) were calculated.[24,25] The SI was considered to be indicative for positively reflux-related symptoms if it was equal to or higher than 50%. The SAP had to be at least 95% to be positive.

The classification of pathological upright, supine or bipositional reflux was based on the percentage of time the esophageal pH was below 4 in upright and supine body position. The upper limit for normal esophageal acid exposure for upright and supine position was two standard deviations above the mean value obtained in healthy volunteers during ambulatory 24-h pH monitoring.[2,26] Pathological upright reflux was defined as acid exposure time > 8.2 % in upright position and normal exposure (< 3.5 %) in supine position. The definition for pathological supine reflux was normal acid exposure (< 8.2%) in upright position and > 3.5 % in supine position. Pathological bipositional reflux was defined as abnormal acid exposure time in both upright (> 8.2 %) and in supine (> 3.5 %) position. Patients with

physiologic esophageal acid exposure did neither meet the criteria for pathological upright nor for supine reflux.

Statistical Analysis

All statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL). Because the aim of this study was to score the effect of surgery in subjective and objective terms, only those patients were included of whom both the preoperative data and the results at 3 months or 5 years after surgery were available. The number of patients for which data were available was determined for each parameter. Values were expressed as mean ± standard error of the mean (SEM). Parametric data were analyzed for differences between the three reflux patterns using a one-way ANOVA and Bonferroni post-hoc test. To determine significant effects of surgery on parametric data the paired-samples *t*-test was used. Groups were compared with the χ^2 test for nominal variables. For these variables effects of surgery were analyzed using the McNemar-Bowker test. Differences were considered statistically significant with a *P* value less than 0.05.

Results

Subdivision in patterns of reflux

A total of 338 consecutive patients underwent Nissen fundoplication for GERD refractory to acid suppressing drugs. Patients were excluded from this study if 24-hour registration was incomplete (*n* = 49). If preoperative acid exposure on 24-hour pH monitoring did not meet the criteria of any reflux pattern, patients were classified as having physiologic esophageal acid exposure and were excluded (*n* = 43). In this group, all but two patients had a physiologic acid exposure for total time as well (< 5.8%[26]). During follow-up subjective and / or objective outcome data were incomplete in 12 patients. These patients were excluded from the analysis.

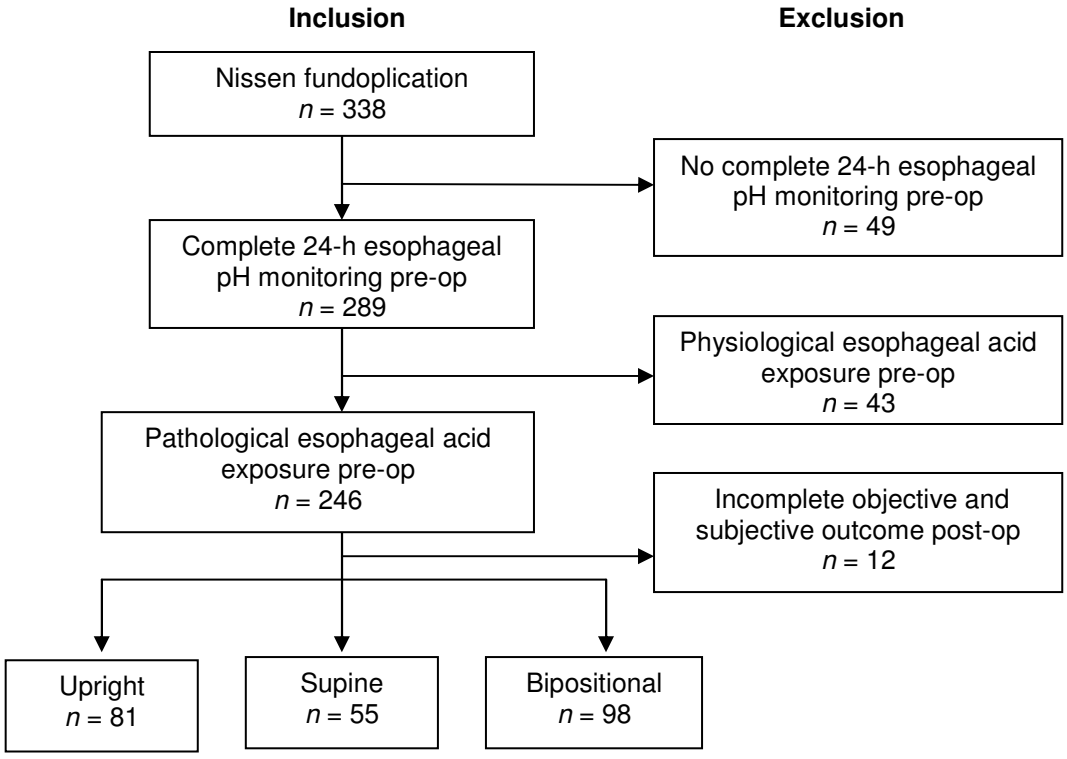
Table 1 Patient characteristics

	Upright	**Supine**	**Bipositional**
Patients	81	55	98
Age (years)	41.6 (16-80)	44.7 (20-85)	43.7 (17-77)
Male / female sex	50 / 31	32 / 23	62 / 36
Body Mass Index (BMI) *	26.5 (0.5)	27.2 (0.8)	26.5 (0.4)
Hiatal hernia (cm) *	2.5 (0.3)	3.0 (0.4)	3.4 (0.3)

* values are given as mean (SEM)

The remaining patients (*n* = 234) were classified as having pathological upright reflux (*n* = 81), supine reflux (*n* = 55) and bipositional reflux (*n* = 98; fig. 1). Patient characteristics and mean hiatal hernia size was similar in these three subgroups (table 1).

Figure 1 Study profile



Clinical outcome

Eighty-six percent of the patients with isolated upright reflux scored their reflux symptoms as resolved or improved (Visick I and II) five years after fundoplication. In the supine group Visick I-II was reached in 98% and in the bipositional reflux group in 95%. Improvement of reflux symptoms after surgery was similar in the three reflux patterns (fig. 2). There were no differences in quality of life (fig. 3) and the use of acid suppressing drugs (fig. 4) between the groups before surgery, at three months and five years. The improvement in quality of life was significant in the supine and bipositional reflux groups at three months (51 (4.7)→68 (4.3); P = 0.015 and 50 (2.8)→63 (2.5); $P < 0.001$). At five years, the effect on quality of life

became significant in the upright group (55 (3.2)→64 (3.5); $P = 0.024$), flawed in the supine group (51 (4.7)→60 (5.5); $P = 0.264$) and stabilized in the bipositional group (50 (2.8)→65 (3.0); $P < 0.001$). The percentage of patients using acid suppressing drugs was similarly reduced in all types of GERD at three months (86→4% *vs* 80→8% *vs* 83→6%, respectively; all $P < 0.001$) and five years (86→21% *vs* 80→11% *vs* 83→18%, respectively; all $P < 0.001$), though the use of acid suppressing drugs increased again with time.

Figure 2 Self-rated change in reflux symptoms five years after surgery compared to the preoperative state in patients with pathological upright, supine and bipositional reflux.

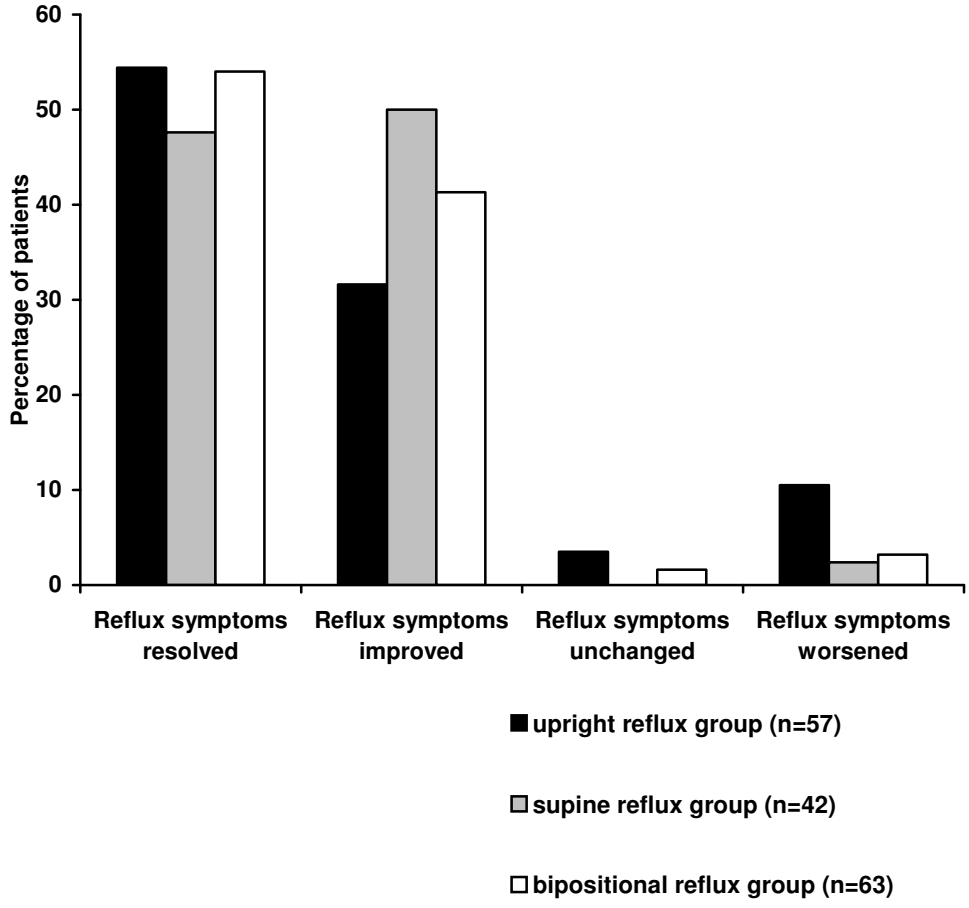
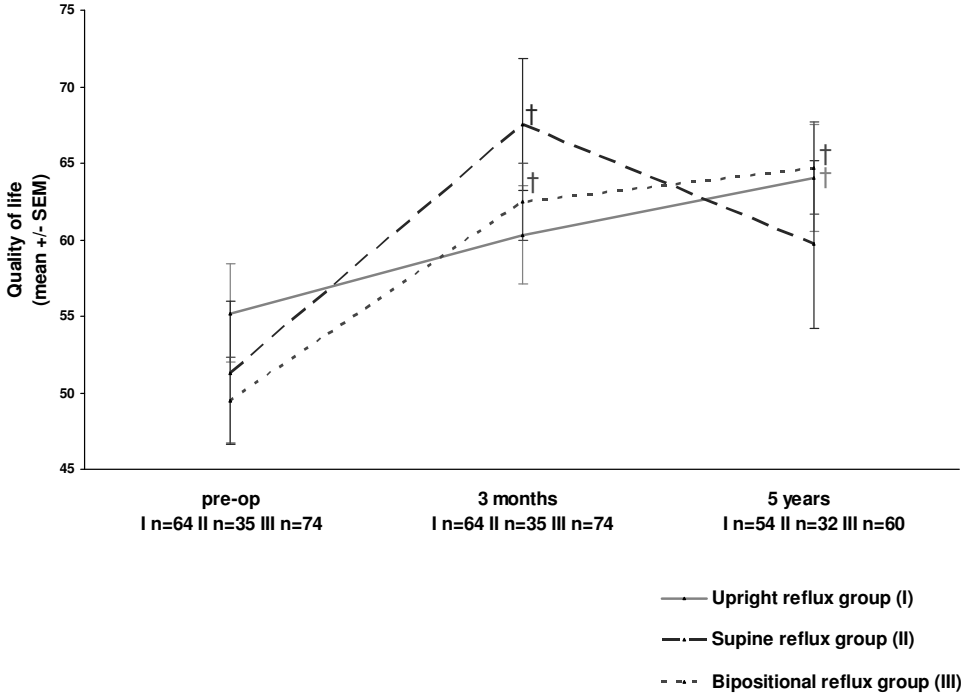
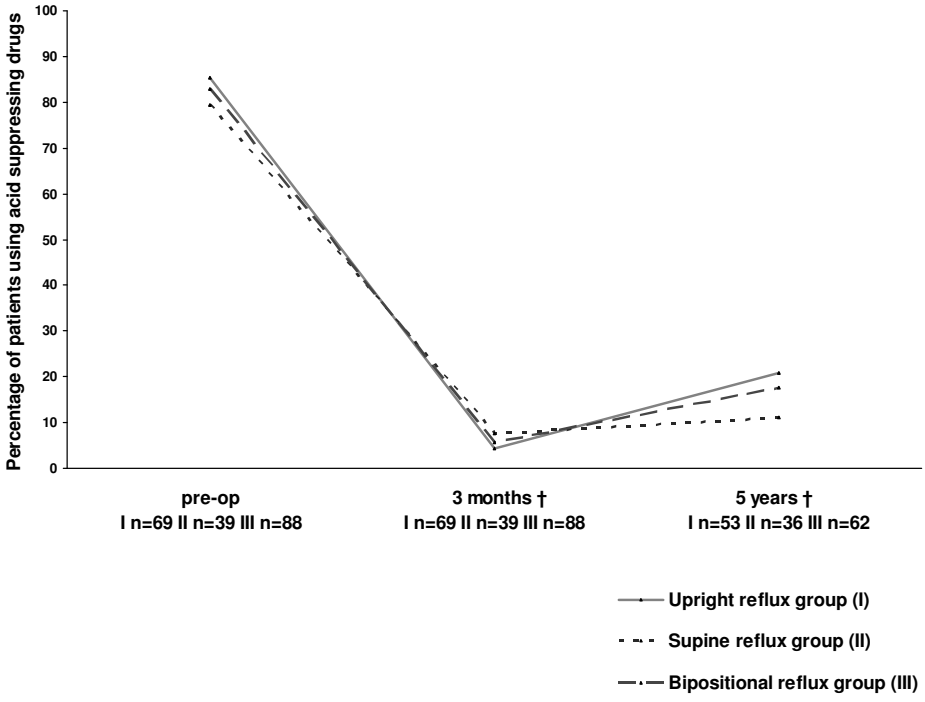


Figure 3 Mean quality of life (VAS score 0-100) preoperatively, three months and five years postoperatively in patients with pathological upright, supine and bipositional reflux.



† $P < 0.05$ versus preoperative results

Figure 4 Percentage of patients using acid suppressing drugs preoperatively, three months and five years postoperatively in patients with pathological upright, supine and bipositional reflux.



† $P < 0.001$ versus preoperative results for all groups

Surgical reintervention was necessary in 28 patients (12.6%) within six years of follow-up. The mean time to reintervention was 14 months. The reoperation rate after 6 years of follow-up was higher in patients with bipositional reflux than in patients with isolated upright or supine reflux before initial surgery (table 2: 20.0% *vs* 8.9 *vs* 4.1; $P = 0.040$ and $P = 0.010$).

Table 2 Percentage of patients with recurrent pathological reflux three months and five years after surgery and number of surgical reinterventions in the preoperatively classified upright, supine and bipositional reflux group. Number of patients for which data were available (n =) is displayed.

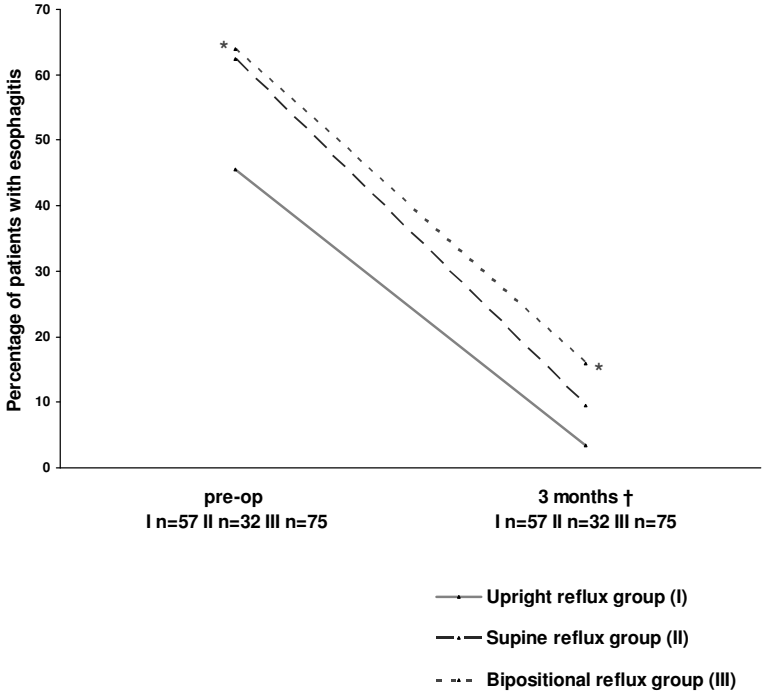
	Upright (I) (%)	**Supine (II) (%)**	**Bipositional (III) (%)**
Recurrent pathological reflux			
- 3 months post-op	4 (5.9)	4 (11.1)	18 (22.2) ~
(I *n*=68 II *n*=36 III *n*=81)			
Postoperative reflux pattern:			
Upright	3	1	0
Supine	1	3	13
Bipositional	0	0	5
- 5 years post-op	3 (10.7)	3 (18.8)	9 (40.9) ~
(I *n*=28 II *n*=16 III *n*=22)			
Postoperative reflux pattern:			
Upright	1	1	0
Supine	2	2	8
Bipositional	0	0	1
Surgical reintervention			
- 6 years post-op	7 (8.9)	2 (4.1)	19 (20.0) *
(I *n*=79 II *n*=49 III *n*=95)			
Reoperation indication:			
Recurrent reflux	3	2	6
Dysphagia	3	0	8
Intrathoracical herniation	0	0	4
Other	1	0	1

~ $P < 0.05$ versus upright; * $P < 0.05$ versus upright and supine

Upper GI-endoscopy

When the three groups were compared with respect to the prevalence of esophagitis, patients with pathological upright and supine reflux were similar before and after surgery (fig. 5). The prevalence of esophagitis was higher in the bipositional group compared to the upright group, both pre- (64.0% vs 45.6%; P = 0.035) and three months postoperatively (16.0% vs 3.5%; P = 0.018). Surgical intervention reduced the prevalence of esophagitis in all groups (all P < 0.001).

Figure 5 Percentage of patients with esophagitis on upper endoscopy preoperatively and three months postoperatively in patients with pathological upright, supine and bipositional reflux.

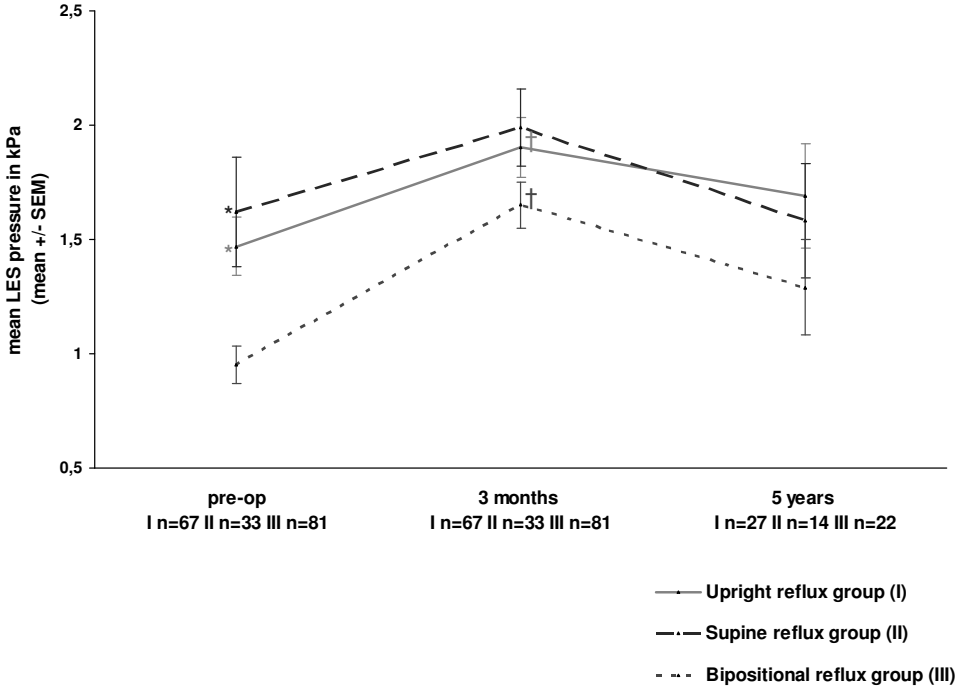


* *P* < 0.05 versus upright reflux group; † *P* < 0.001 versus preoperative results for all groups

Stationary esophageal manometry

Mean LES pressures were similar in the unipositional reflux patterns, both preoperatively and after three months and five years postoperatively (fig. 6). Patients with bipositional GERD had lower LES pressures before surgery compared to the upright and supine group (1.0 (0.1) *vs* 1.5 (0.1) and 1.6 (0.2) kPa; $P = 0.007$ and $P = 0.005$). Operation increased the sphincter pressure in upright and bipositional GERD at three months (to 1.9 (0.1) and 1.7 (0.1) kPa; $P = 0.003$ and $P < 0.001$). The effect in patients with isolated supine reflux was not significant however (2.0 (0.2) $P = 0.126$). Surgery did not have a long-term effect on LES pressure in all groups. Three months and five years after fundoplication there were no significant differences in mean sphincter pressure between the three groups.

Figure 6 Mean preoperative, three months and five years postoperative lower esophageal sphincter pressure in patients with pathological upright, supine and bipositional reflux**.**

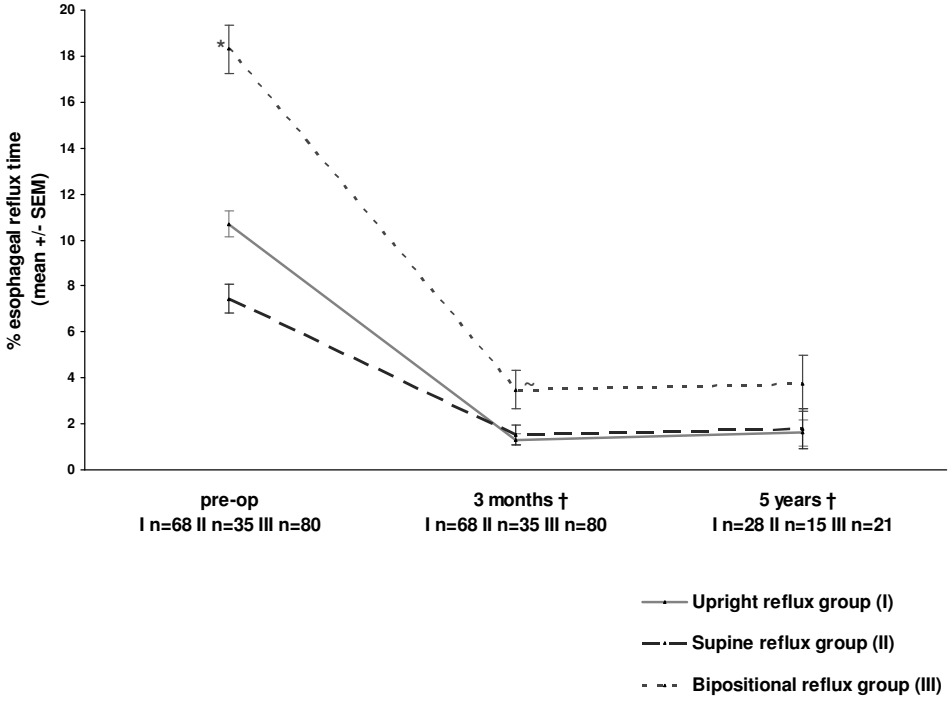


* $P < 0.01$ versus bipositional reflux group; † $P < 0.001$ versus preoperative results

24-hour esophageal pH monitoring

The results of operation on 24-hour pH measurements are shown in figure 7. The upright reflux group had a higher total acid exposure (% of time with pH < 4) before surgery compared to the supine group (10.7 (0.6) and 7.5 (0.6)). This difference approached significance (P = 0.074). Patients with bipositional GERD had higher total acid exposure before surgery compared to the upright and supine group (18.3 (1.0); both P < 0.001). Three months postoperatively, this difference was only significant between the bipositional and upright group, while esophageal acid exposure was not pathological in either group any more (3.5 (0.8) *vs* 1.3 (0.3); P = 0.039).

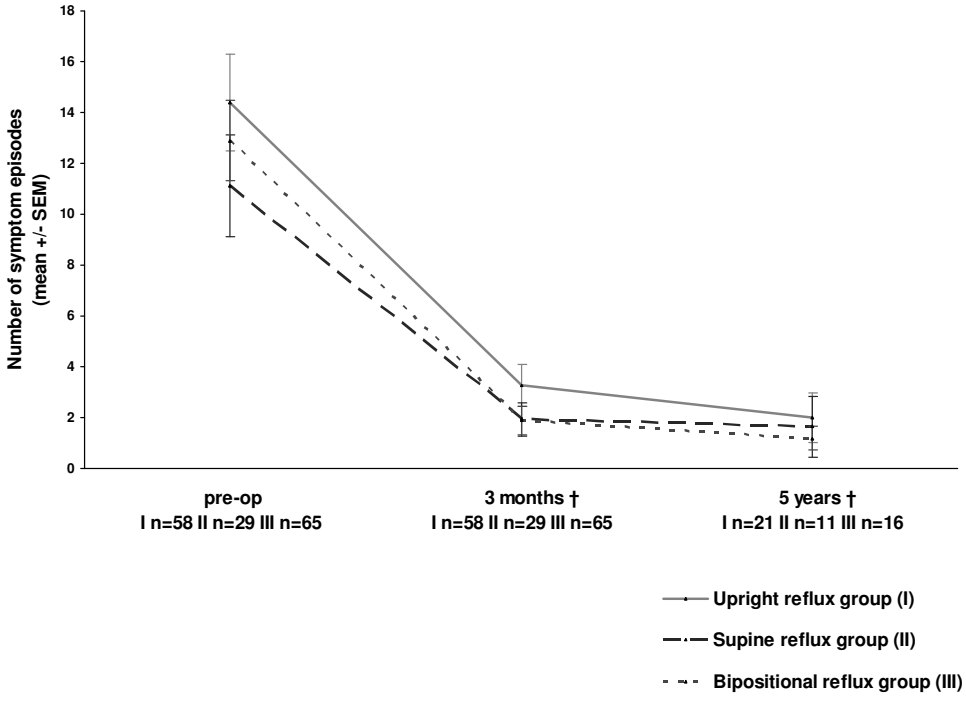
Figure 7 Mean preoperative, three months and five years postoperative total acid exposure in patients with pathological upright, supine and bipositional reflux.



* P < 0.05 versus upright and supine reflux group; ~ P < 0.05 versus upright reflux group; † P < 0.001 versus preoperative results for all groups

In the upright, supine and bipositional group, total acid exposure remained reduced to values within the physiological range after five years (10.7 (0.6)→1.6 (0.6) *vs* 7.5 (0.6)→1.8 (0.9) *vs* 18.3 (1.0)→3.8 (1.2), respectively; all $P < 0.001$). Five years after surgery there were no significant differences in total acid exposure between the three groups.

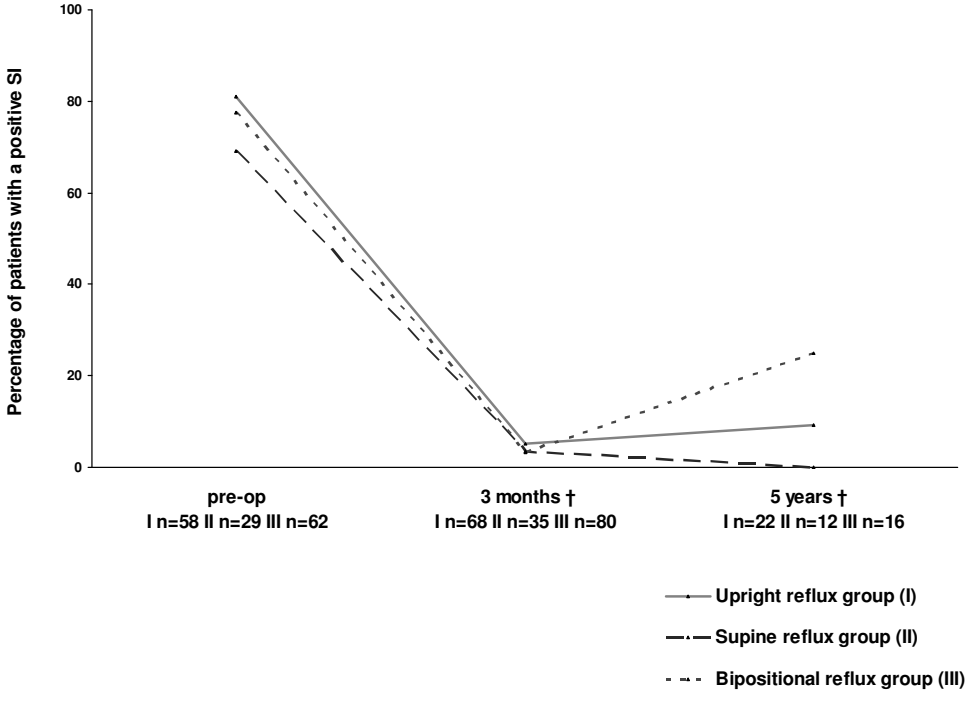
Figure 8 Number of symptom episodes during 24-hour esophageal pH monitoring in patients with pathological upright, supine and bipositional reflux.



† $P < 0.05$ versus preoperative results for all groups

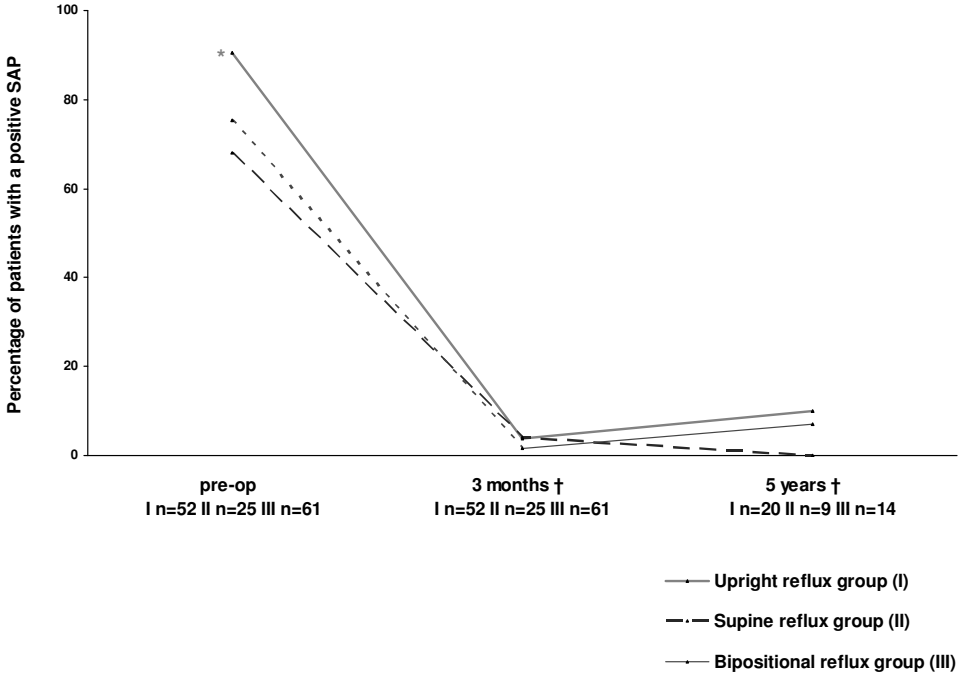
Before surgery and at three months and five years after surgery, the three groups did not differ in the number of symptom episodes during pH monitoring (fig. 8) or the symptom correlation scores (fig. 9 and 10). The only exception was a higher percentage of patients with a positive SAP before surgery in the upright reflux group compared to the other groups (both $P < 0.05$). Surgery not only reduced esophageal acid exposure, but also the number of symptom episodes recorded during the 24-h pH study (all $P < 0.05$) and the percentage of patients with a positive SI (all $P < 0.001$) and SAP (all $P < 0.001$) both at three months and five years. Recurrent pathological reflux after fundoplication was more common in patients with a bipositional reflux pattern before surgery, compared to those with isolated upright reflux (table 2: at three months in 22.2% *vs* 5.9%; $P = 0.005$ and at five years 40.9 vs 10.7%; $P = 0.013$).

Figure 9 Symptom index (SI) during 24-hour esophageal pH monitoring in patients with pathological upright, supine and bipositional reflux.



† $P < 0.001$ versus preoperative results for all groups

Figure 10 Symptom association probability (SAP) during 24-hour esophageal pH monitoring in patients with pathological upright, supine and bipositional reflux.



* $P < 0.05$ versus supine and bipositional reflux group; † $P < 0.001$ versus preoperative results for all groups

Discussion

Because endoscopic alternatives for antireflux surgery are “around the corner”, GERD patients, gastroenterologists and surgeons need detailed information on the long-term results of surgery, not only to weigh the upcoming alternatives against the long-term effect of surgery, but also to know whether the preoperative reflux pattern in the different subgroups, has an impact on outcome of surgery.

The first step in this counseling process is inform the patient about the choice between medical treatment and surgery. Lundell and co-workers have been the first to compare long- term effectiveness of medical and surgical therapy for GERD in patients who responded to both regimens, in two consecutive randomized controlled trials.[27,28] Three-year results demonstrated that long-term symptomatic effectiveness after LNF (90%) is similar to that after esomeprazole treatment (93%).[28] At six months the percentage of patients with normalization of acid exposure, however, was significantly higher after LNF (86% *vs* 56%).[29]

Just as we have done in this study, Lundell et al performed subgroup analysis and showed that both acid exposure in upright and supine body position were better controlled after LNF.[29] In contrast to our study, subgroup analysis of LOTUS’ patients with upright, supine and bipositional reflux before surgery has not been performed so a more balanced comparison between their results and ours can not be presented.

The information currently available on the preoperative pattern of reflux as a predictor of surgical outcome remains controversial, especially in patients with isolated upright reflux. The present study aimed to shed more light on the pattern of reflux in relation to long-term outcome. A homogeneous surgical cohort was studied in which all patients had symptoms that were refractory to acid suppression, with or without esophagitis. This prospective study has the highest degree of completeness, the longest duration of follow-up and is the first to combine subjective and objective outcome.

The current results support the view that pathological bipositional reflux represents the most severe form of the disease.[5,8-11,30,31] Patients with bipositional reflux have the highest total esophageal acid exposure and prevalence of esophagitis and lowest LES pressure, both before and after surgery. The concept that isolated upright reflux is associated with moderate manifestations[12,27] and an earlier phase of the disease[5,11] compared to isolated supine reflux is still widely accepted, in spite of the fact that evidence supporting this view is controversial. In accordance with other reports,[9,10,12] the present study demonstrates that patients with pathologic upright reflux have similar preoperative total acid exposure compared to supine reflux patients. In contrast, Fein *et al*.[5] and Hong *et al*.[11] found lower total acid

exposure in upright reflux patients before surgery. At least part of this discrepancy can be explained by the use of different categorization of reflux patterns. More than a third of the patients in the upright reflux group described by these authors had abnormal composite acid scores, but did not meet the criteria for either pathological upright or supine reflux. These patients were classified as pathological reflux according to their dominant reflux pattern. All but three of the patients with physiological acid exposure time were classified as having isolated upright reflux. These patients probably had less severe GERD and consequently the mean total acid exposure was likely to be lower in the upright groups.

In 1976, DeMeester *et al*. reported a significant difference in the prevalence of esophagitis of any grade between patients with pathological upright and supine reflux.[3] Our study and other recent studies could not confirm this difference between patients with upright and supine reflux.[5,12,30,32] In general, no differences in GERD manifestations and response to treatment were found between patients with pathological upright and supine reflux. The assumption that isolated upright reflux is associated with early or mild disease therefore appears to be incorrect and cannot be put forward as a valid reason for withholding surgery from these patients.

In contrast, patients with pathological bipositional reflux were found to have more severe GERD manifestations and higher recurrence and reoperation rates compared to patients with unipositional reflux. Despite these differences in disease severity, symptoms, quality of life, use of acid suppressing drugs, esophagitis, LES pressure and acid exposure improved equally up to five years after surgery, irrespective of the reflux pattern. The improvement of physiologic parameters in the three groups is in accordance with the only two studies in which objective outcome was compared, using manometry and pH-monitoring.[10-11] These assessments, however, were performed at nine and one months and no further follow-up was reported. In accordance with several other reports on outcome after antireflux surgery[11,33-35] and earlier published results from our group, the low percentages of patients with a positive SI and SAP indicate that postoperative symptoms are hardly related to reflux and therefore recurrent symptoms do not indicate recurrent acid reflux. For that reason, general improvement of reflux symptoms and quality of life were chosen as subjective outcome measures, instead of individual symptoms.

The reoperation rate for the whole group was 12.6% within six years. The reported eoperation rate after laparoscopic antireflux surgery varies from 2% to 8% in twelve months.[36,37] The present study's reoperation rate at twelve months after initial surgery is in accordance with these reports (6.7%). Reoperation rates of case series from single, usually expert, centers differ considerably from those of population based studies and randomized controlled trials. [38] Publication bias,

selection bias and referral bias probably explain the difference in these results. A recent meta-analysis of randomized controlled trials demonstrated that recurrence of reflux after Nissen fundoplication occurs in 16.5% after a mean follow-up of 16 months. [38] The pooled reoperation rate after a mean follow-up of 30 months was 9.6%. The recurrence rate (14% at 3 months and 23% at 60 months) and reoperation rate of the present study (12.6% at 72 months) are largely in line with these results, considering the extended length of follow-up. We therefore feel that the present reoperation and recurrence rates are representative for surgical results in experienced, not necessarily expert, units. The severity of GERD in bipositional reflux patients is reflected by a higher incidence of recurrent reflux and reoperation rate compared to unipositional reflux. In the bipositional reflux group almost twice as many patients underwent reoperation because of recurrent reflux, which is probably a manifestation of more severe reflux disease. Moreover, reintervention for dysphagia occurred even more when compared to the unipositional reflux patterns. Another recent report has also demonstrated that patients with manifestations of more severe gastroesophageal reflux disease prior to fundoplication have a higher recurrence rate after surgery. [39] The only two studies that postoperatively objectified reflux in bipositional reflux patients, report recurrent reflux in 26% at one month[10] and in 25% at nine months after surgery.[11] The current study's recurrence rate at three months for these patients is in line with these reports (22%).

A limitation of the current study is the fact that some patients refused to comply with parts of the postoperative study protocol, possibly leading to a selection bias. We know from earlier studies that subgroups of patients who refuse objective long-term evaluation, have an over-representation of asymptomatic patients, who realize they will not benefit from further invasive testing. This might explain the high percentage of patients with recurrent pathological acid exposure in the three groups at five years.

In conclusion, this study has added valuable data to solve the controversy on the long-term outcome of antireflux surgery in patients with isolated upright reflux. Combination of objective and subjective evaluation brings forth the new insight that patients with pathological upright reflux have similarly severe objective GERD manifestations compared to patients with isolated supine reflux, before and five years after Nissen fundoplication. Furthermore, the study supports the concept that pathological bipositional reflux is associated with more severe disease compared to unipositional reflux, and more difficult to deal with by antireflux surgery. Despite this difference in disease severity, all three pathological reflux patterns respond favorably to antireflux surgery on the long-term. Therefore, patients with pathological upright, supine and bipositional reflux all are good candidates for

antireflux surgery and, consequently, antireflux surgery should not be withheld from patients with isolated pathological upright reflux. Patients with pathological bipositional reflux, however, should be informed about their higher chance of recurrence and reoperation.

References

(1) Dent J, El Serag HB, Wallander MA, et al. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut*. 2005;54:710-717

(2) Jamieson JR, Stein HJ, DeMeester TR, et al. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. *Am J Gastroenterol*. 1992;87:1102-1111

(3) DeMeester TR, Johnson LF, Joseph GJ, et al. Patterns of gastroesophageal reflux in health and disease. *Ann Surg*. 1976;184:459-470

(4) DeMeester TR, Bonavina L, Albertucci M. Nissen fundoplication for gastroesophageal reflux disease. Evaluation of primary repair in 100 consecutive patients. *Ann Surg*. 1986;204:9-20

(5) Fein M, Hagen JA, Ritter MP, et al. Isolated upright gastroesophageal reflux is not a contraindication for antireflux surgery. *Surgery*. 1997;122:829-835

(6) Gillen P, Thornton J, Byrne PJ, et al. Implications of upright gastro-oesophageal reflux. *Br J Surg*. 1994;81:239-240

(7) Mughal MM, Bancewicz J, Marples M. Oesophageal manometry and pH recording does not predict the bad results of Nissen fundoplication. *Br J Surg*. 1990;77:43-45

(8) Cowgill SM, Al Saadi S, Villadolid D, et al. Upright, supine, or bipositional reflux: Patterns of reflux do not affect outcome after laparoscopic Nissen fundoplication. *Surg Endosc*. 2007;21:2193-8

(9) Wayman J, Myers JC, Jamieson GG. Preoperative gastric emptying and patterns of reflux as predictors of outcome after laparoscopic fundoplication. *Br J Surg*. 2007;94:592-598

(10) Meneghetti AT, Tedesco P, Galvani C, et al. Outcomes after laparoscopic Nissen fundoplication are not influenced by the pattern of reflux. *Dis Esophagus*. 2008;21:165-169

(11) Hong D, Swanstrom LL, Khajanchee YS, et al. Postoperative objective outcomes for upright, supine, and bipositional reflux disease following laparoscopic Nissen fundoplication. *Archives of Surgery*. 2004;139:848-852

(12) Winslow ER, Frisella MM, Soper NJ, et al. Patients with upright reflux have less favorable postoperative outcomes after laparoscopic antireflux surgery than those with supine reflux. *J Gastrointest Surg*. 2002;6:819-829

(13) Papasavas PK, Keenan RJ, Yeaney WW, et al. Prediction of postoperative gas bloating after laparoscopic antireflux procedures based on 24-h pH acid reflux pattern. *Surg Endosc*. 2003;17:381-385

(14) Kamolz T, Bammer T, Granderath FA, et al. Comorbidity of aerophagia in GERD patients: outcome of laparoscopic antireflux surgery. *Scand J Gastroenterol*. 2002;37:138-143

(15) Power C, Maguire D, McAnena O. Factors contributing to failure of laparoscopic Nissen fundoplication and the predictive value of preoperative assessment. *Am J Surg*. 2004;187:457-463

(16) Bais JE, Bartelsman JF, Bonjer HJ, et al. Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. *Lancet*. 2000;355:170-174

(17) Draaisma WA, Buskens E, Bais JE, et al. Randomized clinical trial and follow-up study of cost-effectiveness of laparoscopic versus conventional Nissen fundoplication. *Br J Surg*. 2006;93:690-697

(18) Draaisma WA, Ruurda JP, Scheffer RC, et al. Randomized clinical trial of standard laparoscopic versus robot-assisted laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease. *Br J Surg*. 2006;93:1351-1359

(19) Rijnhart-de Jong HG, Draaisma WA, Smout AJ, et al. The Visick score: a good measure for the overall effect of antireflux surgery? *Scand J Gastroenterol*. 2008;43:787-793

(20) de Boer AG, van Lanschot JJ, Stalmeier PF, et al. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? *Qual Life Res*. 2004;13:311-320

(21) Nord E. The validity of a visual analogue scale in determining social utility weights for health states. *Int J Health Plann Manage*. 1991;6:234-242

(22) Savary M and Miller G. The oesophagus. Gasmann SA, ed *Handbook and atlas of endoscopy,* Solothurn, Switzerland: Verlag Gossman. 1978;135-142

(23) Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut*. 1999;45:172-180

(24) Wiener GJ, Richter JE, Copper JB, et al. The symptom index: a clinically important parameter of ambulatory 24-hour esophageal pH monitoring. *Am J Gastroenterol*. 1988;83:358-361

(25) Weusten BL, Roelofs JM, Akkermans LM, et al. The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. *Gastroenterology*. 1994;107:1741-1745

(26) Richter JE, Bradley LA, DeMeester TR, et al. Normal 24-hr ambulatory esophageal pH values. Influence of study center, pH electrode, age, and gender. *Dig Dis Sci*. 1992;37:849-856

(27) Myrvold HE, Lundell L, Miettinen P, et al. The cost of long term therapy for gastro-oesophageal reflux disease: a randomised trial comparing omeprazole and open antireflux surgery. *Gut*. 2001;49:488-494

(28) Lundell L, Attwood S, Ell C, et al. Comparing laparoscopic antireflux surgery with esomeprazole in the management of patients with chronic gastro-oesophageal reflux disease: a 3-year interim analysis of the LOTUS trial. *Gut*. 2008;57:1207-1213

(29) Hatlebakk JG, Lundell LR, Galmiche JP, et al. Initial Control of Acid Reflux After Laparoscopic Anti-Reflux Surgery (Lars) Compared to Chronic Use of Esomeprazole (ESO) 20-40mg Daily. *Gastroenterology*. 2008;134: Suppl.1, A-125

(30) Campos GM, Peters JH, DeMeester TR, et al. The pattern of esophageal acid exposure in gastroesophageal reflux disease influences the severity of the disease. *Arch Surg*. 1999;134:882-887

(31) Ouatu-Lascar R, Lin OS, Fitzgerald RC, et al. Upright versus supine reflux in gastroesophageal reflux disease. *J Gastroenterol Hepatol*. 2001;16:1184-1190

(32) de Caestecker JS, Blackwell JN, Pryde A, et al. Daytime gastro-oesophageal reflux is important in oesophagitis. *Gut*. 1987;28:519-526

(33) Khajanchee YS, O'Rourke RW, Lockhart B, et al. Postoperative symptoms and failure after antireflux surgery. *Arch Surg*. 2002;137:1008-1013

(34) Lord RV, Kaminski A, Oberg S, et al. Absence of gastroesophageal reflux disease in a majority of patients taking acid suppression medications after Nissen fundoplication. *J Gastrointest Surg*. 2002;6:3-9

(35) Jenkinson AD, Kadirkamanathan SS, Scott SM, et al. Relationship between symptom response and oesophageal acid exposure after medical and surgical treatment for gastro-oesophageal reflux disease. *Br J Surg*. 2004;91:1460-1465

(36) Huttl TP, Hohle M, Meyer G, et al. [Antireflux surgery in Germany. Results of a representative survey with analysis of 2,540 antireflux operations]. *Chirurg*. 2002;73:451-461

(37) Jamieson GG, Watson DI, Britten-Jones R, et al. Laparoscopic Nissen fundoplication. *Ann Surg*. 1994;220:137-145

(38) Catarci M, Gentileschi P, Papi C, et al. Evidence-based appraisal of antireflux fundoplication. *Ann Surg*. 2004;239:325-33

(39) Omura N, Kashiwagi H, Yano F, et al. Prediction of recurrence after laparoscopic fundoplication for erosive reflux esophagitis based on anatomy-function-pathology (AFP) classification. *Surg Endosc*. 2007;21:427-430

3

Oesophageal acid hypersensitivity is not a contraindication to Nissen fundoplication

J.A.J.L. Broeders[1]
W.A. Draaisma[1]
A.J. Bredenoord[2]
D.R. de Vries[2]
H.G. Rijnhart-de Jong[1]
A.J.P.M. Smout[2]
H.G. Gooszen[1]

[1]Dep. of Surgery, University Medical Center Utrecht
[2]Dep. of Gastroenterology, University Medical Center Utrecht

15th annual meeting of the European Surgical Association
Venice, Italy, April 2008
11th world congress of the International Society for Diseases of the Esophagus
Budapest, Hungary, September 2008

British Journal of Surgery 2009; 96:1023-30.

Abstract

Background: The Rome III criteria classify patients with a positive relationship between symptoms and reflux episodes but a physiological oesophageal acid exposure time as having gastro-oesophageal reflux disease (GORD) with an acid hypersensitive oesophagus. The long-term outcome of antireflux surgery in these patients was investigated.

Methods: Outcomes of Nissen fundoplication in 28 patients with GORD refractory to proton-pump inhibitors (PPIs) and oesophageal acid hypersensitivity (group 1) were compared with those of 126 patients with pathological acid exposure (group 2).

Results*:* Fundoplication had a similar effect in both groups. Three months after surgery, total acid exposure time and the prevalence of oesophagitis had decreased, whereas mean lower oesophageal pressure had increased. The percentage of patients using PPIs was reduced from 82**.6** to 4**.3** per cent in group 1 and from 86.1 to 7.4 per cent in group 2 (both $P < 0.001$). Quality of life measured on a scale from 0 to 100 improved from 52 to 69 ($P = 0.009$) and 64 ($P < 0.001$) respectively. The percentage of patients with resolved or improved symptoms at 5 years was similar.

Conclusion: Patients with oesophageal acid hypersensitivity benefit from Nissen fundoplication as much as those with pathological acid exposure.

Introduction

Gastro-oesophageal reflux disease (GORD) involves a spectrum of abnormalities. Hiatus hernia, endoscopic oesophagitis and lower oesophageal sphincter (LOS) incompetence are all common, but few patients exhibit all features of the disease[1]. It has been estimated that 10–15 per cent of patients with GORD have normal oesophageal total acid exposure[2]. Thus the absence of pathological acid exposure does not preclude gastro-oesophageal reflux as the cause of symptoms[1;3]. A subset of patients with reflux-induced heartburn and regurgitation caused by physiological acid exposure cannot, therefore, be identified exclusively on the basis of oesophageal acid exposure time[4]. This subgroup with a normal oesophageal acid exposure time, exhibit a positive temporal association between symptoms and reflux episodes during 24-h pH monitoring[3;5;6]. This association can be expressed numerically by calculating the symptom index[7] (SI; percentage of reflux-related symptoms) or by the more robust symptom association probability (SAP; probability that the observed association between reflux and symptoms does not occur by chance)[8,9].

In recent decades, GORD has undergone several redefinitions. The Rome III criteria classify patients with a positive relationship between symptoms and reflux episodes (SAP+) but a physiological oesophageal acid exposure time (pH–) as having GORD[9]. These patients are said to suffer from oesophageal acid hypersensitivity[6]. The outcome of antireflux surgery in patients with oesophageal acid hypersensitivity is unknown. The purpose of this study was to determine the long-term subjective and objective results of antireflux surgery in patients with GORD and oesophageal acid hypersensitivity (SAP+, pH–) refractory to proton-pump inhibitor (PPI) therapy. A group of contemporary patients with pathological acid exposure time (SAP+, pH+), was used for comparison.

Methods

A consecutive cohort of patients underwent laparoscopic Nissen fundoplication for GORD refractory to PPI therapy and was followed for 5 years. GORD refractory to PPI therapy was defined as reflux symptoms persisting over 6 months despite use of double-dose PPI (more than 40 mg omeprazole in 24 h or comparable therapy), with a positive relationship between symptoms and reflux during 24-h pH monitoring. Two groups of patients with intractable symptoms were identified from this cohort; patients with oesophageal acid hypersensitivity and group 2; patients with pathological acid exposure. Patients were included in the study if preoperative 24-h pH monitoring, including positive symptom association analysis, was completed and subjective or objective outcome was registered after surgery.

A 360° Nissen fundoplication was constructed in all patients after full mobilization of the oesophagus, division of the short gastric vessels and posterior crural repair. Overall results of surgical outcome have been published previously[10-12].

Patients were asked to fill out a questionnaire on quality of life and use of acid-suppressing drugs before surgery, and 3 months and 5 years later, and to rate the change in reflux symptoms compared with before operation. Surgical reintervention and indications for reintervention were recorded up to 6 years after the initial procedure. For objective outcome assessment, all patients were asked to undergo upper endoscopy, stationary oesophageal manometry and 24-h pH monitoring both before and 3 months after surgery, and those patients that participated in the randomised controlled trial[10] were asked to undergo additional stationary oesophageal manometry and 24-h pH testing at 5 years.

Visick grading was used to describe the effect of surgery on symptoms and was graded as: complete resolution (grade I), improvement (grade II), no effect of surgery (grade III) or deterioration (grade IV) always in comparison with before operation.[13] This scoring system was used to monitor the subjective effect of surgery because it has been documented to correlate well with heartburn, the most prominent symptom of GORD[14] and it obviates the need for scoring all symptoms separately. Quality of life was measured on a visual analogue scale (VAS) validated for quality of life assessment after oesophageal surgery[15]. The scale ranged from 0 (worst possible health) to 100 (perfect health)[16]. These data and the records of preoperative and postoperative upper endoscopy, manometry, 24-h pH monitoring, use of acid-suppressing drugs and surgical reintervention were collected prospectively.

The presence of oesophagitis and hiatal hernia size were determined endoscopically. Oesophagitis grading was performed initially according to the classification of Savary and Miller[17], but later according to the Los Angeles classification[18]. Moderate oesophagitis was defined as Savary–Miller classification 1–2 or Los Angeles grade A–B, whereas Savary–Miller classification 3–4 or Los Angeles grade C–D were classified as severe oesophagitis.

Oesophageal manometry was performed 48 h after stopping medication that could affect oesophageal motility, following standardised methods which have been published previously.[11]

Ambulatory 24-h pH monitoring was performed according to previously described methodology[11], after suspending medication that could affect the results at least 7 days beforehand. Classification into pathological or physiological oesophageal acid exposure was based on the percentage of time with pH < 4. The upper limit for physiological oesophageal acid exposure in the upright and supine position was defined as two standard deviations above the mean value obtained in healthy

volunteers during ambulatory 24-h pH monitoring[19;20]. Physiological acid exposure time was defined as the combination of an acid exposure time of less than 8.2 per cent in the upright position, an acid exposure time below 3.5 per cent in the supine position and less than 5.8 per cent of the total time with pH < 4[19;20]. Oesophageal acid hypersensitivity was defined as a positive relationship between symptom episodes and reflux episodes (SAP+ and/or SI+) but a physiological oesophageal acid exposure time during 24-h pH testing (pH–). Subgroup analysis was performed in patients with oesophageal acid hypersensitivity who had a total acid exposure time of 4.0 per cent or less[21].

Statistical analysis

Because the aim of this study was to score the effect of surgery in subjective and objective terms, only patients for whom both preoperative data and the results at 3 months or 5 years after surgery were available were included. The number of patients for whom data were available was determined for each variable. Continuous variables were expressed as mean(s.e.m.) and differences between the two groups were analysed using an independent *t* test. A paired-samples *t* test was used to determine significant effects of surgery on quantitative data. The χ^2 test was used to compare nominal variables between groups and effects of surgery on these variables were analysed using the McNemar–Bowker test. Kaplan-Meier analysis was used to evaluate the surgical reintervention rate. $P < 0.050$ was considered statistically significant. Statistical analysis was performed using SPSS® version 15.0 (SPSS, Chicago, Illinois, USA).

Results

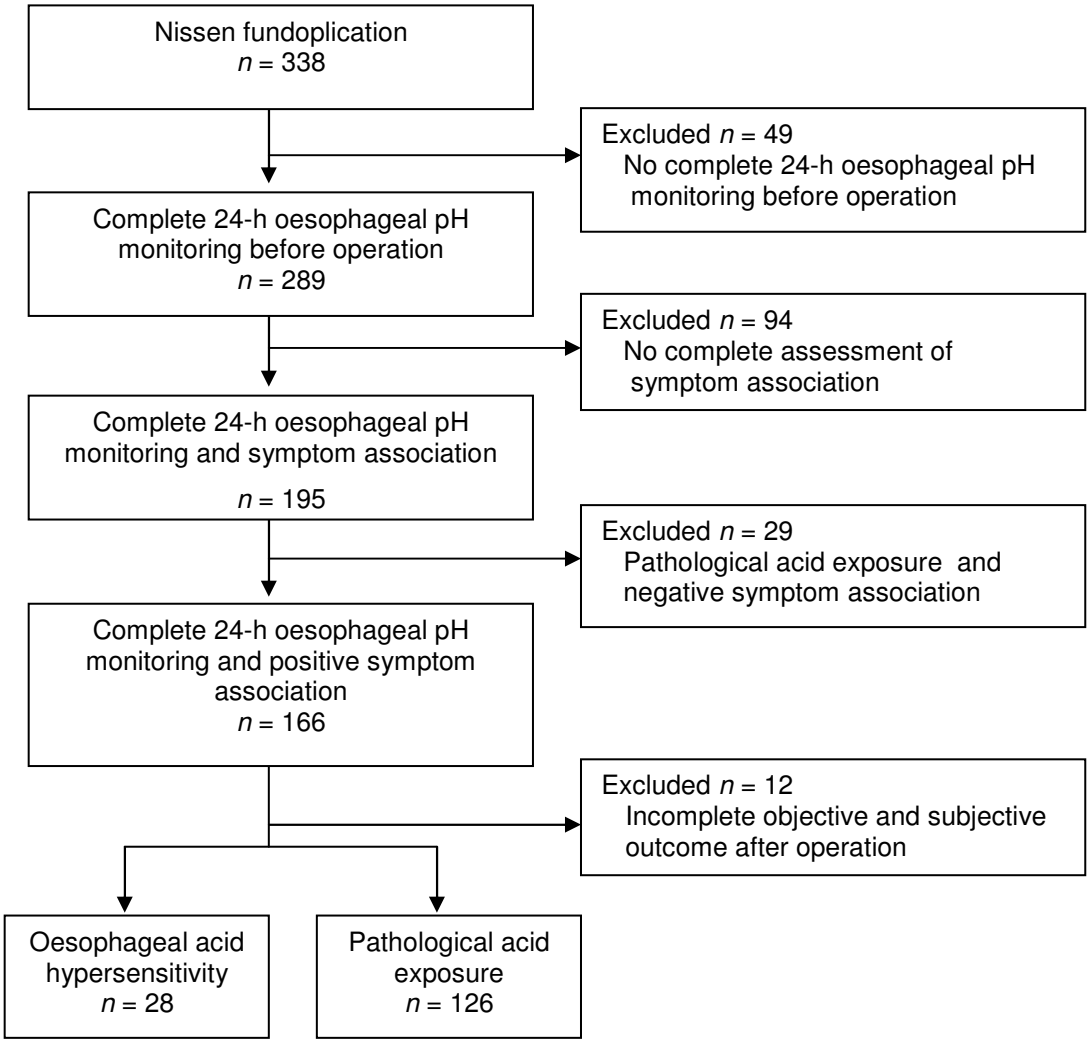
From a total of 338 patients, 154 had full registration of subjective or objective outcome and preoperative 24-h pH monitoring with positive symptom association (*Fig. 1*). There were 28 patients with oesophageal acid hypersensitivity and 126 with pathological acid exposure and symptoms related to reflux episodes. Patient characteristics and mean hiatal hernia size were similar in the two groups (*Table 1*).

Table 1 Characteristics of patients with oesophageal acid hypersensitivity (group 1) or pathological acid exposure (group 2)

	Group 1 (*n* = 28)	**Group 2** (*n* = 126)
Age (years)†	40.0 (19–62)	43.2 (16–80)
Sex ratio (M : F)	20 : 8	80 : 46
Body mass index (kg/m^2)*	26.0 (0.9)	26.3 (0.4)
Hiatal hernia (cm)*	2.5 (0.5)	2.8 (0.2)

† Values are median(range); * Values are mean(s.e.m.)

Figure 1 Study profile



Clinical outcome

The effect of surgery on reflux symptoms was similar in both groups (*Fig. 2*). At 5 years, 85 and 88 per cent of patients in groups 1 and 2 respectively scored their reflux symptoms as being resolved or improved (Visick I and II). There were no differences between the two groups before surgery or at 3 months and 5 years after operation in quality of life or the use of acid-suppressing drugs. The improvement in quality of life was significant in both groups 1 and 2 at 3 months ($P = 0.009$ and $P < 0.001$ respectively) and at 5 years ($P = 0.043$ and $P < 0.001$) respectively (*Fig. 3*). The proportion of patients using acid-suppressing drugs was greatly reduced 3 months after surgery in groups 1 and 2 (both $P < 0.001$) (*Table 2*). This reduction remained significant at 5 years after surgery (both $P < 0.001$), although the use of acid-suppressing drugs had increased in both groups. Surgical reintervention was necessary in four (14.3 per cent) of 28 patients in group 1 and 17 (13.5 per cent) of 126 in group 2 within 6 years of follow-up ($P = 0.857$).

Figure 2 Self-rated change in reflux symptoms 5 years after operation compared with before surgery in patients with oesophageal acid hypersensitivity (group 1; $n = 20$) or pathological acid exposure (group 2; $n = 78$)

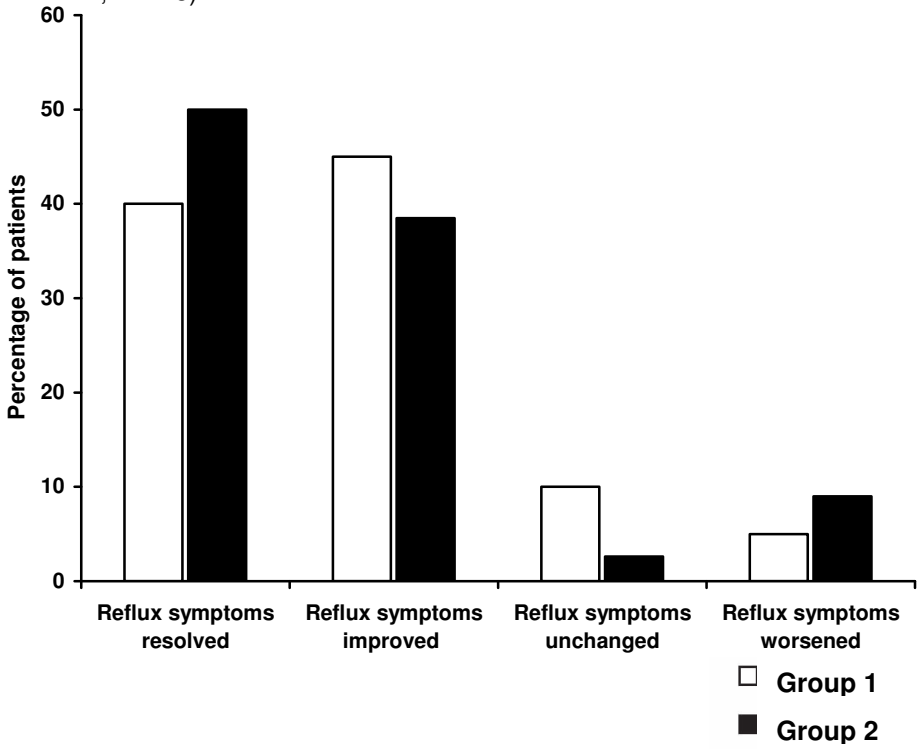
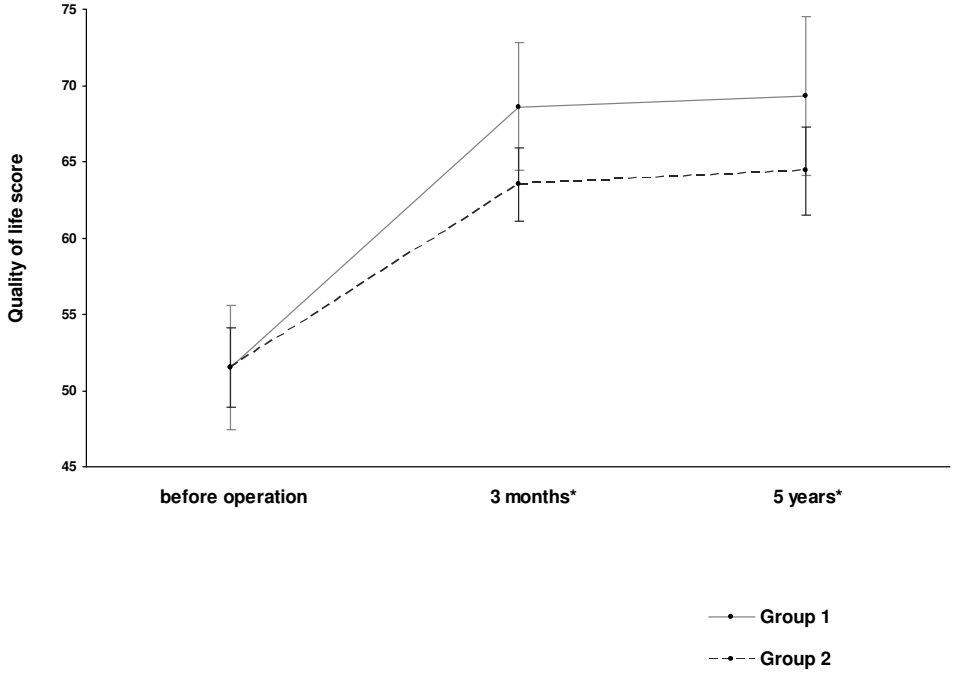


Figure 3 Mean(s.e.m.) quality of life score, measured on a visual analogue scale from 0 to 100, before operation, 3 months and 5 years after surgery in patients with oesophageal acid hypersensitivity (group 1; 23 patients before operation and at 3 months, 18 at 5 years) or pathological acid exposure (group 2; 93 patients before operation and at 3 months, 69 at 5 years).



* $P < 0.050$ *versus* preoperative results for both groups (paired-samples *t*-test)

Table 2 Objective outcome after Nissen fundoplication in patients with oesophageal acid hypersensitivity (group 1) or pathological acid exposure (group 2)

	Group 1	Group 2
Patients using acid-suppressing drugs	19 (83)	93 (86.1)
- Before surgery (group 1, *n* = 23; group 2, *n* = 108)	1 (4)	8 (7.4)
- 3 months (group 1, *n* = 23; group 2, *n* = 108)†	4 (20)	11 (15)
- 5 years (group 1, *n* = 20; group 2, *n* = 72)†		
Patients with oesophagitis		
- Before surgery (group 1, *n* = 20; group 2, *n* = 103)	8 (40)	61 (59.2)
- 3 months (group 1, *n* = 20; group 2, *n* = 103)†	0 (0)	12 (11.7)
Mean lower oesophageal sphincter pressure (kPa)*		
- Before surgery (group 1, *n* = 25; group 2, *n* = 111)	1.1(0.1)	1.1(0.1)
- 3 months (group 1, *n* = 25; group 2, *n* = 111)	1.7(0.2)‡	1.8(0.1)‡
- 5 years (group 1, *n* = 12; group 2, *n* = 34)	1.5(0.5)	1.6(0.2)‡
Total oesophageal acid exposure time (%)*		
- Before surgery (group 1, *n* = 24; group 2, *n* = 113)	3.9(0.3)§	13.2(0.8)
- 3 months (group 1, *n* = 24; group 2, *n* = 113)†	0.8(0.2)§	2.4(0.5)
- 5 years (group 1, *n* = 12; group 2, *n* = 34)	2.6(1.2)	2.3(0.8)‡
No. of reflux symptoms during 24-h pH monitoring*		
- Before surgery (group 1, *n* = 23; group 2, *n* = 112)	12.5(4.2)	15.8(1.3)
- 3 months (group 1, *n* = 23; group 2, *n* = 112)	3.4(1.3)‡	2.9(0.5)‡
- 5 years (group 1, *n* = 12; group 2, *n* = 34)	3.5(1.5)	2.0(0.7)‡
Patients with a positive SI		
- Before surgery (group 1, *n* = 23; group 2, *n* = 111)	17 (74)	96 (86.5)
- 3 months (group 1, *n* = 23; group 2, *n* = 111)†	2 (9)	5 (4.5)
- 5 years (group 1, *n* = 12; group 2, *n* = 34)†	1 (8)	3 (9)
Patients with a positive SAP		
- Before surgery (group 1, *n* = 22; group 2, *n* = 110)	20 (91)§	110 (100)
- 3 months (group 1, *n* = 22; group 2, *n* = 110)†	3 (14)	4 (3.6)
- 5 years (group 1, *n* = 11; group 2, *n* = 34)†	1 (9)	3 (9)

Values in parentheses are percentages unless indicated otherwise;
* values are mean(s.e.m.). † $P < 0.010$ *versus* before surgery for both groups (McNemar-Bowker and paired-samples *t*-test); ‡ $P < 0.050$ *versus* before surgery (paired-samples *t*-test); § $P < 0.010$ *versus* group 2 (independent *t*-test and χ^2 test).

Upper gastrointestinal endoscopy

Before surgery, eight patients in group 1 had moderate oesophagitis and none had severe oesophagitis. Fifty-four patients in group 2 had moderate oesophagitis and seven had severe oesophagitis. Surgery reduced the prevalence of oesophagitis in both groups (both $P < 0.001$). Oesophagitis was more prevalent in group 2 than group 1 both before and after operation, although not significantly so ($P = 0.113$ and $P = 0.108$ respectively).

Stationary oesophageal manometry

Mean LOS pressures were similar in both groups before and after surgery (*Table 2*). Fundoplication increased LOS pressure in both groups at 3 months ($P = 0.015$ for group 1 and $P < 0.001$ for group 2) and at 5 years ($P = 0.350$ and $P = 0.006$ respectively).

24-hour oesophageal pH monitoring

The results of operation on total acid exposure are shown in *Table 2*. Total acid exposure (percentage of total time with pH < 4) was higher in group 2 both before and 3 months after surgery ($P < 0.001$ and $P = 0.008$ respectively). Surgery reduced total acid exposure to physiological values in both groups at 3 months (both $P < 0.001$). At 5 years after surgery, the total acid exposure had not changed in group 2 and was still significantly lower than before surgery ($P < 0.001$) but the reduction in group 1 became less pronounced ($P = 0.314$ *versus* preoperative value).

Surgery not only reduced the oesophageal acid exposure time, but also the number of symptom episodes in both groups ($P = 0.044$ and $P < 0.001$ at 3 months), the percentage of patients with a positive SI at 3 months (both $P < 0.001$) and at 5 years ($P = 0.008$ and $P < 0.001$) and the percentage of patients with a positive SAP at 3 months (both $P < 0.001$) and 5 years ($P = 0.004$ and $P < 0.001$). There was no difference between groups in the number of symptoms recorded during pH monitoring before or after surgery (*Table 2*).

Subgroup analysis was performed in patients with oesophageal acid hypersensitivity who had an acid exposure time of 4.0 per cent or less. The outcomes of this group for all subjective and objective endpoints did not differ from those for the oesophageal acid hypersensitivity group as a whole. The only exception was that the quality of life score was higher in this subgroup 3 months after surgery (mean(s.e.m.) 82 (4) on VAS), and was significantly greater than the score in the pathological acid exposure group ($P < 0.001$).

Discussion

Patients with GORD and an acid hypersensitive oesophagus have a lower sensory threshold for pain during oesophageal acid perfusion, suggesting that their symptoms result from a heightened perception of physiological reflux events[1;3;22]. These patients, who are refractory to PPI therapy and have a total acid exposure time within the physiological range, are not uncommon. This study has confirmed that patients diagnosed with an acid hypersensitive oesophagus are equally good candidates for antireflux surgery as patients with pathological acid exposure.

Conventional 24-h pH monitoring is the most useful test for distinguishing between physiological and pathological, and also symptomatic and asymptomatic reflux. The cut-off points for distinguishing between pathological and physiological reflux are arbitrary; those reported for the upright position vary from 4.6 to 16.0 per cent and those for supine reflux from 1.2 to 11.2 per cent[21;23-25]. Patients with severe symptoms can have borderline pathological reflux and asymptomatic controls can have pathological acid exposure[1]. The normal values for pathological and physiological reflux used in the present study are higher than the cut-off value of 4 per cent applied in other centres[21]. It is known that body position and movement strongly influence gastro-oesophageal reflux[26], and consequently normal values for ambulatory data are higher than cut-off values from hospitalized patients. The higher normal values used in the present study were determined for the authors' laboratory based on the 95th percentiles of ambulatory 24-h pH registrations in 32 healthy volunteers[27]. Subgroup analysis of the patients with oesophageal acid hypersensitivity with an acid exposure time no more than 4.0 per cent demonstrated that the outcome in this group was similar to that for the oesophageal acid hypersensitivity group as a whole. These data indicate that distinguishing between pathological and physiological reflux, and consequently withholding surgery from patients with physiological acid exposure, is flawed. A positive temporal relationship between reflux episodes and symptoms during 24-h pH monitoring seems more important in determining whether or not a patient suffers from GORD and would benefit from antireflux surgery.

Multichannel oesophageal impedance monitoring has demonstrated that weakly acidic reflux (pH between 4 and 7) does not contribute to oesophageal acid exposure time but can trigger typical GORD symptoms such as regurgitation and heartburn[28]. Patients with oesophageal acid hypersensitivity have a similar number of weakly acidic reflux episodes and a comparable proportion of proximally extending reflux episodes to patients with pathological total acid exposure[29]. This may explain the severe symptomatology in absence of excessive amounts of acid reflux, but does not account for the presence of oesophagitis in this group.

No patient in the oesophageal acid hypersensitivity group had severe oesophagitis, but a substantial proportion of patients had evidence of moderate oesophagitis on preoperative upper gastrointestinal endoscopy. Other studies have reported oesophagitis in about 20 per cent of patients with physiological acid exposure[30;31]. In a study of endoscopy-positive patients with GORD and a normal preoperative pH test, the grade of oesophagitis was comparable to that in patients with abnormal pH tests[32]. In another study patients with endoscopic oesophagitis did not have more severe reflux than those without[33]. These observations suggest that there must be considerable interindividual differences in oesophageal mucosal resistance to explain the development of oesophagitis in patients with a physiological acid exposure time. Patients with non-erosive GORD who have physiological acid exposure display the same degree of dilatation of epithelial intercellular spaces (DIS) at electron microscopy as patients with pathological total acid exposure[34]. The occurrence of DIS has been shown to correlate with a decrease in transepithelial resistance to gastric refluxate and increased epithelial permeability, facilitating access of hydrogen ions to stimulate intraepithelial acid-sensitive nociceptors and may be associated with acid hypersensitivity[35;36].

PPI treatment is less effective in patients with oesophageal acid hypersensitivity than in those with a pathological acid exposure time[37]. PPI therapy only reduces the acidity of the refluxate and so weakly acidic reflux episodes persist during PPI treatment. These are probably responsible for persistent symptoms during PPI therapy[28;38]. In contrast to PPI therapy, antireflux surgery effectively reduces both acidic and non-acidic reflux[39]. The exact mechanism is uncertain, but these data confirm recently published figures indicating that a positive symptom correlation for non-acid reflux predicts a good symptomatic response to fundoplication[40].

Several other studies have investigated the results of fundoplication in patients with symptomatic physiological acid exposure, but report limited outcome parameters and short follow-up. The results remain controversial; some authors reported worse outcome after Nissen fundoplication for patients with physiological preoperative acid exposure[32;41;42] while others reported results similar to those of patients with pathological acid exposure[43-46]. A limitation of this study is the fact that oesophageal acid hypersensitivity was not confirmed by a second separate 24-h pH test before surgery. Therefore, patients with pathological acid exposure, but a false-negative pH recording, might have been classified as having oesophageal acid hypersensitivity. However, this type of bias is essentially ruled out by the observation that total oesophageal acid exposure was significantly lower in the hypersensitive group than pathological acid exposure group during pH testing 3 months after surgery. This finding confirms the reproducibility of the pH tests used to classify patients before surgery. Patients with a normal test monitored on an

asymptomatic day are more likely to have an abnormal second test than a normal test on a typically symptomatic day[47]. The number of reflux symptoms during pH monitoring was similar in groups 1 and 2, all with a positive correlation with reflux episodes. This excludes the possibility that the oesophageal acid hypersensitivity group consisted of patients with pathological exposure, who had a false-negative test on an asymptomatic day during 24-h pH monitoring. Only those patients that participated in the randomised controlled trial[10] were asked to undergo invasive testing, like oesophageal manometry and 24-h pH testing at 5 years. These and all other patients were to fill out a questionnaire to assess subjective outcome at 5 years. This is a distinct limitation of this study. In addition, some patients refused to participate in parts of the postoperative protocol, which may have led to selection bias. Earlier studies[48], however, demonstrated that subgroups of patients who refuse objective long-term evaluation have an over-representation of asymptomatic patients, who see no benefit in repeated invasive testing.

The cumulative reoperation rate in the study group was 13.6 per cent within 6 years. At 12 months after initial surgery the rate was 3.6 per cent, which is in line with reported rates a year after laparoscopic antireflux surgery (2–8 per cent)[49;50].

Patients with GORD refractory to PPI therapy who have oesophageal acid hypersensitivity benefit from Nissen fundoplication as much as those with pathological acid exposure. Surgical treatment should not be withheld from these patients.

References

(1) Howard PJ, Maher L, Pryde A, Heading RC. Symptomatic gastro-oesophageal reflux, abnormal oesophageal acid exposure, and mucosal acid sensitivity are three separate, though related, aspects of gastro-oesophageal reflux disease. Gut 1991; 32(2):128-132.

(2) Eriksen CA, Cullen PT, Sutton D, Kennedy N, Cuschieri A. Abnormal esophageal transit in patients with typical reflux symptoms but normal endoscopic and pH profiles. Am J Surg 1991; 161(6):657-661.

(3) Trimble KC, Pryde A, Heading RC. Lowered oesophageal sensory thresholds in patients with symptomatic but not excess gastro-oesophageal reflux: evidence for a spectrum of visceral sensitivity in GORD. Gut 1995; 37(1):7-12.

(4) Kahrilas PJ, Quigley EM. Clinical esophageal pH recording: a technical review for practice guideline development. Gastroenterology 1996; 110(6):1982-1996.

(5) Clouse RE, Richter JE, Heading RC, Janssens J, Wilson JA. Functional esophageal disorders. Gut 1999; 45 Suppl 2:II31-II36.

(6) Shi G, Bruley d, V, Scarpignato C, Le RM, Galmiche JP. Reflux related symptoms in patients with normal oesophageal exposure to acid. Gut 1995; 37(4):457-464.

(7) Wiener GJ, Richter JE, Copper JB, Wu WC, Castell DO. The symptom index: a clinically important parameter of ambulatory 24-hour esophageal pH monitoring. Am J Gastroenterol 1988; 83(4):358-361.

(8) Weusten BL, Roelofs JM, Akkermans LM, Van Berge-Henegouwen GP, Smout AJ. The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. Gastroenterology 1994; 107(6):1741-1745.

(9) Galmiche JP, Clouse RE, Balint A, Cook IJ, Kahrilas PJ, Paterson WG et al. Functional esophageal disorders. Gastroenterology 2006; 130(5):1459-1465.

(10) Bais JE, Bartelsman JF, Bonjer HJ, Cuesta MA, Go PM, Klinkenberg-Knol EC et al. Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. Lancet 2000; 355(9199):170-174.

(11) Draaisma WA, Ruurda JP, Scheffer RC, Simmermacher RK, Gooszen HG, Rijnhart-de Jong HG et al. Randomized clinical trial of standard laparoscopic versus robot-assisted laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease. Br J Surg 2006; 93(11):1351-1359.

(12) Draaisma WA, Buskens E, Bais JE, Simmermacher RK, Rijnhart-de Jong HG, Broeders IA et al. Randomized clinical trial and follow-up study of cost-effectiveness of laparoscopic versus conventional Nissen fundoplication. Br J Surg 2006; 93(6):690-697.

(13) VISICK AH. A study of the failures after gastrectomy. Ann R Coll Surg Engl 1948; 3(5):266-284.

(14) Rijnhart-de Jong HG, Draaisma WA, Smout AJ, Broeders IA, Gooszen HG. The Visick score: a good measure for the overall effect of antireflux surgery? Scand J Gastroenterol 2008; 43(7):787-793.

(15) de Boer AG, van Lanschot JJ, Stalmeier PF, van Sandick JW, Hulscher JB, de Haes JC et al. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? Qual Life Res 2004; 13(2):311-320.

(16) Nord E. The validity of a visual analogue scale in determining social utility weights for health states. Int J Health Plann Manage 1991; 6(3):234-242.

(17) Savary M., Miller G. The oesophagus. In: Savary M., Miller G., eds. Handbook and atlas of endoscopy. Solothurn, Switzerland: Verlag Gassman, 1978: 135-142.

(18) Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999; 45(2):172-180.

(19) Jamieson JR, Stein HJ, DeMeester TR, Bonavina L, Schwizer W, Hinder RA et al. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. Am J Gastroenterol 1992; 87(9):1102-1111.

(20) Richter JE, Bradley LA, DeMeester TR, Wu WC. Normal 24-hr ambulatory esophageal pH values. Influence of study center, pH electrode, age, and gender. Dig Dis Sci 1992; 37(6):849-856.

(21) Johnson LF, DeMeester TR. Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. Am J Gastroenterol 1974; 62(4):325-332.

(22) Rodriguez-Stanley S, Robinson M, Earnest DL, Greenwood-Van MB, Miner PB, Jr. Esophageal hypersensitivity may be a major cause of heartburn. Am J Gastroenterol 1999; 94(3):628-631.

(23) De Caestecker JS. Twenty-four-hour oesophageal pH monitoring: advances and controversies. Neth J Med 1989; 34 Suppl:S20-S39.

(24) Gignoux C, Bonnet-Eymard PO, Hostein J, Fournet J. Enregistrement ambulatoire du pH oesophagien pendant 24 heures dans une population de 27 témoins: analyse des facteurs techniques et méthodologiques influençant les résultats. Gastroenterol Clin Biol 1987; 11:17-23.

(25) Johnsson F, Joelsson B, Isberg PE. Ambulatory 24 hour intraesophageal pH-monitoring in the diagnosis of gastroesophageal reflux disease. Gut 1987; 28(9):1145-1150.

(26) De Caestecker JS, Blackwell JN, Pryde A, Heading RC. Daytime gastro-oesophageal reflux is important in oesophagitis. Gut 1987; 28(5):519-526.

(27) Smout AJ, Breedijk M, van der ZC, Akkermans LM. Physiological gastroesophageal reflux and esophageal motor activity studied with a new system for 24-hour recording and automated analysis. Dig Dis Sci 1989; 34(3):372-378.

(28) Vela MF, Camacho-Lobato L, Srinivasan R, Tutuian R, Katz PO, Castell DO. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. Gastroenterology 2001; 120(7):1599-1606.

(29) Bredenoord AJ, Weusten BL, Timmer R, Smout AJ. Characteristics of gastroesophageal reflux in symptomatic patients with and without excessive esophageal acid exposure. Am J Gastroenterol 2006; 101(11):2470-2475.

(30) Trimble KC, Douglas S, Pryde A, Heading RC. Clinical characteristics and natural history of symptomatic but not excess gastroesophageal reflux. Dig Dis Sci 1995; 40(5):1098-1104.

(31) Shi G, Bruley d, V, Scarpignato C, Le RM, Galmiche JP. Reflux related symptoms in patients with normal oesophageal exposure to acid. Gut 1995; 37(4):457-464.

(32) Khajanchee YS, Hong D, Hansen PD, Swanstrom LL. Outcomes of antireflux surgery in patients with normal preoperative 24-hour pH test results. Am J Surg 2004; 187(5):599-603.

(33) Pace F, Santalucia F, Bianchi PG. Natural history of gastro-oesophageal reflux disease without oesophagitis. Gut 1991; 32(8):845-848.

(34) Caviglia R, Ribolsi M, Maggiano N, Gabbrielli AM, Emerenziani S, Guarino MP et al. Dilated intercellular spaces of esophageal epithelium in nonerosive reflux disease patients with physiological esophageal acid exposure. Am J Gastroenterol 2005; 100(3):543-548.

(35) Lynn RB. Mechanisms of esophageal pain. Am J Med 1992; 92(5A):11S-19S.

(36) Tobey NA, Hosseini SS, Argote CM, Dobrucali AM, Awayda MS, Orlando RC. Dilated intercellular spaces and shunt permeability in nonerosive acid-damaged esophageal epithelium. Am J Gastroenterol 2004; 99(1):13-22.

(37) de Vries DR, van Herwaarden MA, Smout AJ, Samsom M. Patients with physiological acid exposure and positive symptom association scores: a distinct group within the GORD spectrum. Neurogastroenterol Motil 2009.

(38) Mainie I, Tutuian R, Shay S, Vela M, Zhang X, Sifrim D et al. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. Gut 2006; 55(10):1398-1402.

(39) Bredenoord AJ, Draaisma WA, Weusten BL, Gooszen HG, Smout AJ. Mechanisms of acid, weakly acidic and gas reflux after anti-reflux surgery. Gut 2008; 57(2):161-166.

(40) Mainie I, Tutuian R, Agrawal A, Adams D, Castell DO. Combined multichannel intraluminal impedance-pH monitoring to select patients with persistent gastro-oesophageal reflux for laparoscopic Nissen fundoplication. Br J Surg 2006; 93(12):1483-1487.

(41) Campos GM, Peters JH, DeMeester TR, Oberg S, Crookes PF, Tan S et al. Multivariate analysis of factors predicting outcome after laparoscopic Nissen fundoplication. J Gastrointest Surg 1999; 3(3):292-300.

(42) Thibault R, Coron E, Sebille V, Sacher-Huvelin S, Bruley d, V, Gournay J et al. Antireflux surgery for non-erosive and erosive reflux disease in community practice. Aliment Pharmacol Ther 2006; 24(4):621-632.

(43) Bell RC, Hanna P, Brubaker S. Laparoscopic fundoplication for symptomatic but physiologic gastroesophageal reflux. J Gastrointest Surg 2001; 5(5):462-467.

(44) Booth MI, Stratford J, Thompson E, Dehn TC. Laparoscopic antireflux surgery in the treatment of the acid-sensitive oesophagus. Br J Surg 2001; 88(4):577-582.

(45) del GG, Tolone S, del GF, Aggarwal R, d'Alessandro A, Allaria A et al. Prospective assessment of patient selection for antireflux surgery by combined multichannel intraluminal impedance pH monitoring. J Gastrointest Surg 2008; 12(9):1491-1496.

(46) Leeder PC, Watson DI, Jamieson GG. Laparoscopic fundoplication for patients with symptoms but no objective evidence of gastroesophageal reflux. Dis Esophagus 2002; 15(4):309-314.

(47) Booth MI, Stratford J, Dehn TC. Patient self-assessment of test-day symptoms in 24-h pH-metry for suspected gastroesophageal reflux disease. Scand J Gastroenterol 2001; 36(8):795-799.

(48) Draaisma WA, Rijnhart-de Jong HG, Broeders IA, Smout AJ, Furnee EJ, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. Ann Surg 2006; 244(1):34-41.

(49) Huttl TP, Hohle M, Meyer G, Schildberg FW. [Antireflux surgery in Germany. Results of a representative survey with analysis of 2,540 antireflux operations]. Chirurg 2002; 73(5):451-461.

(50) Jamieson GG, Watson DI, Britten-Jones R, Mitchell PC, Anvari M. Laparoscopic Nissen fundoplication. Ann Surg 1994; 220(2):137-145.

4

The impact of symptom-reflux association analysis on long-term outcome after Nissen fundoplication

J.A.J.L. Broeders[1]
W.A. Draaisma[1]
A.J. Bredenoord[2]
A.J.P.M. Smout[2]
I.A.M.J. Broeders[3]
H.G. Gooszen[1]

[1]Dep. of Surgery, University Medical Center Utrecht
[2]Dep. of Gastroenterology, University Medical Center Utrecht
[3]Dep.of Surgery, Meander Medical Center, Amersfoort

11th world congress of the International Society for Diseases of the Esophagus
Budapest, Hungary, September 2008

British Journal of Surgery 2011; 98:247-54.

Abstract

Background: A positive symptom association probability (SAP) is regarded as an important selection criterion for antireflux surgery by many physicians. However, no data corroborate the relationship between symptom–reflux association and outcome, nor is it clear what impact a negative SAP has on the outcome of antireflux surgery in patients with abnormal oesophageal acid exposure. This study evaluated long-term outcomes of Nissen fundoplication in SAP– and SAP+ patients.

Methods: Five-year outcome of Nissen fundoplication in proton-pump inhibitor (PPI)-refractory patients with pathological acid exposure was compared between those with (SAP+, 109) and without (SAP–, 29 patients) a positive SAP. Symptoms, quality of life (QoL), PPI use, endoscopic findings, manometry and acid exposure were evaluated.

Results: At 5 years' follow-up, relief of reflux symptoms (95 *versus* 87 per cent), reduction in PPI use (80 to 25 per cent *versus* 85 to 14 per cent; $P < 0.050$) and improvement in QoL were all comparable between the SAP– and SAP+ groups. Reduction in acid exposure time (13.4 to 1.6 per cent *versus* 11.1 to 0.2 per cent of total time; $P < 0.010$), improvement in oesophagitis (44 to 6 per cent *versus* 61 to 13 per cent; $P < 0.050$) and increase in lower oesophageal sphincter pressure were also comparable between groups.

Conclusion: The subjective and objective outcomes of fundoplication in patients with pathological acid exposure are comparable among those with a positive and negative SAP. Patients with pathological acid exposure and a negative SAP can also benefit from antireflux surgery.

Introduction

Twenty-four-hour ambulatory oesophageal pH monitoring has been the standard for diagnosis of gastro-oesophageal reflux disease (GORD) since its first description by DeMeester[1]. This pH monitoring allows categorization between pathological and physiological acid exposure. In addition, the DeMeester score has been proposed to provide a quantitative description of a patient's pH profile[2]. Patients with severe symptoms, however, can have borderline pathological reflux and asymptomatic controls can have pathological acid exposure[3]. Owing to substantial interindividual differences, overall reproducibility for the diagnosis of GORD is low, at only 70–80 per cent[4–7]. A pathological pH profile provides no evidence of whether the patient's complaints are indeed caused by acid reflux episodes[8].

Analysis of the temporal relationship between symptoms and reflux episodes during 24-h pH monitoring is the only method that can adequately identify acid reflux. Verification of the cause of symptoms and analysis of the association between reflux and symptoms becomes important when endoscopic or surgical intervention is planned. The most frequently used indices are the Symptom Index (SI)[9], the Symptom Association Probability (SAP)[10] and the Symptom Sensitivity Index (SSI)[11]. The latter has essentially been abandoned. The SI compares the individual with a composite group of patients with GORD and a group of normal controls. The SAP, in contrast to the SI and SSI, takes the number of the reflux episodes and symptoms into account. The SAP also calculates the likelihood that the observed distribution of a patient's symptoms and reflux episodes is not brought about by chance, using the symptomatic reaction to reflux as a control. The SAP is the most robust analysis, with the highest reproducibility[12] and has been used in the study unit for more than 10 years to decide on surgical treatment in proton-pump inhibitor (PPI)-refractory reflux disease[10].

In up to half of patients with pathological oesophageal acid exposure, a positive association between symptom occurrence and reflux episodes during 24-h pH monitoring is lacking[3]. Before the start of a randomized controlled trial (RCT) in 1997[13], antireflux surgery was withheld from patients with PPI-refractory GORD, pathological acid exposure and a negative symptom association based on SAP score, presuming their outcome to be worse compared to SAP+ patients. From 1997 onwards, patients with typical GORD symptoms, pathological acid reflux and a negative SAP had surgery, if they turned out to be refractory to PPI treatment administered for over 6 months. So far, no data have been published on the outcome of surgery in these patients.

The purpose of this study was to compare the long-term subjective and objective outcomes between those with and without a positive SAP in patients undergoing Nissen fundoplication for PPI-refractory GORD with pathological acid exposure.

Methods

A consecutive cohort of patients who underwent laparoscopic Nissen fundoplication for GORD refractory to PPI therapy was prospectively followed for 5 years, most as participants of a RCT[13–15]. Surgical treatment was proposed to patients with heartburn and regurgitation for more than 6 months, who showed an insufficient response to at least 40 mg omeprazole daily. If 40 mg omeprazole was insufficient to suppress symptoms, the dose was increase to 40 mg two or three times daily. If symptoms recurred after return to 40 mg daily, the GORD was considered to be refractory to PPI therapy. Patients were included in the present study if preoperative 24-h pH monitoring had shown pathological acid exposure, symptom–reflux association analysis had been completed, and subjective or objective parameters registered before and after surgery. Patients were excluded if data on both subjective and objective outcome were incomplete.

A 360° Nissen fundoplication was constructed in all patients after mobilization of the oesophagus, division of the short gastric vessels and posterior crural repair. All surgeons who participated in the RCT[13] had gone through the learning curve, defined by Watson and colleagues[16] as more than five fundoplications by an experienced laparoscopic surgeon and over 20 procedures by a less experienced laparoscopic surgeon. Subsequent patients underwent fundoplication by surgeons with experience of more than 30 laparoscopic fundoplications[14,15].

All patients were asked to fill out a questionnaire on individual GORD symptoms[17], general improvement of reflux symptoms[18,19], use of antisecretory drugs and quality of life[20] before, and at 3 months and 5 years after surgery. The frequency and severity of heartburn, regurgitation and dysphagia were registered. In addition, after surgery patients rated the change in their reflux symptoms compared with preoperative status (Visick grading). For objective outcome assessment, upper endoscopy was performed before and 3 months after surgery. All patients were asked to undergo stationary oesophageal manometry and 24-h pH monitoring before operation, and at 3 months and 5 years after surgery.

Clinical outcome

The effect of surgery on symptoms was scored using the Visick grading system: complete resolution (grade I), improvement (grade II), no effect of surgery (grade III) or deterioration (grade IV)[18,19]. Visick scores were used to give an overall

impression of the patient's appreciation of antireflux surgery. These scores correlate well with heartburn[18] and a validated questionnaire[21] for reflux symptoms[22]. Cardinal symptoms and dysphagia were assessed using a grading system that combined frequency and severity, resulting in grades ranging from 0 (symptom absent) to 3 (symptom frequent and severe)[17]. A visual analogue scale validated for quality-of-life assessment after oesophageal surgery was used to evaluate impact on quality of life[20]. The scale[23] ranged from 0 (worst possible health status) to 100 and has previously been used to assess quality of life after Nissen fundoplication[13–15,24]. These data and the records on use of acid-suppressing drugs, upper endoscopy, manometry and 24-h pH monitoring were collected prospectively for up to 5 years after surgery. Surgical reinterventions and indications for reintervention were registered for up to 6 years.

Upper gastrointestinal endoscopy

Experienced gastroenterologists evaluated the presence of oesophagitis, and the presence and size of any hiatal hernia during endoscopy. Oesophagitis was initially graded according to the Savary–Miller classification[25] and from 1999 onwards according to the Los Angeles classification[26].

Stationary oesophageal manometry

Any medication that could affect oesophageal motility was stopped 7 days before manometry. Pressures were recorded using a water-perfused system with a multiple-lumen catheter with an incorporated sleeve sensor (Dentsleeve, Adelaide, Australia). After transnasal introduction, the catheter was retracted in order to determine the distal and proximal border of the lower oesophageal sphincter (LOS). The sleeve sensor was positioned at this level, and intraluminal oesophageal pressures were recorded at 5, 10 and 15 cm above the proximal border of the LOS. Finally, the manometric response to ten standard 5-ml water bolus swallows was recorded. The gastric baseline pressure (registered 2 cm below the distal margin of the sleeve sensor) was the zero reference point for all measurements.

Twenty-four-hour oesophageal pH monitoring

Medication that could affect results was suspended at least 7 days before ambulatory 24-h pH testing. A pH glass electrode (model LOT440; Medical Instruments Corporation, Solothurn, Switzerland) was positioned 5 cm above the manometrically determined upper margin of the LOS. A digital data logger recorded the tracing and the patient registered reflux symptoms and body position in a diary (Medical Measurements Systems, Enschede, The Netherlands). Twenty-four-hour

pH monitoring was standardized and patients were instructed to press a button on the digital data logger at the beginning of each heartburn, acid regurgitation or chest pain episode[10]. A dedicated software program was used to analyse the 24-h recordings automatically (Medical Measurements Systems). If patients experienced symptoms during the test, the SAP (probability that the observed association between reflux and symptoms does not occur by chance)[10] and SI (percentage of reflux-related symptoms)[27] were calculated. A SAP value of at least 95 per cent and a SI of 50 per cent or more were considered positive. The primary analysis compared the outcome of antireflux surgery of patients with a negative (SAP–) or positive (SAP+) SAP. An additional analysis compared the various outcome measures for patients with a positive and negative symptom correlation based on SI score.

Based on the percentage of time with pH < 4, patients were classified into those with pathological and those with physiological oesophageal acid exposure. The upper limit for physiological oesophageal acid exposure in upright and supine body positions was two standard deviations above the mean value obtained in healthy volunteers during ambulatory 24-h pH monitoring[7,28]. Consequently, pathological acid exposure was defined as an acid exposure time of more than 8.2 per cent in the upright body position, an acid exposure time of more than 3.5 per cent in the supine position, or percentage of total time with pH < 4 exceeding 5.8 per cent[7,28].

Statistical analysis

Because the aim of this study was to evaluate the effect of surgery in subjective and objective terms, only patients with data available before surgery and also at 3 months or 5 years after operation were included. For each parameter the number of patients with available data was determined. Continuous variables were expressed as median (interquartile range). The two-tailed Mann–Whitney *U* test was used to determine the significance of differences in continuous data between groups. Significant effects of surgery on continuous variables within groups were evaluated using the Wilcoxon signed rank test. The χ^2 test was used to compare groups for nominal variables and effects of surgery on such variables were analysed using the McNemar–Bowker test. $P < 0.050$ was considered statistically significant. Statistical analysis was performed using SPSS® version 15.0 (SPSS, Chicago, Illinois, USA).

Results

Between January 1997 and October 2005, a total of 338 patients underwent laparoscopic Nissen fundoplication for GORD refractory to PPI therapy. Of these,

138 had completed a preoperative 24-h pH monitoring study showing pathological acid exposure, a symptom association analysis, and had full registration of subjective or objective outcome (*Fig. 1*). Twenty-nine patients with a negative SAP were compared with 109 patients with a positive SAP. Patient characteristics and hiatal hernia size were comparable between the two groups (*Table 1*).

Figure 1 Study profile

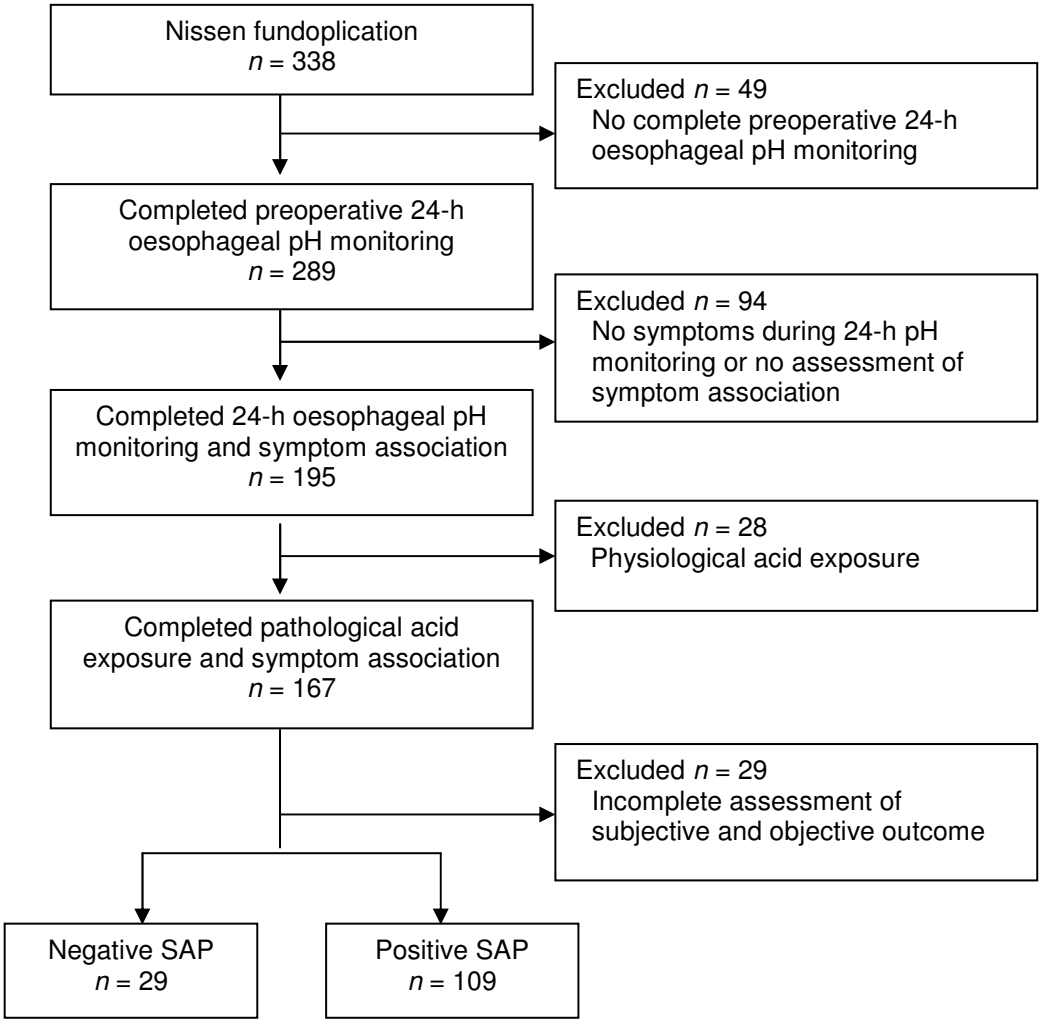
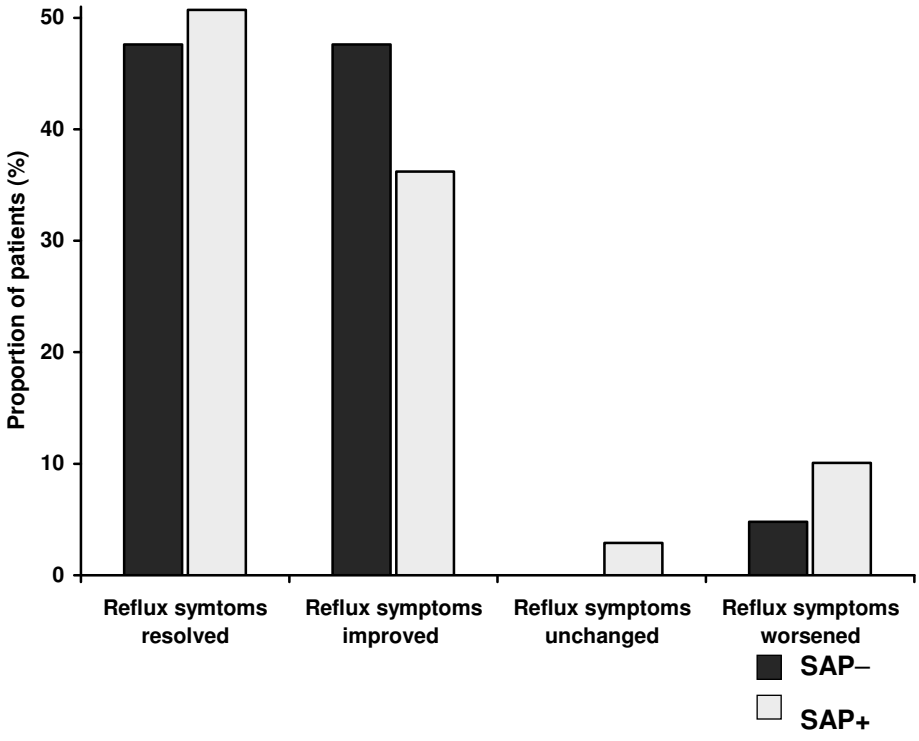


Table 1 Characteristics of patients with a negative or positive symptom asociation probability

	SAP– (n = 29)	SAP+ (n = 109)
Age (years)*	42.2 (18–85)	42.9 (16–80)
Sex ratio (M : F)	18 : 11	72 : 37
Body mass index (kg/m^2)†	25.9 (23.9–30.4)	25.8 (24.0–29.1)
Prevalence of hiatal hernia	13 / 15 (86.7)	58 / 74 (78.4)
Hiatal hernia (cm)†	3.0 (2.0–5.0)	3.0 (1.0–4.0)

Values in parentheses are percentages unless indicated otherwise; values are *median (range) and †median (interquartile range). SAP, symptom association probability.

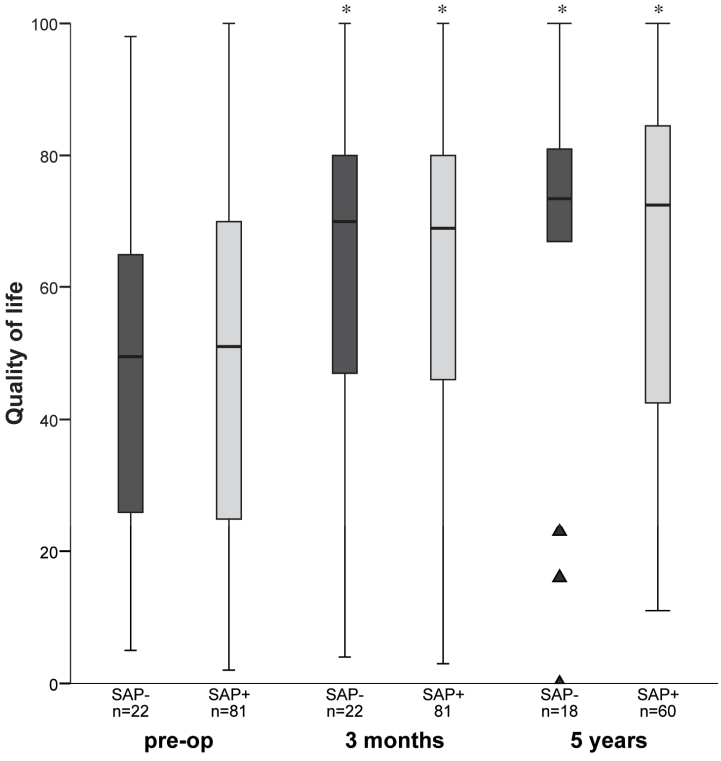
Figure 2 Self-rated change in reflux symptoms (Visick grading[18,19]) 5 years after surgery compared with preoperative status in 21 patients with a negative symptom association probability (SAP–) and 69 patients with a positive SAP (SAP+).



Clinical outcome

At 5 years, the effect of surgery on reflux symptoms was similar in the two groups (*Fig. 2*), with resolution or improvement of symptoms (Visick grades I and II) in 95 per cent (20 of 21) and 87 per cent (60 of 69) of patients in the SAP– and SAP+ group respectively. Postoperative heartburn scores were comparable (P = 0.842). The reduction in severity of heartburn and regurgitation was no different between the groups, and no high-grade symptoms were present in the SAP– group. There were no differences in postoperative dysphagia (*Table 2*). Quality of life increased similarly both in SAP– and SAP+ groups at 3 months and 5 years after surgery (*Fig. 3*).

Figure 3 Quality of life,score on a visual analogue scale[20], before operation, and after 3 months and 5 years in patients with a negative (SAP–) or positive (SAP+) symptom association probability.



Median (horizontal bar), interquartile range (box) and range (error bars) are shown. * P < 0.050 *versus* before surgery.

Table 2 Postoperative symptom results at 5 years' follow-up and surgical reintervention at 6 years' follow-up in patients with a negative or positive symptom association probability

	SAP–	SAP+
Use of acid-suppressing drugs		
Before surgery (SAP–, *n* = 25; SAP+, *n* = 95)	20 (80)	81 (85)
3 months (SAP–, *n* = 25; SAP+, *n* = 95)	1 (4)*	6 (6)*
5 years (SAP–, *n* = 20; SAP+, *n* = 63)	5 (25)*	9 (14)*
Heartburn grade[17] (5 years)		
0	13 (62)	45 (64)
1	8 (38)	19 (27)
2	0 (0)	4 (6)
3	0 (0)	2 (3)
Regurgitation grade[17] (5 years)		
0	15 (75)	49 (73)
1	5 (25)	12 (18)
2	0 (0)	6 (9)
3	0 (0)	0 (0)
Dysphagia grade[17] (5 years)		
0	9 (47)	37 (56)
1	7 (37)	20 (30)
2	3 (16)	6 (9)
3	0 (0)	3 (5)
Surgical reintervention (6 years) (SAP–, *n* = 29; SAP+, *n* = 109)	4 (14)	14 (12.8)
Recurrent reflux	2	7
Dysphagia	2	5
Intrathoracic herniation	0	1
Other	0	1

Values in parentheses are percentages. SAP, symptom association probability; *n,* number of patients for whom data were available. * $P < 0.050$ *versus* before surgery (McNemar–Bowker test).

Table 3 Postoperative objective outcome measures at 3 months' and 5 years' follow-up in patients with a negative or positive symptom association probability

	SAP–	SAP+
Patients with oesophagitis		
Before surgery (SAP–, *n* = 18; SAP+, *n* = 89)	8 (44)	54 (61)
3 months (SAP–, *n* = 18; SAP+, *n* = 89)	1 (6)†	12 (13)†
Mean lower oesophageal sphincter pressure (kPa)*		
Before surgery (SAP–, *n* = 22; SAP+, *n* = 97)	1.3 (0.7–1.5)	1.0 (0.5–1.5)
3 months (SAP–, *n* = 22; SAP+, *n* = 97)	1.5 (1.2–2.0)†	1.7 (1.2–2.2)‡
5 years (SAP–, *n* = 8; SAP+, *n* = 31)	1.2 (0.6–2.2)	1.3 (1.0–2.0)‡
Patients with recurrent pathological reflux		
3 months (SAP–, *n* = 22; SAP+, *n* = 99)	3 (14)	13 (13)
Total oesophageal acid exposure time (%)*		
Before surgery (SAP–, *n* = 21; SAP+, *n* = 98)	13.4 (9.3–20.4)	11.1 (7.8–16.0)
3 months (SAP–, *n* = 21; SAP+, *n* = 98)	0.8 (0.5–2.0)‡	0.6 (0.1–1.9)‡
5 years (SAP–, *n* = 8; SAP+, *n* = 31)	1.6 (0.2–7.2)‡	0.2 (0–2.3)‡

Values in parentheses are percentages unless indicated otherwise; * values are median (interquartile range). SAP, symptom association probability; *n,* number of patients for whom data were available. † $P < 0.050$, ‡ $P < 0.010$ *versus* before surgery (McNemar–Bowker test and Wilcoxon signed rank test).

The proportion of patients using acid-suppressing drugs was reduced 3 months after surgery from 80 per cent (20 of 25) to 4 per cent (1 of 25) in the SAP– group and from 85 per cent (81 of 95) to 6 per cent (6 of 95) in the SAP+ group (SAP– *versus* SAP+ at 3 months: $P = 0.660$) (*Table 2*). Four (14 per cent) of 29 patients in the SAP– group and 14 (12.8 per cent) of 109 in the SAP+ group underwent surgical reintervention within 6 years of follow-up. Main indications were recurrent reflux and dysphagia (*Table 2*). The surgical reintervention rate was comparable between groups ($P = 0.882$).

Objective postoperative outcome

Three months after operation, the prevalence of oesophagitis at upper gastrointestinal endoscopy had decreased similarly in both groups (*Table 3*). LOS pressure at stationary oesophageal manometry was also comparable in SAP– and SAP+ groups, both before and after surgery (*Table 3*). The total oesophageal acid exposure over 24 h (percentage of time with pH < 4) did not differ between the

groups at 3 months and 5 years after surgery (*Table 3*). Surgery reduced the total acid exposure to physiological values in both groups, to 0.8 and 0.6 per cent at 3 months in SAP– and SAP+ groups respectively. The total acid exposure time did not increase when follow-up was extended to 5 years: 1.6 *versus* 0.2 per cent respectively (*Table 3*).

When various subjective and objective outcome measures were compared between patients with a positive and negative symptom correlation based on the SI score, similar findings were obtained. There were no significant differences between positive and negative SI groups.

Discussion

This study has shown that patients with pathological oesophageal acid exposure benefit from fundoplication, irrespective of whether they have a negative or positive symptom association for acid reflux. These results suggest that antireflux surgery should not be withheld from patients with GORD featuring pathological acid exposure and a negative symptom association.

The study was based on a prospective data set, but the study hypothesis was proposed retrospectively. About a fifth of the study cohort had a negative symptom association. The two study groups were similar with respect to all parameters, before and after surgery, except for the preoperative SAP score. There was selection bias owing to the retrospective nature of the study, and it is unknown how many patients were not offered surgery based on a negative SAP score. Moreover, some patients with a positive SAP might have been better off when continued on medical treatment.

The overall short-term surgical results of this consecutive cohort of patients have been reported previously[13–15], whereas the present report describes long-term follow-up and focuses on the impact of symptom–reflux association on outcome after antireflux surgery. In general, patients with a positive symptom correlation and pathological acid exposure are considered good candidates for antireflux surgery, whereas surgeons tend to withhold antireflux surgery from those with pathological acid exposure but a negative symptom correlation.

In contrast to the present results in patients with pathological acid exposure, previous studies have suggested that patients with physiological acid exposure and a positive symptom association have a better response to surgical therapy than those with physiological acid exposure and a negative score[29–32]. The differences between previous reports and the present findings might be explained by a type I error because the SAP– group here was relatively small. The study population, however, was larger than in the other studies[29–32] and a trend towards a more

favourable outcome in patients with a positive symptom correlation was not observed, rendering a type I error less likely.

A more appropriate explanation for the discrepancy between previous reports and the present results lies in the interpretation of the predictive values of symptom correlation scores as diagnostic tests for GORD. In general, the positive predictive values of the SI, SSI and SAP in confirming the diagnosis GORD are high, whereas negative predictive values are low[33], and this is particularly useful in the event of diagnostic uncertainty. Consequently, in patients with physiological acid exposure, a high positive predictive value of symptom association enables physicians to discriminate between patients with functional dyspepsia (pH–, SAP–)[34] and those with oesophageal acid hypersensitivity (pH–, SAP+)[35]. The first category will not benefit from surgery whereas the second most probably will. In contrast, all patients included in the present study had GORD confirmed by a pathological acid exposure time during 24-h pH monitoring. As a result, the high positive predictive value of symptom correlation had limited additional diagnostic value in these patients. In accordance with the documented low negative predictive value of symptom association scores in diagnosing GORD[33], patients in the SAP– group had a good outcome after surgery despite a negative symptom association. Consequently, the present results indicate that the added value of SAP scoring in selecting patients for surgery is limited in those with pathological acid exposure. In addition, similar results were obtained based on SI score. This underlines the generalizability of the reported results: patients with pathological acid exposure and positive or negative symptom correlation scores (SAP or SI) have comparable outcomes after antireflux surgery.

The present results confirm those of previous studies demonstrating that patients may respond satisfactorily to PPI therapy even when there is no association between symptoms and reflux[33]. Similarly, the effect of PPI therapy has been evaluated in a patient cohort that was classified by the same criteria as used here. The effects of PPI therapy on symptoms and quality of life were similar in patients with pathological acid exposure and a negative (SAP–) or positive (SAP+) symptom association[36]. Others have recently shown that patients with pathological acid exposure who do not experience symptoms or only atypical symptoms during 24-h pH monitoring may still obtain a good result from antireflux surgery[37].

Intraluminal impedance monitoring is a novel diagnostic instrument for GORD and detects reflux independently of the acidity of the refluxate. The present study quantified only the relationship between symptoms and acid reflux during pH-metry, whereas impedance monitoring evaluates the association between symptoms and both acid, weakly acidic and alkaline reflux. The accuracy of determination of the relationship between reflux and symptoms is higher when

reflux is detected with combined pH–impedance monitoring than when detected with pH monitoring alone[12,38]. As a result, combined pH–impedance monitoring probably has a higher positive and negative predictive value than pH-metry. Therefore, impedance monitoring may increase the accuracy of preoperative investigations in patients with a negative SAP. Larger studies using combined pH–impedance monitoring are warranted to reproduce and confirm the results of this relatively small study, before definite conclusions can be drawn.

The reoperation rate in the present study is high compared with published rates. However, a recent meta-analysis of RCTs demonstrated that 9.6 per cent of patients needed surgical reintervention at a mean follow-up of 2.5 years after fundoplication[39]. The reoperation rate in present study (13.0 per cent at 6 years) is largely in line with these results, considering the extended length of follow-up. The present reoperation rate seems representative of surgical results in experienced, but not necessarily expert, units.

This study is limited by the fact that a substantial group of patients was excluded from the analysis owing to incomplete 24-h pH monitoring or lack of symptom association analysis. Patients with GORD and physiological acid exposure are a distinct group, and were excluded to ensure that symptom association was the only difference between study groups. The fact that some patients refused parts of the postoperative study protocol is certainly a limitation that may have led to bias. From earlier studies, however, it is known that 90 per cent of patients who refuse objective long-term evaluation are asymptomatic and see no benefit in repeated invasive testing[40]. This might explain the relatively high percentage of patients with recurrent pathological acid exposure in this cohort.

References

(1) Jamieson JR, Stein HJ, DeMeester TR, Bonavina L, Schwizer W, Hinder RA *et al*. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. *Am J Gastroenterol* 1992; **87**: 1102–1111.

(2) Johnson LF, DeMeester TR. Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. *Am J Gastroenterol* 1974; **62**: 325–332.

(3) Howard PJ, Maher L, Pryde A, Heading RC. Symptomatic gastro-oesophageal reflux, abnormal oesophageal acid exposure, and mucosal acid sensitivity are three separate, though related, aspects of gastro-oesophageal reflux disease. *Gut* 1991; **32**:128–132.

(4) Emde C, Armstrong D, Castiglione F, Cilluffo T, Riecken EO, Blum AL. Reproducibility of long-term ambulatory esophageal combined pH/manometry. *Gastroenterology* 1991; **100**: 1630–1637.

(5) Wang H, Beck IT, Paterson WG. Reproducibility and physiological characteristics of 24-hour ambulatory esophageal manometry/pH-metry. *Am J Gastroenterol* 1996; **91**: 492–497.

(6) Johnsson F, Joelsson B. Reproducibility of ambulatory oesophageal pH monitoring. *Gut* 1988; **29**: 886–889.

(7) Jamieson JR, Stein HJ, DeMeester TR, Bonavina L, Schwizer W, Hinder RA *et al*. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. *Am J Gastroenterol* 1992; **87**: 1102–1111.

(8) Rokkas T, Sladen GE. Ambulatory esophageal pH recording in gastroesophageal reflux: relevance to the development of esophagitis. *Am J Gastroenterol* 1988; **83**: 629–632.

(9) Ward BW, Wu WC, Richter JE, Lui KW, Castell DO. Ambulatory 24-hour esophageal pH monitoring. Technology searching for a clinical application. *J Clin Gastroenterol* 1986; **8**(Suppl 1): 59–67.

(10) Weusten BL, Roelofs JM, Akkermans LM, Van Berge-Henegouwen GP, Smout AJ. The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. *Gastroenterology* 1994; **107**: 1741–1745.

(11) Breumelhof R, Smout AJ. The symptom sensitivity index: a valuable additional parameter in 24-hour esophageal pH recording. *Am J Gastroenterol* 1991; **86**: 160–164.

(12) Aanen MC, Bredenoord AJ, Numans ME, Samson M, Smout AJ. Reproducibility of symptom association analysis in ambulatory reflux monitoring. *Am J Gastroenterol* 2008; **103**: 2200–2208.

(13) Bais JE, Bartelsman JF, Bonjer HJ, Cuesta MA, Go PM, Klinkenberg-Knol EC *et al*. Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. *Lancet* 2000; **355**: 170–174.

(14) Draaisma WA, Ruurda JP, Scheffer RC, Simmermacher RK, Gooszen HG, Rijnhart-de Jong HG *et al*. Randomized clinical trial of standard laparoscopic *versus* robot-assisted laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease. *Br J Surg* 2006; **93**: 1351–1359.

(15) Draaisma WA, Buskens E, Bais JE, Simmermacher RK, Rijnhart-de Jong HG, Broeders IA *et al*. Randomized clinical trial and follow-up study of cost-effectiveness of laparoscopic *versus* conventional Nissen fundoplication. *Br J Surg* 2006; **93**: 690–697.

(16) Watson DI, Baigrie RJ, Jamieson GG. A learning curve for laparoscopic fundoplication. Definable, avoidable, or a waste of time? *Ann Surg* 1996; **224**: 198–203.

(17) Horbach JM, Masclee AA, Lamers CB, Gooszen HG. Prospective evaluation of 24 hour ambulatory pH metry in Belsey Mark IV antireflux surgery. *Gut* 1994; **35**: 1529–1535.

(18) Rijnhart-de Jong HG, Draaisma WA, Smout AJ, Broeders IA, Gooszen HG. The Visick score: a good measure for the overall effect of antireflux surgery? *Scand J Gastroenterol* 2008; **43**: 787–793.

(19) Visick AH. A study of the failures after gastrectomy. *Ann R Coll Surg Engl* 1948; **3**: 266–284.

(20) de Boer AG, van Lanschot JJ, Stalmeier PF, van Sandick JW, Hulscher JB, de Haes JC *et al*. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? *Qual Life Res* 2004; **13**: 311–320.

(21) Velanovich V, Karmy-Jones R. Measuring gastroesophageal reflux disease: relationship between the Health-Related Quality of Life score and physiologic parameters. *Am Surg* 1998; **64**: 649–653.

(22) Zéman Z, Rózsa S, Tihanyi T, Tarkó E. Psychometric documentation of a quality-of-life questionnaire for patients undergoing antireflux surgery (QOLARS). *Surg Endosc* 2005; **19**: 257–261.

(23) Nord E. The validity of a visual analogue scale in determining social utility weights for health states. *Int J Health Plann Manage* 1991; **6**: 234–242.

(24) Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. Ten-year outcome of laparoscopic and conventional Nissen fundoplication: randomized clinical trial. *Ann Surg* 2009; **250**: 698–706.

(25) Savary M, Miller G. The oesophagus. In *Handbook and Atlas of Endoscopy*, M Savary, G Miller (eds). Gossman: Solothurn, 1978; 135–142.

(26) Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP *et al*. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999; **45**: 172–180.

(27) Wiener GJ, Richter JE, Copper JB, Wu WC, Castell DO. The symptom index: a clinically important parameter of ambulatory 24-hour esophageal pH monitoring. *Am J Gastroenterol* 1988; **83**: 358–361.

(28) Richter JE, Bradley LA, DeMeester TR, Wu WC. Normal 24-hr ambulatory esophageal pH values. Influence of study center, pH electrode, age, and gender. *Dig Dis Sci* 1992; **37**: 849–856.

(29) Bell RC, Hanna P, Brubaker S. Laparoscopic fundoplication for symptomatic but physiologic gastroesophageal reflux. *J Gastrointest Surg* 2001; **5**: 462–467.

(30) Booth MI, Stratford J, Thompson E, Dehn TC. Laparoscopic antireflux surgery in the treatment of the acid-sensitive oesophagus. *Br J Surg* 2001; **88**: 577–582.

(31) del Genio G, Tolone S, del Genio F, Aggarwal R, d'Alessandro A, Allaria A *et al*. Prospective assessment of patient selection for antireflux surgery by combined multichannel intraluminal impedance pH monitoring. *J Gastrointest Surg* 2008; **12**: 1491–1496.

(32) Mainie I, Tutuian R, Agrawal A, Adams D, Castell DO. Combined multichannel intraluminal impedance–pH monitoring to select patients with persistent gastro-oesophageal reflux for laparoscopic Nissen fundoplication. *Br J Surg* 2006; **93**: 1483–1487.

(33) Taghavi SA, Ghasedi M, Saberi-Firoozi M, izadeh-Naeeni M, Bagheri-Lankarani K, Kaviani MJ *et al*. Symptom association probability and symptom sensitivity index: preferable but still suboptimal predictors of response to high dose omeprazole. *Gut* 2005; **54**: 1067–1071.

(34) Galmiche JP, Clouse RE, Bálint A, Cook IJ, Kahrilas PJ, Paterson WG *et al*. Functional esophageal disorders. *Gastroenterology* 2006; **130**: 1459–1465.

(35) Shi G, Bruley des Varannes S, Scarpignato C, Le RM, Galmiche JP. Reflux related symptoms in patients with normal oesophageal exposure to acid. *Gut* 1995; **37**: 457–464.

(36) Aanen MC, Weusten BL, Numans ME, de Wit NJ, Samsom M, Smout AJ. Effect of proton-pump inhibitor treatment on symptoms and quality of life in GERD patients depends on the symptom–reflux association. *J Clin Gastroenterol* 2008; **42**: 441–447.

(37) Chin KF, Myers JC, Jamieson GG, Devitt PG. Symptoms experienced during 24-h pH monitoring and their relationship to outcome after laparoscopic total fundoplication. *Dis Esophagus* 2008; **21**: 445–451.

(38) Bredenoord AJ, Weusten BL, Timmer R, Conchillo JM, Smout AJ. Addition of esophageal impedance monitoring to pH monitoring increases the yield of symptom association analysis in patients off PPI therapy. *Am J Gastroenterol* 2006; **101**: 453–459.

(39) Catarci M, Gentileschi P, Papi C, Carrara A, Marrese R, Gaspari AL *et al*. Evidence-based appraisal of antireflux fundoplication. *Ann Surg* 2004; **239**: 325–337.

(40) Draaisma WA, Rijnhart-de Jong HG, Broeders IA, Smout AJ, Furnee EJ, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. *Ann Surg* 2006; **244**: 34–41.

5

Long-term outcome of Nissen fundoplication in non-erosive and erosive gastro-oesophageal reflux disease

J.A.J.L. Broeders[1]
W.A. Draaisma[1]
A.J. Bredenoord[2]
A.J.P.M. Smout[2]
I.A.M.J. Broeders[3]
H.G. Gooszen[1]

[1]Dep. of Surgery, University Medical Center Utrecht
[2]Dep.of Gastroenterology, University Medical Center Utrecht
[3]Dep. of Surgery, Meander Medical Center, Amersfoort

16th annual meeting of the European Association for Endoscopic Surgery
Stockholm, Sweden, June 2008
11th world congress of the International Society for Diseases of the Esophagus
Budapest, Hungary, September 2008

British Journal of Surgery 2010; 97:845-52.

Abstract

Background: Non-erosive (NERD) and erosive (ERD) gastro-oesophageal reflux disease (GORD) show similar severity of symptoms and impact on quality of life (QoL). Prospective data on long-term outcomes of antireflux surgery in NERD are lacking.

Methods: Subjective and objective 5-year outcomes of Nissen fundoplication were compared in 96 patients with NERD and 117 with ERD, operated on for proton-pump inhibitor (PPI)-refractory GORD.

Results: Preoperative and postoperative QoL, PPI use, acid exposure time, symptom–reflux correlation, lower oesophageal sphincter (LOS) pressure and reoperation rates were similar in the two groups. At 5 years, relief of reflux symptoms was similar (NERD 89 per cent *versus* ERD 96 per cent), PPI use showed a similar reduction (82 to 21 per cent *versus* 81 to 15 per cent respectively; both $P<0.001$) and QoL score improved equally (50.3 to 65.2 ($P<0.001$) *versus* 52.0 to 60.7 ($P=0.016$)). Five patients with NERD developed erosions after surgery; oesophagitis healed in 87.2 per cent of patients with ERD. Reduction in total acid exposure time (NERD 12.7 to 2.0 per cent *versus* ERD 13.8 to 2.9 per cent; both $P<0.001$) and increase in LOS pressure (1.3 to 1.8 kPa *versus* 1.2 to 1.8 kPa; both $P<0.001$) were similar. The reintervention rate was comparable (NERD 15 per cent *versus* ERD 12.8 per cent).

Conclusion: Patients with PPI-refractory NERD and ERD benefit equally from Nissen fundoplication. The absence of mucosal lesions on endoscopy in patients with proven PPI-refractory reflux disease is not a reason to refrain from antireflux surgery.

Introduction

Patients with gastro-oesophageal reflux disease (GORD) can be subdivided into those with erosive (ERD) and non-erosive (NERD) reflux disease, based on upper gastrointestinal endoscopy findings[1]. The Montreal criteria define NERD as troublesome reflux-associated symptoms and the absence of mucosal breaks at endoscopy[2]. Up to 70 per cent of patients with GORD have no endoscopic evidence of oesophagitis[3,4]. In these patients, the assumption that reflux is the cause of symptoms is confirmed by 24-h ambulatory oesophageal pH monitoring or a positive response to inhibition of gastric acid secretion. Impairment of quality of life (QoL) and severity of symptoms are similar in patients with NERD and ERD[5–8]. Symptom severity and frequency cannot be used to differentiate between these two groups. A systematic review of literature has demonstrated that 30–40 per cent of patients with NERD do not have an adequate response to high-dose proton-pump inhibitors (PPIs)[7,9–11]. In addition, patients with NERD have lower response and higher relapse rates than patients with ERD[7,12–15]. The diminished response to PPI-treatment supports a greater role for surgery in NERD than in ERD.

Until recently, however, NERD was considered a milder form of GORD and physicians were reluctant to refer these patients for surgery[16,17]. Previous studies of antireflux surgery in NERD are contradictory and lack objective outcome assessment. Some report similar[18–22] whereas others report worse[23,24] subjective outcomes following antireflux surgery in NERD. Only one study[22] measured outcomes objectively. The purpose of the present study was to compare long-term results of antireflux surgery in PPI-refractory patients with NERD and ERD.

Methods

The study involved a consecutive cohort of patients undergoing standardized assessment and Nissen fundoplication for refractory GORD, with information recorded in a prospectively created database, followed up for 5 years[25–27]. Surgical treatment was offered to PPI-refractory patients with heartburn and regurgitation as their predominant symptoms. Patients were considered PPI refractory if 40 mg omeprazole was insufficient for lasting suppression of symptoms and if, following an increase in dosage to 40 mg two or three times daily, symptoms recurred after return to 40 mg maintenance treatment daily. Patients were included in the present study if upper endoscopy had been performed before surgery, preoperative 24-h pH monitoring demonstrated pathological reflux, and objective or subjective outcome had been registered after surgery.

A 360° Nissen fundoplication was constructed in all patients after full mobilization of the oesophagus, division of the short gastric vessels, and posterior crural repair.

Patients were asked to complete a questionnaire on QoL and use of acid-suppressing drugs before surgery, and at 3 months and 5 years after surgery. Frequency and severity of heartburn, regurgitation and dysphagia were registered prospectively until 5 years, and all patients were asked to rate the change in their reflux symptoms compared with symptoms before operation (Visick score). Surgical reinterventions and indications for reintervention were recorded for up to 5 years after the primary procedure. For objective outcome assessment, all patients were asked to undergo upper endoscopy, stationary oesophageal manometry and 24-h pH monitoring at the gastrointestinal research unit of the University Medical Centre Utrecht 3 months before and 3 months after surgery. The patients who had participated in a randomized controlled trial[25] were asked to undergo further stationary oesophageal manometry and 24-h pH testing at 5 years.

Visick grading was used to assess the effect of surgery on symptoms: grade I, complete resolution; grade II, improvement; grade III, no effect of surgery and grade IV, deterioration, compared with before operation[28]. This scoring system was applied to give an overall impression of the benefit of antireflux surgery because it shows a good correlation with heartburn, the most prominent symptom of GORD[29]. Visick scores correlate well to a validated questionnaire[30] for reflux symptoms[31]. Heartburn, regurgitation and dysphagia were assessed using a combined frequency and severity grading system, which ranges from grade 0 (symptom absent) to grade 3 (symptom frequent and severe)[32]. The impact on QoL was measured using a visual analogue scale, validated for QoL assessment after oesophageal surgery[33]. The scale of this instrument ranged from zero (worst possible health) to 100 (perfect health)[34]. These data were collected prospectively for up to 5 years after surgery in consecutive patients.

Baseline upper gastrointestinal endoscopy was performed 3 months before surgery, after acid-suppressing drugs had been stopped for 7 days. The presence of oesophagitis and hiatal hernia were determined endoscopically. Grading of oesophagitis was performed initially according to the Savary–Miller classification[35], and from 1999 onwards according to the Los Angeles classification[1].

Manometric studies were performed with patients off any medication that could affect oesophageal motility. A water-perfused system with a multiple-lumen catheter with an incorporated sleeve sensor (Dentsleeve, Adelaide, Australia) was used. After transnasal introduction, the catheter was retracted to determine the distal border of the lower oesophageal sphincter (LOS). The sleeve sensor was positioned at the level of the LOS and intraluminal oesophageal pressures were recorded at 5, 10 and 15 cm above the proximal margin. Thereafter, the manometric response to ten standardized wet swallows was studied (5-ml water

bolus). The gastric baseline pressure was registered 2 cm below the distal margin of the sleeve sensor and served as the zero reference point.

Ambulatory 24-h pH testing was performed after ceasing medication that could affect results for 7 days. After transnasal introduction, a catheter with a pH glass electrode (model LOT440; Medical Instruments, Solothurn, Switzerland) was positioned 5 cm above the manometrically determined upper border of the LOS. The 24-h pH recordings were stored in a digital data logger (Medical Measurement Systems, Enschede, The Netherlands), and patients registered reflux symptoms and body position in a diary. In addition, patients were instructed to press a button on the digital data logger when they experienced a symptom. The recordings were analysed automatically using the MMS Database® software program version 8.11 (Medical Measurement Systems, Enschede, The Netherlands). The symptom index (SI) and symptom association probability (SAP) were calculated when the patient recorded symptom episodes. A SI of at least 50 per cent was considered to be positive. A SAP value of 95 per cent or more was considered positive, because the chance of the relationship between symptoms and reflux being coincidental is less than 5 per cent at this cut-off value.

Classification into pathological or physiological oesophageal acid exposure was based on the percentage of time with pH below 4. The upper limit for physiological oesophageal acid exposure in upright and supine body position was two standard deviations above the mean value obtained in healthy volunteers during ambulatory 24-h pH monitoring[36,37]. Pathological acid exposure was defined as an acid exposure time of 8.2 per cent or more in upright body position, and/or an acid exposure time of 3.5 per cent or more in supine position and 5.8 per cent or more.

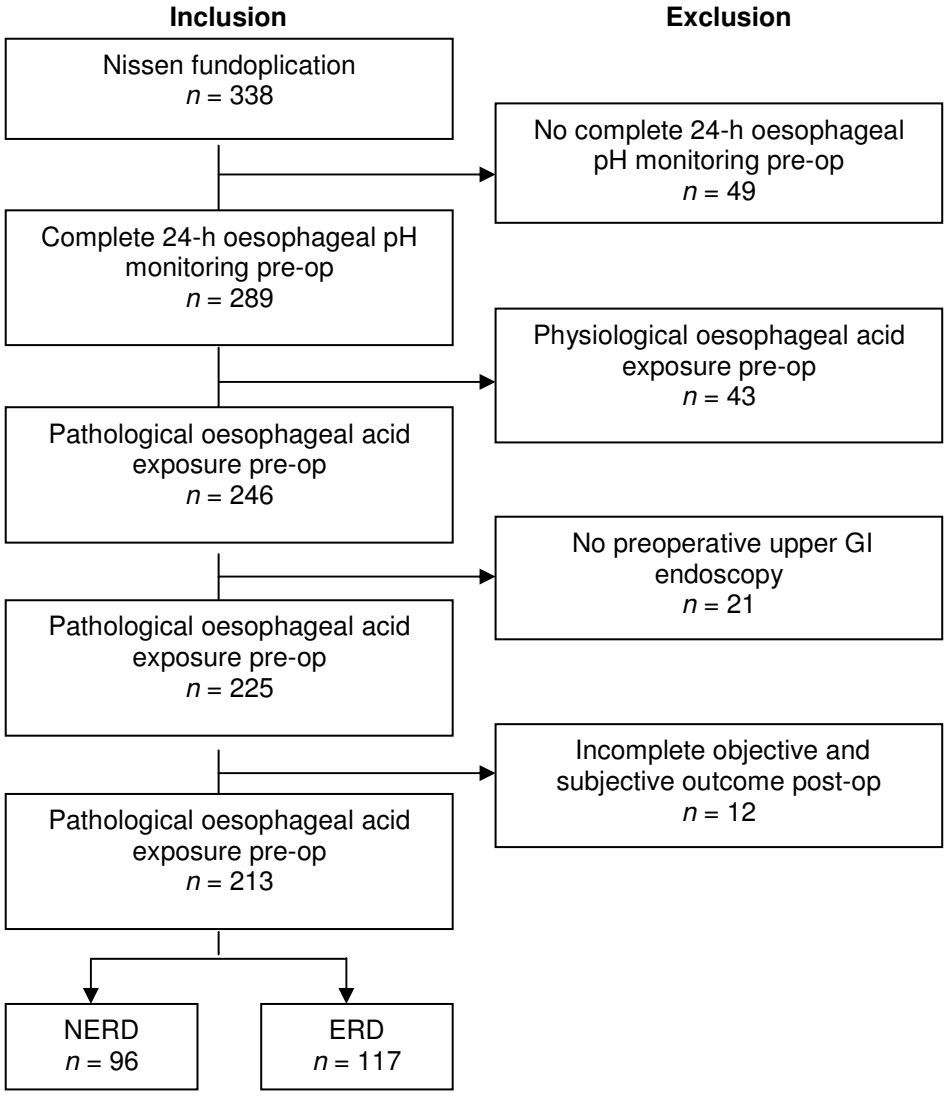
Statistical analysis

Because the aim of this study was to evaluate the effect of surgery in subjective and objective terms, patients were included only when both preoperative data and the results at 3 months or 5 years after surgery were available. The number of patients for whom data were available was reported for each parameter. Continuous values were expressed as mean(s.e.m). For parametric data, one-way ANOVA and the Bonferroni *post hoc* test were used to analyse differences between groups. Significant effects of surgery on parametric data were evaluated using the paired-samples *t* test. For nominal variables, the χ^2 test was used to compare groups, analysing the effects of surgery with the McNemar–Bowker test. Correlations between groups were determined by means of the Spearman coefficient. Kaplan–Meier analysis was used to evaluate the surgical reintervention rate. Statistical analysis was performed using SPSS® version 15.0 (SPSS, Chicago, Illinois, USA). $P<0.050$ was considered statistically significant.

Results

Of a total of 338 patients, 213 had pathological acid exposure during 24-h pH monitoring, complete upper gastrointestinal endoscopy, and full registration of subjective or objective outcomes (*Fig. 1*). A group of 96 patients with NERD was compared with 117 patients with ERD. Mean age (43.9 (range 19–85) *versus* 43.1 (range 17–77) years), proportion of male patients (61.5 *versus* 59.8 per cent), body mass index (mean(s.e.m.) 26.5(0.5) *versus* 26.4(0.4) kg/m^2) and proportion of laparoscopic approaches (69.8 *versus* 74.1 per cent) were similar for patients with NERD and ERD respectively. Mean(s.e.m.) hiatal hernia size was smaller in the NERD group, although not significantly so (2.7(0.3) *versus* 3.3(0.2) cm; $P = 0.128$).

Figure 1 Study profile



Clinical outcome

General improvement of reflux symptoms after surgery was similar in the two groups (*Fig. 2*). Heartburn, regurgitation and dysphagia grades were similar at 5 years (*Table 1*). At that stage, 68 (89 per cent) of 76 and 66 (96 per cent) 69 of patients scored their reflux symptoms as being resolved or improved (Visick I or II) in NERD and ERD groups respectively. There were no differences between groups before surgery, at 3 months or 5 years regarding QoL (*Fig. 3*) or the use of acid-suppressing drugs. The mean(s.e.m.) improvement in QoL score was significant in both groups at 3 months (NERD: 50.3(3.2) to 60.2(3.0), $P = 0.015$; ERD: 52.0(2.6) to 64.1(2.5), $P < 0.001$) and 5 years (NERD: 50.3(3.2) to 65.2(3.0), $P < 0.001$; ERD: 52.0(2.6) to 60.7(3.3), $P = 0.016$).

Figure 2 Self-rated change in reflux symptoms 5 years after surgery compared to the preoperative state in NERD and ERD (Visick score). Number of patients for which data were available (*n*=) and percentages for this group are given

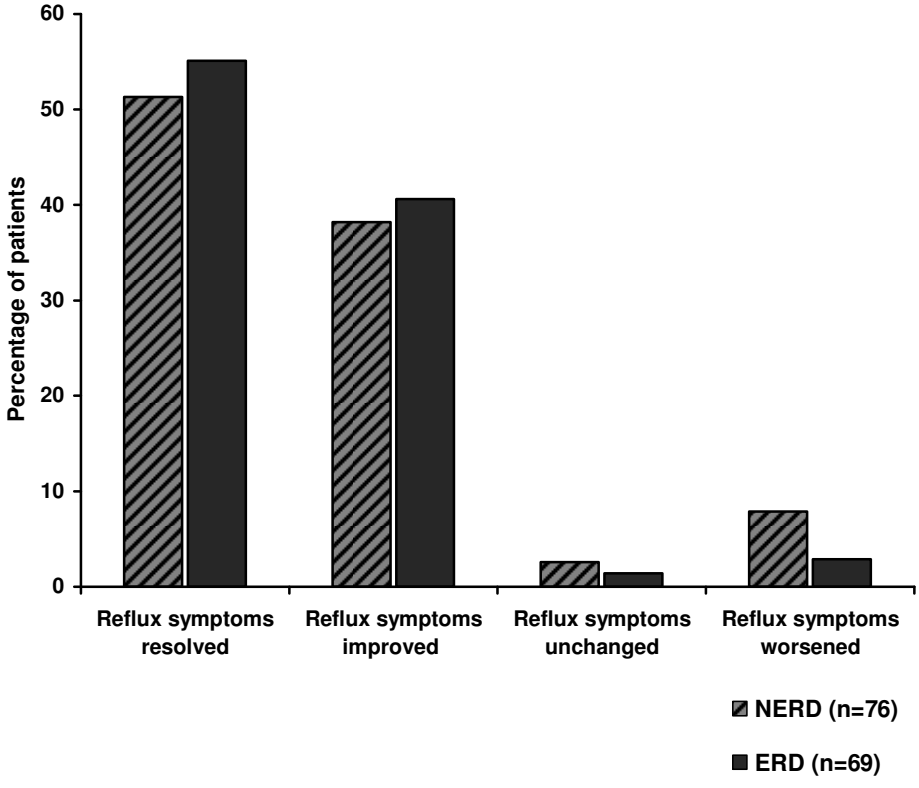
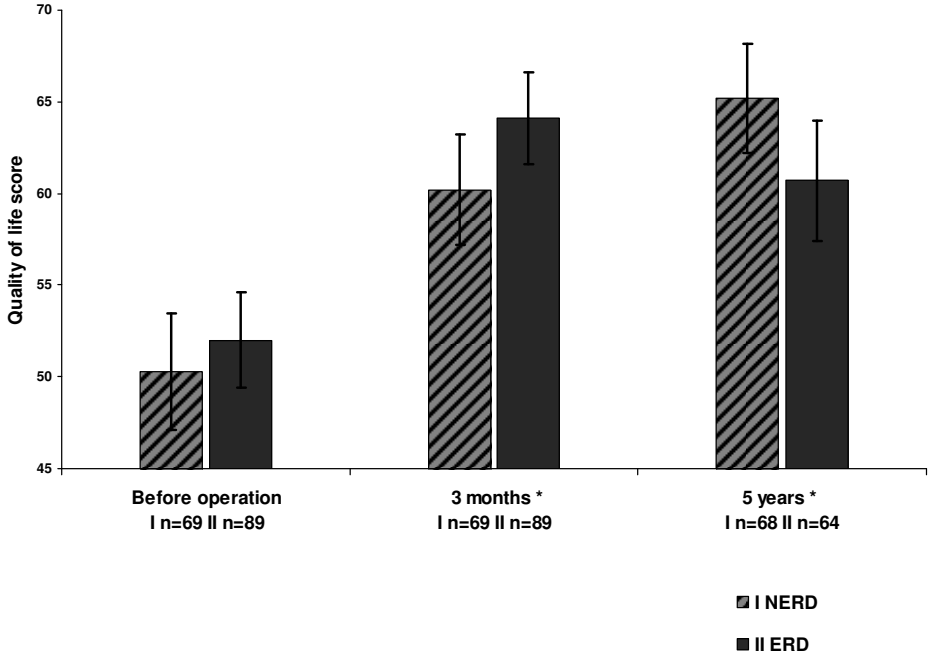


Table 1 Heartburn, regurgitation and dysphagia grades 5 years after surgery and the number of surgical reinterventions at 5 years, in NERD and ERD. Number of patients for which data were available (n =) and positive percentage for this group are given

	NERD	ERD
Heartburn		
Grade 0	47 [61.8]	47 [67.1]
Grade 1	24 [31.6]	18 [25.7]
Grade 2	3 [3.9]	5 [7.1]
Grade 3	2 [2.6]	-
Regurgitation		
Grade 0	52 [72.2]	50 [73.5]
Grade 1	15 [20.8]	15 [22.1]
Grade 2	5 [6.9]	3 [4.4]
Grade 3	-	-
Dysphagia		
Grade 0	30 [41.7]	39 [56.5]
Grade 1	32 [44.4]	24 [34.8]
Grade 2	7 [9.7]	5 [7.2]
Grade 3	3 [4.2]	1 [1.4]
Surgical reintervention		
NERD n=96 ERD n=117	14 [14.6%]	15 [12.8%]
Reoperation indication:		
Recurrent reflux	7	5
Dysphagia	6	5
Intrathoracic herniation	0	4
Other	1	1

The proportion of patients using acid-suppressing drugs was greatly reduced 3 months after surgery in both NERD (68/83 (82%) to 6/83 (7%)) and ERD (79/97(81%) to 4/97 (4%)) groups (both $P < 0.001$). This reduction remained significant at 5 years (68/83 (82%) to 15/71(21%) and 79/97 (81%) to 10/66 (15%) respectively; both $P < 0.001$). The use of acid-suppressing drugs increased similarly over time in the two groups. No significant correlation was found in either group between antisecretory drug use and total acid exposure at five years (NERD: $r_S = -1.151$, $P = 0.451$; ERD: $r_S = -0.324$, $P = 0.093$).

Figure 3 Mean(s.e.m.) quality of life score, measured on a visual analogue scale from 0 to 100 preoperatively, 3 months and 5 years postoperatively in patients with NERD and ERD



* $P < 0.050$ *versus* preoperative results for both groups (paired-samples *t*-test)

Surgical reintervention was necessary in 14 (15 per cent) of 96 patients with NERD and in 15 (12.8 per cent) of 117 patients with ERD within 6 years of follow-up (P = 0.754). All reoperations, except one, were performed within 2.5 years of follow-up. Recurrent reflux and dysphagia were the most common indications for reintervention in both groups (*Table 1*).

Upper gastrointestinal endoscopy

At 3 months after surgery, a similar reduction in the mean size of the hiatal hernia was found in the two groups (NERD: 2.7(0.3) to 0.8(0.2) cm, n = 38; ERD: 3.3(0.2) to 1.3(0.3) cm, n = 32). Oesophagitis was healed in 82 (87 per cent) of 94 patients with ERD, whereas in the NERD group four of 70 patients had grade A oesophagitis after fundoplication, with physiological acid exposure. One patient with NERD developed grade B oesophagitis and recurrent pathological acid exposure, necessitating reoperation.

Stationary oesophageal manometry

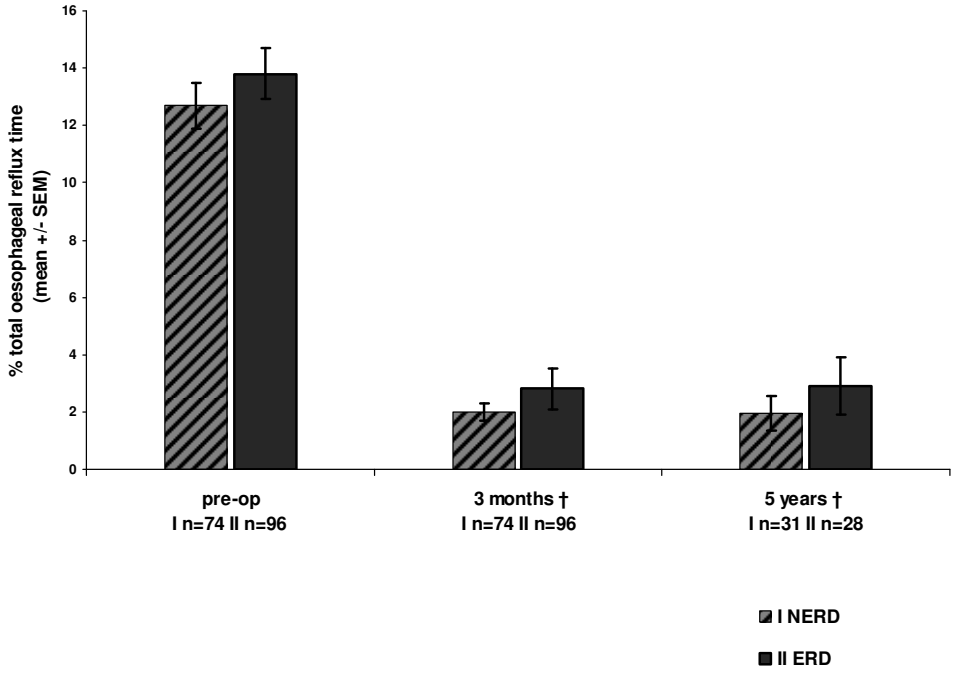
LOS pressures were similar in the two groups, before and after surgery. At 3 months, fundoplication increased LOS pressure in NERD (1.3(0.1) to 1.8(0.1) kPa) and ERD (1.2(0.1) to 1.8(0.1) kPa) (both $P < 0.001$). The effect on LOS pressure decreased 5 years after surgery, especially in the ERD group. In the long-term, LOS pressure was unchanged from the preoperative level in both groups (NERD: 1.3(0.1) to 1.7(0.2) kPa; ERD: 1.2(0.1) to 1.4(0.2) kPa).

24-h oesophageal pH monitoring

Surgery led to a reduction in total acid exposure to physiological values in both groups at 3 months (NERD: 12.7(0.8) to 2.0(0.3) per cent; ERD: 13.8(0.9) to 2.8(0.7) per cent; both $P<0.001$) (*Fig. 4*) and total acid exposure remained reduced at 5 years (12.7(0.8) to 2.0(0.6) per cent and 13.8(0.9) to 2.9(1.0) per cent respectively; both $P <0.001$). There were no differences in upright, supine and total acid exposure between the groups at any time point, except for a higher preoperative supine acid exposure in patients with ERD (12.7(1.5) *versus* 8.4(1.3) per cent for NERD; P = 0.029).

Groups did not differ in the number of symptoms reported during pH monitoring, and symptom correlation scores were identical before and after surgery (*Table 2*). Compared with preoperative values, in both groups surgery reduced the number of symptom episodes (all $P < 0.001$), the percentage of patients with a positive SI (all $P < 0.001$) and the percentage of patients with a positive SAP (all $P < 0.001$) at 3 months and 5 years.

Figure 4 Mean(s.e.m.) preoperative, three-month and five-year postoperative total acid exposure in patients with NERD and ERD



† $P < 0.001$ *versus* total acid exposure before surgery (paired-samples *t*-test)

Table 2 Number of symptom episodes, percentage of patients with positive Symptom Index (SI) and Symptom Association Probability (SAP) during 24-hour oesophageal pH monitoring preoperatively, 3 months and 5 years postoperatively in patients with NERD and ERD

	NERD	ERD
Number of symptoms*		
Before operation (NERD n=60 ERD n=81)	15.0 (1.7)	12.7 (1.5)
3 months (NERD n=60 ERD n=81) †	3.1 (0.7)	2.1 (0.6)
5 years (NERD n=23 ERD n=21) †	2.6 (1.0)	0.9 (0.3)
Positive Symptom Index		
Before operation (NERD n=57 ERD n=81)	47 [82.5]	62 [76.5]
3 months (NERD n=57 ERD n=81) †	2 [3.5]	3 [3.7]
5 years (NERD n=24 ERD n=22) †	3 [12.5]	3 [13.6]
Positive Symptom Association Probability		
Before operation (NERD n=51 ERD n=79)	42 [82.4]	63 [79.7]
3 months (NERD n=51 ERD n=79) †	1 [2.0]	2 [2.5]
5 years (NERD n=18 ERD n=22) †	2 [11.1]	1 [4.5]

* values are mean(s.e.m.); † $P < 0.001$ *versus* preoperative results for both groups (paired-samples *t*-test and McNemar-Bowker test)

Discussion

This study combined detailed subjective and objective comparison of NERD and ERD, both before surgery and for up to 5 years after fundoplication. The results relate to a specialized centre with a multidisciplinary approach to the management of patients with GORD. Before surgery, patients with NERD and ERD were similar in terms of characteristics related to GORD, at least in the subgroups considered candidates for surgery. They also exhibited the same outcomes after antireflux surgery in both the short and the long term.

NERD and ERD are the two main phenotypic presentations of GORD[38]. Initially, NERD was considered a less severe form of GORD that would progress to erosive disease only in a subset of patients. Recent studies have demonstrated that both progression to erosive oesophagitis and regression from ERD to NERD are rare[4,39,40]. Community-based studies report lower oesophageal acid exposure in NERD compared with ERD[41]. However, only 45 per cent of the patient population in this study had abnormal oesophageal acid exposure. If the studied population is confined to patients with objectively proven pathological acid exposure, oesophageal acid exposure time is comparable in NERD and ERD[41–44]. The present analysis and other studies comparing surgical outcome[18,19,24] have confirmed this preoperative finding. Consequently, the assumption that NERD is associated with early or mild disease appears to be incorrect for patients with objective evidence of reflux disease and cannot be put forward as a valid reason for reluctance to perform antireflux surgery in patients with NERD involving pathological acid exposure.

Several trials that compared the effectiveness of antisecretory drugs have demonstrated that patients with NERD are more prone to develop PPI-refractory GORD and to become candidates for antireflux surgery[7,9,11,13,14]. Before considering antireflux surgery in patients with NERD it is essential to document objectively the relationship between reflux and symptoms, because the *a priori* chance that the symptoms experienced are not caused by GORD is greater in patients without mucosal abnormalities demonstrated by endoscopy. In NERD, healing of oesophagitis after fundoplication cannot be applied as an indicator of success. In the present study, a combination of frequency and severity of typical reflux symptoms, PPI use and QoL assessment was therefore used. Several studies have demonstrated the lack of correlation between symptomatic outcome and results of objective measurements[45–48], and between postoperative PPI use and oesophageal acid exposure after fundoplication[49–52]. As a result it is not possible to evaluate adequately the effect of antireflux surgery based on symptomatic outcome alone, and oesophageal acid exposure, symptom–reflux

correlation and 5-year reoperation rates were therefore key objective outcome measures.

The subjective results of the present study confirmed that patients with NERD have a similar reduction in symptoms[18–20,22] and PPI use[19,20,22] to those found in patients with ERD. A comparative study reported less symptom reduction, a lower QoL and higher PPI use after surgery for NERD[24]. The indication for surgery in that study was mainly unwillingness to continue medical treatment despite good symptomatic relief. In contrast, the present study and the only other study that objectively determined the result of fundoplication[22], focused on patients with PPI-refractory reflux disease; both demonstrated that acid exposure was restored to normal and LOS pressure increased similarly after fundoplication in NERD and ERD.

The reoperation rate for the whole group was 13.6 per cent over 6 years, with no difference between ERD and NERD. This rate is similar to that described in a recent meta-analysis of randomized controlled trials where the pooled reoperation rate after a mean follow-up of 30 months was 9.6 per cent[53]. A potential weakness of the present study is that some patients considered to have NERD may have been misclassified as a result of PPI therapy. A 7-day PPI washout period was probably too short for erosions to recur in all patients. Extending the washout period to 2–3 weeks would be better from a scientific point of view, but seems unethical in patients requiring antireflux surgery for severe symptoms. Another limitation of the present study was the fact that only patients who participated in a randomized controlled trial[25] were asked to undergo invasive testing (oesophageal manometry and 24-h pH testing) at 5 years.

Subjective and objective long-term outcomes of Nissen fundoplication are similar in ERD and NERD, and results are sustained for up to 5 years after surgery. Reintervention rates are comparable for NERD and ERD. The absence of mucosal lesions on endoscopy in patients with proven PPI-refractory reflux disease should not be a reason to refrain from antireflux surgery.

References

(1) Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999; 45(2):172-180.

(2) Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006; 101(8):1900-1920.

(3) Jones RH, Hungin AP, Phillips J. Gastro-esophageal reflux disease in primary care in Europe: clinical presentation and endoscopic findings. Eur J Gen Pract 2008; 1:149-154.

(4) Lind T, Havelund T, Carlsson R, nker-Hansen O, Glise H, Hernqvist H et al. Heartburn without oesophagitis: efficacy of omeprazole therapy and features determining therapeutic response. Scand J Gastroenterol 1997; 32(10):974-979.

(5) Havelund T, Lind T, Wiklund I, Glise H, Hernqvist H, Lauritsen K et al. Quality of life in patients with heartburn but without esophagitis: effects of treatment with omeprazole. Am J Gastroenterol 1999; 94(7):1782-1789.

(6) Wiklund I. Quality of life in patients with gastroesophageal reflux disease. Am J Gastroenterol 2001; 96(8 Suppl):S46-S53.

(7) Carlsson R, Dent J, Watts R, Riley S, Sheikh R, Hatlebakk J et al. Gastro-oesophageal reflux disease in primary care: an international study of different treatment strategies with omeprazole. International GORD Study Group. Eur J Gastroenterol Hepatol 1998; 10(2):119-124.

(8) Venables TL, Newland RD, Patel AC, Hole J, Wilcock C, Turbitt ML. Omeprazole 10 milligrams once daily, omeprazole 20 milligrams once daily, or ranitidine 150 milligrams twice daily, evaluated as initial therapy for the relief of symptoms of gastro-oesophageal reflux disease in general practice. Scand J Gastroenterol 1997; 32(10):965-973.

(9) Bate CM, Green JR, Axon AT, Murray FE, Tildesley G, Emmas CE et al. Omeprazole is more effective than cimetidine for the relief of all grades of gastro-oesophageal reflux disease-associated heartburn, irrespective of the presence or absence of endoscopic oesophagitis. Aliment Pharmacol Ther 1997; 11(4):755-763.

(10) Hatlebakk JG, Hyggen A, Madsen PH, Walle PO, Schulz T, Mowinckel P et al. Heartburn treatment in primary care: randomised, double blind study for 8 weeks. BMJ 1999; 319(7209):550-553.

(11) Richter JE, Kovacs TO, Greski-Rose PA, Huang section, Fisher R. Lansoprazole in the treatment of heartburn in patients without erosive oesophagitis. Aliment Pharmacol Ther 1999; 13(6):795-804.

(12) Dean BB, Gano AD, Jr., Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. Clin Gastroenterol Hepatol 2004; 2(8):656-664.

(13) Galmiche JP, Barthelemy P, Hamelin B. Treating the symptoms of gastro-oesophageal reflux disease: a double-blind comparison of omeprazole and cisapride. Aliment Pharmacol Ther 1997; 11(4):765-773.

(14) Lauritsen K. Management of endoscopy-negative reflux disease:Progresswith short-term treatment. Aliment Pharmacol Ther 1997; 11 (Suppl 2):81-85.

(15) Richter JE, Campbell DR, Kahrilas PJ, Huang B, Fludas C. Lansoprazole compared with ranitidine for the treatment of nonerosive gastroesophageal reflux disease. Arch Intern Med 2000; 160(12):1803-1809.

(16) El-Serag HB, Sonnenberg A. Outcome of erosive reflux esophagitis after Nissen fundoplication. Am J Gastroenterol 1999; 94(7):1771-1776.

(17) Hinder RA, Filipi CJ, Wetscher G, Neary P, DeMeester TR, Perdikis G. Laparoscopic Nissen fundoplication is an effective treatment for gastroesophageal reflux disease. Ann Surg 1994; 220(4):472-481.

(18) Bammer T, Freeman M, Shahriari A, Hinder RA, DeVault KR, Achem SR. Outcome of laparoscopic antireflux surgery in patients with nonerosive reflux disease. J Gastrointest Surg 2002; 6(5):730-737.

(19) Desai KM, Frisella MM, Soper NJ. Clinical outcomes after laparoscopic antireflux surgery in patients with and without preoperative endoscopic esophagitis. J Gastrointest Surg 2003; 7(1):44-51.

(20) Gockel I, Heintz A, Domeyer M, Kneist W, Trinh TT, Junginger T. [Nonerosive and erosive gastroesophageal reflux disease. Long-term results of laparoscopic anterior semifundoplication]. Chirurg 2007; 78(1):35-39.

(21) Watson DI, Foreman D, Devitt PG, Jamieson GG. Preoperative endoscopic grading of esophagitis versus outcome after laparoscopic Nissen fundoplication. Am J Gastroenterol 1997; 92(2):222-225.

(22) Kamolz T, Granderath FA, Schweiger UM, Pointner R. Laparoscopic Nissen fundoplication in patients with nonerosive reflux disease. Long-term quality-of-life assessment and surgical outcome. Surg Endosc 2005; 19(4):494-500.

(23) Fenton P, Terry ML, Galloway KD, Smith CD, Hunter JG, Waring JP. Is there a role for laparoscopic fundoplication in patients with non-erosive reflux disease (NERD)? Gastroenterology 2000; 118(suppl 2):A481.

(24) Thibault R, Coron E, Sebille V, Sacher-Huvelin S, Bruley d, V, Gournay J et al. Antireflux surgery for non-erosive and erosive reflux disease in community practice. Aliment Pharmacol Ther 2006; 24(4):621-632.

(25) Bais JE, Bartelsman JF, Bonjer HJ, Cuesta MA, Go PM, Klinkenberg-Knol EC et al. Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. Lancet 2000; 355(9199):170-174.

(26) Draaisma WA, Buskens E, Bais JE, Simmermacher RK, Rijnhart-de Jong HG, Broeders IA et al. Randomized clinical trial and follow-up study of cost-effectiveness of laparoscopic versus conventional Nissen fundoplication. Br J Surg 2006; 93(6):690-697.

(27) Draaisma WA, Ruurda JP, Scheffer RC, Simmermacher RK, Gooszen HG, Rijnhart-de Jong HG et al. Randomized clinical trial of standard laparoscopic versus robot-assisted laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease. Br J Surg 2006; 93(11):1351-1359.

(28) VISICK AH. A study of the failures after gastrectomy. Ann R Coll Surg Engl 1948; 3(5):266-284.

(29) Rijnhart-de Jong HG, Draaisma WA, Smout AJ, Broeders IA, Gooszen HG. The Visick score: a good measure for the overall effect of antireflux surgery? Scand J Gastroenterol 2008; 43(7):787-793.

(30) Velanovich V, Karmy-Jones R. Measuring gastroesophageal reflux disease: relationship between the Health-Related Quality of Life score and physiologic parameters. Am Surg 1998; 64(7):649-653.

(31) Zeman Z, Rozsa S, Tihanyi T, Tarko E. Psychometric documentation of a quality-of-life questionnaire for patients undergoing antireflux surgery (QOLARS). Surg Endosc 2005; 19(2):257-261.

(32) Horbach JM, Masclee AA, Lamers CB, Gooszen HG. Prospective evaluation of 24 hour ambulatory pH metry in Belsey Mark IV antireflux surgery. Gut 1994; 35(11):1529-1535.

(33) de Boer AG, van Lanschot JJ, Stalmeier PF, van Sandick JW, Hulscher JB, de Haes JC et al. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? Qual Life Res 2004; 13(2):311-320.

(34) Nord E. The validity of a visual analogue scale in determining social utility weights for health states. Int J Health Plann Manage 1991; 6(3):234-242.

(35) Savary M, Miller G. The esophagus. *Handbook and atlas of endoscopy* Solothurn, Switzerland: Verlag Gossman. 1978.

(36) Jamieson JR, Stein HJ, DeMeester TR, Bonavina L, Schwizer W, Hinder RA et al. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. Am J Gastroenterol 1992; 87(9):1102-1111.

(37) Richter JE, Bradley LA, DeMeester TR, Wu WC. Normal 24-hr ambulatory esophageal pH values. Influence of study center, pH electrode, age, and gender. Dig Dis Sci 1992; 37(6):849-856.

(38) Fass R. Erosive esophagitis and nonerosive reflux disease (NERD): comparison of epidemiologic, physiologic, and therapeutic characteristics. J Clin Gastroenterol 2007; 41(2):131-137.

(39) Isolauri J, Luostarinen M, Isolauri E, Reinikainen P, Viljakka M, Keyrilainen O. Natural course of gastroesophageal reflux disease: 17-22 year follow-up of 60 patients. Am J Gastroenterol 1997; 92(1):37-41.

(40) Kuster E, Ros E, Toledo-Pimentel V, Pujol A, Bordas JM, Grande L et al. Predictive factors of the long term outcome in gastro-oesophageal reflux disease: six year follow up of 107 patients. Gut 1994; 35(1):8-14.

(41) Martinez SD, Malagon IB, Garewal HS, Cui H, Fass R. Non-erosive reflux disease (NERD)--acid reflux and symptom patterns. Aliment Pharmacol Ther 2003; 17(4):537-545.

(42) Martinek J, Benes M, Hucl T, Drastich P, Stirand P, Spicak J. Non-erosive and erosive gastroesophageal reflux diseases: No difference with regard to reflux pattern and motility abnormalities. Scand J Gastroenterol 2008; 43(7):794-800.

(43) Shapiro M, Green C, Faybush EM, Esquivel RF, Fass R. The extent of oesophageal acid exposure overlap among the different gastro-oesophageal reflux disease groups. Aliment Pharmacol Ther 2006; 23(2):321-329.

(44) Dickman R, Bautista JM, Wong WM, Bhatt R, Beeler JN, Malagon I et al. Comparison of esophageal acid exposure distribution along the esophagus among the different gastroesophageal reflux disease (GERD) groups. Am J Gastroenterol 2006; 101(11):2463-2469.

(45) Breumelhof R, Smout AJ, Schyns MW, Bronzwaer PW, Akkermans LM, Jansen A. Prospective evaluation of the effects of Nissen fundoplication on gastroesophageal reflux. Surg Gynecol Obstet 1990; 171(2):115-119.

(46) Luostarinen M. Nissen fundoplication for reflux esophagitis. Long-term clinical and endoscopic results in 109 of 127 consecutive patients. Ann Surg 1993; 217(4):329-337.

(47) O'Hanrahan T, Marples M, Bancewicz J. Recurrent reflux and wrap disruption after Nissen fundoplication: detection, incidence and timing. Br J Surg 1990; 77(5):545-547.

(48) Salminen PT, Hiekkanen HI, Rantala AP, Ovaska JT. Comparison of long-term outcome of laparoscopic and conventional nissen fundoplication: a prospective randomized study with an 11-year follow-up. Ann Surg 2007; 246(2):201-206.

(49) Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. Ten-year outcome of laparoscopic and conventional Nissen fundoplication: randomized clinical trial. Ann Surg 2009; 249(12): in press.

(50) Draaisma WA, Rijnhart-de Jong HG, Broeders IA, Smout AJ, Furnee EJ, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. Ann Surg 2006; 244(1):34-41.

(51) Jenkinson AD, Kadirkamanathan SS, Scott SM, Yazaki E, Evans DF. Relationship between symptom response and oesophageal acid exposure after medical and surgical treatment for gastro-oesophageal reflux disease. Br J Surg 2004; 91(11):1460-1465.

(52) Lord RV, Kaminski A, Oberg S, Bowrey DJ, Hagen JA, DeMeester SR et al. Absence of gastroesophageal reflux disease in a majority of patients taking acid suppression medications after Nissen fundoplication. J Gastrointest Surg 2002; 6(1):3-9.

(53) Catarci M, Gentileschi P, Papi C, Carrara A, Marrese R, Gaspari AL et al. Evidence-based appraisal of antireflux fundoplication. Ann Surg 2004; 239(3):325-337.

6

Predictors of objectively identified recurrent reflux after primary Nissen fundoplication

J.A.J.L. Broeders[1]
D.J.G.H. Roks[1]
W.A. Draaisma[1]
A.L.M. Vlek[2]
E.J. Hazebroek[1]
I.A.J.M. Broeders[3]
A.J.P.M. Smout[4]

[1]Dep. of Surgery, University Medical Center Utrecht
[2]Julius Center Health Sciences & Primary Care, University Medical Center Utrecht
[3]Dep. of Surgery, Meander Medical Center, Amersfoort
[4]Dep. of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam

17th annual United European Gastroenterology Week
London, United Kingdom, November 2009
12th world congress of the International Society for Diseases of the Esophagus
Kagoshima, Japan, September 2010

British Journal of Surgery 2011; in press.

Abstract

Background: Laparoscopic Nissen fundoplication is the most frequently performed operation for gastro-oesophageal reflux disease (GORD). Studies on predictors of subjective outcome of fundoplication have yielded inconsistent results. This study identified predictors of objective reflux control after Nissen fundoplication.

Methods: This was a retrospective analysis of prospectively collected data from patients who underwent Nissen fundoplication for proton pump inhibitor refractory GORD with pathological acid exposure in a single centre between 1997 and 2005. The predictive value of demographics, endoscopic hiatal hernia size, oesophagitis, lower oesophageal sphincter pressure, distal oesophageal contraction amplitude, percentage of peristaltic contractions and acid exposure was determined. Endpoints were recurrent pathological acid exposure on 24-h pH monitoring at 6 months and surgical reintervention for recurrent GORD up to 6 years.

Results: Of 177 patients, 22 had recurrent pathological acid exposure at 6 months for which 11 had surgery within 6 years. Only low percentage of peristaltic contractions (odds ratio (OR) 0.97, 95 per cent confidence interval 0.95 to 0.99; $P = 0.004$) and high supine acid exposure (OR 1.03, 1.00 to 1.07; $P = 0.025$) were independent predictors of recurrent pathological acid exposure. The absolute risk of recurrent exposure was 45.5 per cent in patients with both predictors. High supine acid exposure was also an independent predictor of surgical reintervention (OR 1.05, 1.01 to 1.08; $P = 0.006$).

Conclusion: Nissen fundoplication should not necessarily be withheld from patients with poor oesophageal peristalsis or excessive supine acid exposure As about half of patients with both variables experience recurrent pathological acid exposure after primary Nissen fundoplication, surgery should be restricted in this group.

Introduction

Gastro-oesophageal reflux disease (GORD) is the most common upper gastrointestinal tract disorder in the Western world[1]. GORD that is refractory to proton pump inhibitor (PPI) therapy in patients with pathological acid exposure on 24-h pH monitoring is a well accepted indication for antireflux surgery. Laparoscopic Nissen fundoplication is the most frequently performed surgical procedure for GORD[2]. Several studies have attempted to identify predictors of outcome after fundoplication. In 2009 a systematic review found that the quality and consistency of data are mixed, and as a result studies report no or disparate predictive values[3]. The authors concluded that the strength of the associations remains uncertain and that their role in guiding treatment decisions in individual patients requires further clarification[3].

The studies included in the review[3] and subsequently published studies[4–10] that investigated the association between patient characteristics and outcome of primary antireflux surgery all used subjective outcome as endpoint. A predictive model based on objective outcome is expected to yield more consistent results. A prognostic model for the assessment of objective outcome after redo antireflux surgery has been pubished[11].

The aim of the present study was to evaluate preoperative predictors of objective reflux control after primary Nissen fundoplication by analysing the predictive value of pathophysiological parameters for recurrent pathological acid exposure and long-term surgical reintervention for recurrent GORD. The present study design followed the methodological recommendations made in the review: a larger sample size, consistent definitions of preoperative patient characteristics, standardized preoperative investigations and surgical techniques ,and full reporting of clinically important outcomes using validated instruments[3].

Methods

This study was a retrospective analysis of the data from three prospective cohorts of patients who underwent primary Nissen fundoplication for GORD refractory to PPI therapy with pathological acid exposure at a single centre. These patients completed preoperative and postoperative investigations as part of a multicentre randomized controlled trial (RCT)[12], a single-centre RCT[13] and a prospective multicentre cohort study[14] carried out between 1997 and 2005. PPI refractory GORD was defined as heartburn and regurgitation persisting over 6 months despite double-dose PPI use (more than 40 mg omeprazole in 24 h or comparable therapy), with pathological oesophageal acid exposure time registered during 24-h pH monitoring. Demographics (age, sex and body mass index) were recorded

before surgery and collected prospectively in consecutive patients. All patients, both symptomatic and asymptomatic, were asked to undergo upper gastrointestinal endoscopy, oesophageal manometry and 24-h pH-metry before and 6 months after surgery. Patients were followed prospectively for 6 years.

Surgical procedures

All operations were performed between January 1997 and October 2005. Surgical techniques were standardized, and included ligation and division of the short gastric vessels, mobilization of the distal oesophagus, posterior crural repair and construction of a floppy 360° Nissen fundoplication of 2.5–3.0 cm. All surgeons had gone through the learning curve for laparoscopic Nissen fundoplication , as defined by Watson and colleagues[15]: more than five fundoplications by an experienced laparoscopic surgeon and over 20 procedures by a less experienced laparoscopic surgeon.

Upper gastrointestinal endoscopy

The presence of oesophagitis and hiatal hernia size were determined endoscopically. Oesophagitis grading was initially performed according to the Savary–Miller classification[16]. From 1999 onwards, oesophagitis was graded according to the Los Angeles classification[17].

Oesophageal manometry

Manometric studies were undertaken before and 6 months after operation. Patients ceased taking any medication that could affect oesophageal motility 7 days beforehand. A water-perfused system with a multiple-lumen catheter and an incorporated sleeve sensor was used (Dentsleeve Pty, Adelaide, Australia). After transnasal introduction, the catheter was retracted to determine the distal border of the lower oesophageal sphincter (LOS). The sleeve sensor was positioned at the level of the LOS, and intraluminal oesophageal pressures were recorded at 5, 10 and 15 cm above the proximal margin. Thereafter, the manometric response to ten standardized wet swallows was studied (5-ml water bolus). The gastric baseline pressure was registered 2 cm below the distal margin of the sleeve sensor and served as the zero reference point. Mean end-expiratory LOS pressure, mean peak contraction amplitude in the distal part of the oesophagus and the percentage of peristaltic wave contractions in the body of the oesophagus were measured.

The distal amplitude was defined as the average amplitude of two recording sites positioned at 3 and 8 cm above the LOS[18,19]. A peristaltic contraction was defined as a wet swallow followed by a peristaltic wave that was transmitted to the distal oesophagus and resulted in a distal amplitude higher than 30 mmHg[18,19]. A

simultaneous contraction was defined as a wet swallow that was followed by a pressure with an upstroke that occurred simultaneously at 3 and 8 cm above the LOS. The upstroke was considered to be simultaneous if the calculated propagation velocity exceeded 8 cm/s.

Ambulatory 24-h pH monitoring

Ambulatory pH monitoring studies were performed before and 6 months after fundoplication.. Medication that could affect the results was stopped 7 days before testing. A catheter with a pH glass electrode (model LOT440; Medical Instruments Corporation, Solothurn, Switzerland) was positioned 5 cm above the manometrically determined upper border of the LOS after transnasal introduction. A digital data logger (Medical Measurements Systems (MMS), Enschede, The Netherlands) stored the 24-h pH recordings, and patients registered body position and reflux symptoms in a diary. Patients were instructed to press a button on the digital data logger when they experienced a symptom. The recordings were analysed automatically using dedicated software (MMS).

Classification into pathological or physiological oesophageal acid exposure was based on the percentage of time with pH below 4. The upper limit for physiological oesophageal acid exposure in upright and supine body position was two standard deviations above the mean value obtained in healthy volunteers during ambulatory 24-h pH monitoring[20,21]. Pathological acid exposure time was defined as an acid exposure time of at least 8.2 per cent in the upright body position, or an acid exposure time of at least 3.5 per cent in the supine position, or a total time with pH below 4 of at least 5.8 per cent.

Surgical reintervention

Surgical reinterventions, time to reoperation and indication for reintervention were registered for up to 6 years after primary surgery.

Study endpoints

The primary endpoint was recurrent pathological acid exposure on 24-h pH monitoring. The secondary endpoint was surgical reintervention for recurrent GORD in the first 6 years after primary surgery. The value of the following variables in predicting these outcomes was determined: demographics, endoscopic hiatal hernia size, oesophagitis, manometric LOS pressure, distal oesophageal contraction amplitude, percentage of peristaltic contractions and acid exposure.

Statistical analysis

Statistical analysis was performed separately for the primary and secondary endpoints. Continuous variables were expressed as median (interquartile range). For univariable analysis, the significance of all continuous and categorical variables was tested separately by binary logistic regression analysis. Variables with $P < 0.200$ in univariable analysis were entered into a multivariable binary logistic regression model, using backward stepwise selection of variables. Variables with $P < 0.100$ were considered to be significant predictors of outcome. Odds ratios (ORs) were presented with 95 per cent confidence intervals. ORs per unit were reported for continuous variables. In an additional analysis independent predictors were dichotomized at clinically relevant cut-off values. SPSS® version 15.0 was used for statistical analysis (SPSS, Chicago, Illinois, USA).

Results

In the study period 177 patients underwent Nissen fundoplication and met the inclusion criteria of pathological oesophageal acid exposure before surgery and ambulatory 24-hour pH monitoring at 6 months' follow-up.

Recurrent pathological acid exposure

Pathological oesophageal acid exposure persisted or recurred in 22 patients, whereas oesophageal acid exposure normalized to physiological values in the remaining 155. Patient characteristics, hiatal hernia size, presence of oesophagitis and LOS pressure were similar in the two groups, and had no predictive value in univariable analysis (*Table 1*). Patients who developed recurrent pathological oesophageal acid exposure after Nissen fundoplication had significantly reduced oesophageal peristalsis before surgery compared with those who did not. They also had greater supine acid exposure before surgery. There were no significant differences in oesophagitis grade and upright and total acid exposure between the two groups.

Four preoperative variables were entered into the multivariable model: percentage of peristaltic contractions, distal oesophageal contraction amplitude, supine acid exposure and total acid exposure. Multivariable regression analysis demonstrated that the percentage of peristaltic contractions (OR per cent 0.97, 0.95 to 0.99; $P = 0.004$; regression coefficient = –0.030) and supine acid exposure (OR per cent 1.03, 1.00 to 1.07); $P = 0.025$; regression coefficient = 0.034) were independent predictors of recurrent reflux.

The independent predictors from the multivariable model were dichotomized using clinically relevant cut-off values. Normal oesophageal peristalsis was defined as at

Table 1 Univariable analysis of recurrent pathological acid exposure

	Reflux (n = 22)*	No reflux (n = 155)*	Odds ratio†
Demographics			
Age (years)‡	45.8 (36.0–54.6)	42.9 (33.1–52.8)	1.01 (0.98, 1.04)
Sex (M)	15 (68)	95 (61.3)	1.35 (0.52, 3.51)
Body mass index (kg/m^2)‡	26.3 (23.4–28.0)	26.1 (24.0–29.7)	0.92 (0.81, 1.04)
Upper gastrointestinal endoscopy			
Hiatal hernia size (cm)‡	3.5 (2.5–5.3)	3.0 (2.0–4.0)	1.19 (0.92, 1.55)
Oesophagitis	12 of 22 (55)	82 of 142 (57.7)	1.14 (0.46, 2.81)
Mean LOS pressure (kPa)‡	0.7 (0.4–1.3)	1.0 (0.6–1.7)	0.76 (0.45, 1.29)
Oesophageal peristalsis‡			
Peristaltic contractions (%)	90 (58–100)	100 (90–100)	0.97 (0.95, 0.99)
Distal contraction amplitude (kPa)	6.0 (3.6–7.6)	8.1 (5.8–12.2)	0.83 (0.72, 0.96)
Oesophageal acid exposure (% time)‡			
Upright	11.3 (9.1–20.6)	12.9 (8.9–19.4)	1.01 (0.96, 1.06)
Supine	17.3 (8.0–23.9)	4.8 (0.9–14.9)	1.04 (1.01, 1.07)
Total	15.2 (9.6–23.3)	11.1 (7.5–16.1)	1.05 (1.00, 1.10)

Values in parentheses are * percentages and † 95 per cent confidence intervals unless indicated otherwise; ‡ group values are median (interquartile range), with odds ratios per unit. LOS, lower oesophageal sphincter.

Table 2 Univariable analysis of long-term surgical reintervention for recurrent gastro-oesophageal reflux disease

	Surgical reintervention (n = 11)*	No surgical reintervention (n =166)*	Odds ratio†
Demographics			
Age (years)‡	44.4 (33.6–56.0)	43.0 (33.1–53.0)	1.01 (0.96,1.06)
Sex (M)	8 (73)	102 (61.4)	1.67 (0.43, 6.54)
Body mass index (kg/m^2)‡	26.0 (25.0–28.0)	26.1 (23.9–29.4)	0.96 (0.81,1.13)
Upper gastrointestinal endoscopy			
Hiatal hernia size (cm)‡	3.5 (1.8–5.0)	3.0 (2.0–5.0)	0.96 (0.69, 1.32)
Oesophagitis	6 of 11 (55)	88 of 153 (57.5)	1.13 (0.33, 3.86)
Mean LOS pressure (kPa)‡	0.6 (0.4–1.4)	1.0 (0.6–1.7)	0.58 (0.24,1.39)
Oesophageal peristalsis‡			
Peristaltic contractions (%)	90 (80–100)	100 (90–100)	0.99 (0.96, 1.02)
Distal contraction amplitude (kPa)	7.1 (5.3–10.6)	7.6 (5.6–12.0)	0.99 (0.85,1.14)
Oesophageal acid exposure (% time)‡			
Upright	13.7 (8.6–20.7)	12.8 (8.9–19.4)	0.99 (0.92, 1.06)
Supine	22.2 (3.2–46.1)	5.7 (1.1–15.3)	1.05 (1.01,1.08)
Total	19.7 (7.3–24.0)	11.4 (7.6–16.1)	1.05 (0.99,1.10)

Values in parentheses are * percentages and † 95 per cent confidence intervals unless indicated otherwise; ‡ group values are median (interquartile range), with odds ratios per unit. LOS, lower oesophageal sphincter.

least 70 per cent peristaltic contractions, according to the most widely used classification for oesophageal motility[18,19]. Excessive supine acid exposure was defined as at least 8 per cent of the time, as this cut-off resulted in superior prediction of endpoints. Based on this cut-off value, 79 (44.6 per cent) of 177 patients were classified as having excessive supine acid exposure before surgery. Multivariable regression analysis demonstrated that poor oesophageal peristalsis (OR 3.77, 1.12 to 11.96; *P* = 0.024; regression coefficient = 1.327) and excessive supine acid exposure (OR 4.56, 1.57 to 13.30; *P* = 0.005; regression coefficient = 1.518) were independent predictors of recurrent reflux.

The absolute risk of recurrent pathological acid exposure was 4.5 per cent in patients with no excessive supine acid exposure and with normal oesophageal peristalsis. This risk increased to 12.5 per cent in patients with poor oesophageal peristalsis and to 16.9 per cent in patients with excessive supine acid exposure. This risk was as high as 45.5 per cent in patients with both poor oesophageal peristalsis and excessive supine acid exposure.

Long-term surgical reintervention for recurrent gastro-oesophageal reflux disease

The reflux symptoms of 11 of the 22 patients with recurrent pathological acid exposure were well controlled with PPI therapy. The remaining 11 patients underwent reoperation for recurrent PPI refractory reflux symptoms, with pathological acid exposure on 24-h pH monitoring. Another eight surgical reinterventions were performed for persisting dysphagia, two for intrathoracic herniation of the wrap and one for an incisional hernia. Median follow-up was 72 (72–72) months and median time to reintervention 15 (6–22) months.

The 11 patients who underwent surgical reintervention for recurrent GORD were compared with 166 who did not (*Table 2*). Patients who underwent reoperation for recurrent reflux disease alone had significantly greater postoperative supine acid exposure than those who did not require further surgery, but were comparable with respect to all other variables evaluated. Supine acid exposure was also the only independent predictor in multivariable regression analysis (OR per cent 1.05; 1.01 to 1.08; *P* = 0.006, regression coefficient 0.046).

Supine acid exposure was dichotomized at an 8 per cent cut-off for this endpoint as well. Univariable regression analysis demonstrated that excessive supine acid exposure was non-significantly associated with surgical reintervention for recurrent GORD (OR 3.57; 0.91 to 13.93; *P* = 0.067, regression coefficient 1.272). The absolute risk of reoperation for recurrent GORD was 10.1 per cent in patients with excessive supine acid exposure compared with 3.1 per cent in patients without.

Discussion

The search for predictors of objective outcome is legitimate as more than 8 per cent of patients suffer from objectively identified recurrent pathological acid exposure at 5 years after Nissen fundoplication[22]. In the present study, the rate of recurrent pathological acid exposure after Nissen fundoplication was 12.4 per cent, with a surgical reintervention rate for pathological acid exposure of 6.2 per cent up to 6 years after operation. Considering the extended length of follow-up, these results are largely in line with a recent meta-analysis of RCTs in which 16.5 per cent of the patients developed recurrent reflux disease and 9.6 per cent needed surgical reintervention at a mean follow-up of 2.5 years after fundoplication[23].

The present study evaluated predictors of objective reflux control after primary Nissen fundoplication and long-term reoperation for recurrent GORD. Poor preoperative oesophageal peristalsis and excessive supine acid exposure predicted objective reflux control after primary Nissen fundoplication. The presence of both variables before surgery was highly predictive of treatment failure with respect to recurrent pathological acid exposure. Patients with both factors present had a ten times higher risk of recurrence than those without. Demographics, hiatal hernia size, presence of oesophagitis and LOS pressure did not predict outcome after antireflux surgery. The majority of studies in a recently published systematic review confirmed that age, sex and body mass index do not predict outcome after fundoplication[3]. One subsequent study reported age as a weak predictor[8], whereas four studies did not[4–7]. A relationship between sex and outcome was reported by two studies[4,8], but not by two others[6,7]. In contrast to a previous report[24], hiatal hernia size had no predictive value in the present study. The systematic review[3] did not address the impact of hiatal hernia size, but more recent studies did not find a relationship with outcome[6, 8,10]. The presence of oesophagitis had no predictive value in the present series, in line with 11 of 12 reviewed studies[3] and a later report[8].

Confirming the findings of eight of nine reviewed studies[3] as well as three other articles[6,10,19], no significant impact of LOS characteristics on outcome after fundoplication was found here. In contrast, oesophageal peristalsis predicted outcome after Nissen fundoplication; both the percentage of peristaltic contractions and the distal contraction amplitude were negative predictors of recurrent pathological reflux. The first was also an independent predictor of recurrent pathological acid exposure. Previous studies have demonstrated that poor oesophageal peristalsis leads to greater, particularly supine, oesophageal exposure as a result of poorer oesophageal clearance[25–31]. Reduced oesophageal clearance of gastric contents owing to poor oesophageal peristalsis probably

explains the higher rate of recurrent pathological acid exposure. In contrast, the majority of reviewed articles[3] and a recent study[9] found that oesophageal dysmotility had no impact on outcome after fundoplication. However, most of these studies used dysphagia as endpoint, whereas the present study focused on recurrent reflux. Several RCTs have demonstrated that the construction of a total fundoplication is not associated with a higher dysphagia rate in patients with oesophageal motility disorders[32–34]. Other recent studies that focused on predictors of recurrent GORD support the present findings, also reporting that poor oesophageal peristalsis increased the risk of recurrent reflux symptoms[7,8].

Supine and total oesophageal acid exposure times during 24-h pH monitoring are positive predictors of recurrent pathological acid exposure. Previous studies have evaluated only differences in the outcome of fundoplication in patients with pathological acid exposure *versus* those with physiological acid exposure before surgery. Their findings remain inconclusive as three studies reported better, two studies worse and four studies similar outcomes after fundoplication in the patients with pathological acid exposure[3]. In contrast, the present study included only patients with pathological acid exposure before surgery and evaluated acid exposure as a continuous variable. Three studies have previously evaluated the predictive value of excessive acid exposure. Two confirmed the present results, reporting that a DeMeester score of at least 50 increased the risk of recurrence of symptoms[7,35], whereas one study did not[8]. In the present study acid exposure time in the upright body position had no predictive value. In contrast, excessive supine acid exposure was an independent predictor of recurrent pathological reflux and repeat antireflux surgery for GORD. However, these patients should not be denied antireflux surgery as they are likely to gain the most from it.

The present results support the view that objective reflux control after primary Nissen fundoplication is not predicted by preoperative patient characteristics, hiatal hernia size, presence of oesophagitis and LOS pressure. Patients with good oesophageal peristalsis or low supine acid exposure before antireflux surgery have a lower risk of recurrent pathological acid exposure. Nissen fundoplication should not necessarily be withheld from patients with poor oesophageal peristalsis or excessive supine acid exposure As about half of patients with both variables experience recurrent pathological acid exposure after primary Nissen fundoplication, surgery should be restricted in this group. Careful counselling is necessary and can be optimized based on the present results, by providing patients with differentiated information on individual risk of recurrence and reoperation for reflux.

Commentary

Despite very high early success rates after Nissen fundoplication, it is inevitable that a small percentage of patients will develop recurrent reflux in the medium to long term, with a number requiring reoperation at some stage. Most studies show the recurrent reflux rate to be somewhere between 8 and 16·5 per cent; this study is no exception with recurrent reflux in 12·4 per cent of patients and repeat surgery for recurrent reflux in 6·2 per cent. An accurate means of predicting which patients may have a less successful outcome after surgery would therefore be welcome. Several studies have addressed this issue but no clear results are evident. This paper specifically addresses this problem.

It is a retrospective analysis, with all the weaknesses that brings, but the patient numbers are good and the analysis rigorous. Furthermore, as the authors point out, most previous studies have used dysphagia as the endpoint, whereas this one focuses on recurrent reflux and the need for subsequent reoperation. As such, it highlights different factors and produces potentially clinically useful results.

It appears that preoperative dysmotility and high supine acid exposure are independent risk factors, which individually lead to moderately worse surgical outcomes but not to the extent that surgery should be withheld. However, when both of these factors are present, the outcome is significantly worse (45·5 per cent recurrent reflux in this study), suggesting that surgery should be avoided in this situation.

If the results of this study can be reproduced, the findings would be of great clinical significance and could potentially be employed to reduce the incidence of poor surgical outcomes following Nissen fundoplication.

R. Ackroyd

Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

References

(1) Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005; **54**: 710–717.

(2) Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. Ten-year outcome of laparoscopic and conventional Nissen fundoplication: Randomized clinical trial. *Ann Surg* 2009; **250**: 698–706.

(3) Ip S, Tatsioni A, Conant A, Karagozian R, Fu L, Chew P *et al*. Predictors of clinical outcomes following fundoplication for gastroesophageal reflux disease remain insufficiently defined: a systematic review. *Am J Gastroenterol* 2009; **104**: 752–758.

(4) Beck PE, Watson DI, Devitt PG, Game PA, Jamieson GG. Impact of gender and age on the long-term outcome of laparoscopic fundoplication. *World J Surg* 2009; **33**: 2620–2626.

(5) Pizza F, Rossetti G, Limongelli P, Del Genio G, Maffettone V, Napolitano V *et al*. Influence of age on outcome of total laparoscopic fundoplication for gastroesophageal reflux disease. *World J Gastroenterol* 2007; **13**: 740–747.

(6) Morgenthal CB, Lin E, Shane MD, Hunter JG, Smith CD. Who will fail laparoscopic Nissen fundoplication? Preoperative prediction of long-term outcomes. *Surg Endosc* 2007; **21**: 1978–1984.

(7) Hafez J, Wrba F, Lenglinger J, Miholic J Fundoplication for gastroesophageal reflux and factors associated with the outcome 6 to 10 years after the operation: multivariate analysis of prognostic factors using the propensity score. *Surg Endosc* 2008; **22**: 1763–1768.

(8) Oelschlager BK, Quiroga E, Parra JD, Cahill M, Polissar N, Pellegrini CA. Long-term outcomes after laparoscopic antireflux surgery. *Am J Gastroenterol* 2008; **103**: 280–287.

(9) Pizza F, Rossetti G, Del Genio G, Maffettone V, Brusciano L, Del Genio A. Influence of esophageal motility on the outcome of laparoscopic total fundoplication. *Dis Esophagus* 2008; **21**: 78–85.

(10) Riedl O, Gadenstätter M, Lechner W, Schwab G, Marker M, Ciovica R. Preoperative lower esophageal sphincter manometry data neither impact manifestations of GERD nor outcome after laparoscopic Nissen fundoplication. *J Gastrointest Surg* 2009; **13**: 1189–1197.

(11) Furnée EJ, Draaisma WA, Broeders IA, Smout AJ, Vlek AL, Gooszen HG. Predictors of symptomatic and objective outcomes after surgical reintervention for failed antireflux surgery. *Br J Surg* 2008; **95**: 1369–1374.

(12) Bais JE, Bartelsman JF, Bonjer HJ, Cuesta MA, Go PM, Klinkenberg-Knol EC *et al*. Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. *Lancet* 2000; **355**: 170–174.

(13) Draaisma WA, Ruurda JP, Scheffer RC, Simmermacher RK, Gooszen HG, Rijnhart-de Jong HG *et al*. Randomized clinical trial of standard laparoscopic *versus* robot-assisted laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease. *Br J Surg* 2006; **93**: 1351–1359.

(14) Draaisma WA, Buskens E, Bais JE, Simmermacher RK, Rijnhart-de Jong HG, Broeders IA *et al*. Randomized clinical trial and follow-up study of cost-effectiveness of laparoscopic *versus* conventional Nissen fundoplication. *Br J Surg* 2006; **93**: 690–697.

(15) Watson DI, Baigrie RJ, Jamieson GG. A learning curve for laparoscopic fundoplication. Definable, avoidable, or a waste of time? *Ann Surg* 1996; **224**: 198–203.

(16) Savary M, Miller G (eds.) *The Esophagus: Handbook and Atlas of Endoscopy.* Gassmann: Solothurn, 1978.

(17) Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP *et al*. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999; **45**: 172–180.

(18) Richter JE. Oesophageal motility disorders. *Lancet* 2001; **358**: 823–828.

(19) Spechler SJ, Castell DO. Classification of oesophageal motility abnormalities. *Gut* 2001; **49**: 145–151.

(20) Richter JE, Bradley LA, DeMeester TR, Wu WC. Normal 24-hr ambulatory esophageal pH values. influence of study center, pH electrode, age, and gender. *Dig Dis Sci* 1992; **37**: 849–856.

(21) Jamieson JR, Stein HJ, DeMeester TR, Bonavina L, Schwizer W, Hinder RA *et al*. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. *Am J Gastroenterol* 1992; **87**: 1102–1111.

(22) Draaisma WA, Rijnhart-de Jong HG, Broeders IA, Smout AJ, Furnee EJ, Gooszen HG Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. *Ann Surg* 2006; **244**: 34–41.

(23) Catarci M, Gentileschi P, Papi C, Carrara A, Marrese R, Gaspari AL *et al*. Evidence-based appraisal of antireflux fundoplication. *Ann Surg* 2004; **239**: 325–337.

(24) Power C, Maguire D, McAnena O. Factors contributing to failure of laparoscopic Nissen fundoplication and the predictive value of preoperative assessment. *Am J Surg* 2004; **187**: 457–463.

(25) Achem AC, Achem SR, Stark ME, DeVault KR. Failure of esophageal peristalsis in older patients: association with esophageal acid exposure. *Am J Gastroenterol*. 2003; **98**: 35–39.

(26) Lee J, Anggiansah A, Anggiansah R, Young A, Wong T, Fox M. Effects of age on the gastroesophageal junction, esophageal motility, and reflux disease. *Clin Gastroenterol Hepatol* 2007; **5**: 1392–1398.

(27) Fornari F, Blondeau K, Durand L, Rey E, Diaz-Rubio M, De Meyer A *et al*. Relevance of mild ineffective oesophageal motility (IOM) and potential pharmacological reversibility of severe IOM in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2007; **26**: 1345–1354.

(28) Bremner RM, DeMeester TR, Crookes PF, Costantini M, Hoeft SF, Peters JH *et al*. The effect of symptoms and nonspecific motility abnormalities on outcomes of surgical therapy for gastroesophageal reflux disease. *J Thorac Cardiovasc Surg* 1994; **107**: 1244–1249.

(29) Diener U, Patti MG, Molena D, Fisichella PM, Way LW Esophageal dysmotility and gastroesophageal reflux disease. *J Gastrointest Surg* 2001; **5**: 260–265.

(30) Leite LP, Johnston BT, Barrett J *et al*. Ineffective esophageal motility (IEM): the primary finding in patients with nonspecific esophageal motility disorder. *Dig Dis Sci* 1997; **42**: 1859–1865.

(31) Ho SC, Chang CS, Wu CY, Chen GH. Ineffective esophageal motility is a primary motility disorder in gastroesophageal reflux disease. *Dig Dis Sci* 2002; **47**: 652–656.

(32) Fibbe C, Layer P, Keller J, Strate U, Emmermann A, Zornig C. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized, clinical, and manometric study. *Gastroenterology* 2001; **121**: 5–14.

(33) Booth MI, Stratford J, Jones L, Dehn TC. Randomized clinical trial of laparoscopic total (Nissen) *versus* posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. *Br J Surg* 2008; **95**: 57–63.

(34) Chrysos E, Tsiaoussis J, Zoras OJ, Athanasakis E, Mantides A, Katsamouris A *et al*. Laparoscopic surgery for gastroesophageal reflux disease patients with impaired esophageal peristalsis: total or partial fundoplication? *J Am Coll Surg* 2003; **197**: 8–15.

(35) Horvath KD, Jobe BA, Herron DM, Swanstrom LL. Laparoscopic Toupet fundoplication is an inadequate procedure for patients with severe reflux disease. *J Gastrointest Surg* 1999; **3**: 583–591.

7

Impact of ineffective oesophageal motility and wrap type on dysphagia after laparoscopic fundoplication

J.A.J.L. Broeders
I.G. Sportel
G.G. Jamieson
R.S. Nijjar
N. Granchi
J. C. Myers
S. K. Thompson

Discipline of Surgery, Royal Adelaide Hospital, University of Adelaide, Australia

International Society for Diseases of the Esophagus Australasian Section
Hobart, Australia, February 2011

British Journal of Surgery 2011; in press.

Abstract

Introduction: Laparoscopic 360° fundoplication is the most common operation for gastro-oesophageal reflux disease, but is associated with postoperative dysphagia in some patients. Patients with ineffective oesophageal motility may have a higher risk of developing postoperative dysphagia, but this remains unclear.

Methods: From 1991 to 2010, 2040 patients underwent primary laparoscopic fundoplication for gastro-oesophageal reflux disease and met inclusion criteria: 90° (n=343), 180° (n=498), and 360° fundoplication (n=1199). Primary peristalsis and distal contraction amplitude during oesophageal manometry were determined for 1354 patients. Postoperative dysphagia scores [0-45] were recorded at three and 12 months, then annually. Oesophageal dilatations and/or reoperations for dysphagia were recorded.

Results: Preoperative oesophageal motility did not influence postoperative dysphagia scores, need for dilatation, and/or reoperation up to 6 years. Three-month dysphagia scores were lower after 90°(8.0±0.6;*P*<0.001) and 180°(9.8±0.5;*P*=0.003) compared with 360° fundoplication (11.9±0.4), but these differences diminished after 6 years of follow-up. Dilatations and reoperations for dysphagia were lower after 90° (2.6% and 0.6%, respectively) and 180° (4.4% and 1.0%, respectively), compared with 360° fundoplication (9.8%; *P*<0.001 and 6.8%; *P*<0.001, respectively).

Conclusion: Tailoring the degree of fundoplication according to preoperative oesophageal motility by standard manometric parameters has no long-term impact on postoperative dysphagia. There is however a proportionate increase in short-term dysphagia scores with increasing degree of wrap, and a corresponding proportionate increase in dilatations and reoperations for dysphagia. These differences in dysphagia scores diminish with time.

Introduction

Gastro-oesophageal reflux disease (GORD) is a common upper gastrointestinal disorder affecting 10-20% of the Western population on a weekly basis.[1] Accepted indications for antireflux surgery include persistent symptoms despite adequate medical therapy, complications of severe GORD and an unwillingness to take lifelong medication[2-4]. Laparoscopic 360° fundoplication is the most common operation for GORD, with similar reflux control and fewer incisional hernia corrections compared with open fundoplication[5]. A recent meta-analysis, however, indicated that 14% of patients suffer from dysphagia two years after laparoscopic 360° fundoplication[6]. Seven percent of these patients required endoscopic dilatation and 3% underwent surgical reintervention[7,8]. Many centres now advocate a partial fundoplication for some patients, particularly those with abnormal preoperative oesophageal manometry[9].

Ineffective oesophageal motility is often found in patients with GORD and may be an important factor in the pathogenesis of the disease, but whether cause or effect remains unclear. Definitions of ineffective oesophageal motility vary. Values ranging from 30 to 60 per cent abnormal swallows have been proposed [10-14]. It is often assumed that patients with ineffective motility prior to surgery are more likely to develop postoperative dysphagia[9;15-17], although two randomised controlled trials failed to demonstrate that outcome was worse in patients with ineffective motility, compared to those with normal oesophageal motility[18;19]. The conservative cut-off values for ineffective motility of both trials have been criticised and could explain why no differences were found[20-22]. In addition, the studies had relatively small sample sizes and short follow-up times, so may not have been sufficiently powered to detect subtle differences in dysphagia scores. These studies also lacked objective assessments for severe dysphagia such as endoscopic dilatation and revisional surgery.

The aim of this large long-term cohort study was to determine the impact of preoperative ineffective oesophageal motility assessed by conventional manometry on the incidence of dysphagia after fundoplication. A secondary aim was to determine the influence of fundal wrap type on postoperative dysphagia. A large prospective cohort of patients with long-term follow-up after 90°, 180°, and 360° fundoplications was evaluated. Validated dysphagia scores, dilatations and surgical reinterventions for dysphagia were analysed to answer the question of whether a threshold for preoperative ineffective oesophageal motility exists above which a partial fundoplication should be considered.

Methods

Study design and participants

Since the introduction of minimally invasive antireflux surgery in 1991, patients who underwent primary laparoscopic fundoplication in the Royal Adelaide Hospital, Flinders Medical Centre, and various private hospitals in Adelaide have been entered into a prospective database. This database was designed to record preoperative work-up, perioperative characteristics and annual follow-up of patients who participated in five randomised controlled trials[23-27] plus those who underwent primary laparoscopic fundoplication (outside the trials) during the same time period. Data were recorded on the password-protected database with de-identification prior to analysis, complying with institutional research ethics guidelines.

Adults with objective evidence of GORD with either an abnormal 24-hour pH study (oesophageal pH <4 for more than 4% of time) or oesophagitis on upper endoscopy (minimum Savary-Miller grade Ia) were included[28]. Patients who underwent a partial 270° fundoplication for GORD were excluded due to small numbers in this group. Other exclusion criteria included nutcracker oesophagus (mean distal oesophageal peristaltic wave amplitude > 180 mm Hg)[11]; achalasia (incomplete relaxation of the lower oesophageal sphincter (LOS) with nadir pressure >8 mm Hg above gastric pressure and aperistalsis of the body of the oesophagus)[11] and patients with a large hiatal hernia (intrathoracic herniation of more than 50% of the stomach).

The operative techniques for both partial and total laparoscopic fundoplications have been described elsewhere[29-31]. Short gastric vessels were not routinely divided and only taken if necessary to create a Nissen fundoplication without tension. Routine posterior hiatal repair was performed after 1995. A 90° anterior wrap was constructed in a similar manner to a 180° anterior wrap, except that it covered only 25% of the circumference of the intra-abdominal oesophagus. A 360° tension free fundoplication was usually performed over a 52 Fr bougie. Aside from trial patients, the type of wrap performed was influenced by surgeon preference.

Oesophageal manometry

A water perfused multi-lumen oesophageal motility catheter (Dentsleeve Pty. Ltd, Adelaide, Australia) was used to perform oesophageal manometry. The catheter was introduced transnasally and positioned for continuous measurement of LOS pressure. Studies were performed in three centres, and included at least one distal channel for gastric pressure and multiple oesophageal body channels. The manometric protocol included a 5-min rest period and a series of ten standardised 5-mL water swallows. Basal LOS pressure was sampled during the 5-min rest

period (mm Hg, referenced to basal intragastric pressure). Residual LOS pressure on water swallow induced sphincter relaxation was also recorded (mm Hg). Parameters for oesophageal function included mean distal peristaltic contraction amplitude (mm Hg) and successful peristalsis of water swallows, expressed as a percentage. For the primary analysis, data were categorised according to the Castell criteria for ineffective oesophageal motility. This classification system defines ineffective motility as at least 30% abnormal swallows. Castell criteria for an abnormal water swallow during manometry include: distal oesophageal peristaltic wave amplitude <30 mm Hg, simultaneous contractions with amplitudes <30 mm Hg, failed peristalsis in which the peristaltic wave does not traverse the entire length of the distal oesophagus or absent peristalsis.[10;11] A secondary analysis was performed based on the "new Castell criteria" for abnormal water swallows, where these criteria were met for at least 50% of swallows[13].

Clinical outcomes

An independent research nurse collected all preoperative data, perioperative details and follow-up questionnaire information. Follow-up consisted of postal questionnaire and telephone interview at three months and annually. The primary endpoint was the validated modified dysphagia score[24,32]. This score quantifies the ability to swallow nine food items with increasing viscosity and solidity, ranging from 0 to 45 (0=no dysphagia, 45=severe dysphagia). Secondary endpoints recorded were dilatation and surgical reintervention for dysphagia up to five years postoperatively. Dilatations for dysphagia were obtained from self-reporting on the postal questionnaire and subsequent case-note confirmation. Reoperations for reasons other than dysphagia were recorded and follow-up data after dilatations and re-operations were excluded from further analysis.

Statistical analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL). Continuous variables were expressed as mean ± standard error of the mean (SEM). Correlations between continuous variables that were not normally distributed were determined using Spearman correlations (Rs). Predictive value of preoperative manometry data was analysed using univariate binary logistic regression and reported as odds ratio (OR) per unit with 95% confidence intervals and Nagelkerke R^2 values. Differences in non-parametric data between groups were analysed using the Mann-Whitney U test and the chi-squared test was used for ordinal variables. Kaplan-Meier survival curves including log-rank tests were used to evaluate differences between groups regarding time to dilatation and time to reoperation. Subgroup analyses were performed for patients with randomly

allocated fundoplications[23;25;27] and for patients who underwent 360° fundoplication alone.

Results

Patient population

Eleven local upper gastrointestinal surgeons contributed all of their antireflux surgical patients to the database and an additional four upper gastrointestinal surgeons (based in other states in Australia) contributed a minimum of ten patients to the randomised trials. Although all surgeons were experienced in minimally invasive surgery, this study includes their learning curves. Some surgeons did express a preference for partial fundoplication where the patient was female, elderly, or had poor preoperative motility.

From October 1991 to April 2010, 2185 patients underwent primary fundoplication for GORD and were included in a prospective computerised database. Of these, 145 patients were excluded for various reasons (Figure 1). In total, 2040 patients were included and divided into three groups according to wrap type: 90° (n=343 [17%]), 180° (n=498 [24%]) and 360° (n=1199 [59%]) fundoplication**.** Three-hundred-and-sixty degree fundoplication has been performed since 1991, and 180° and 90° fundoplications were introduced in 1993 and 1997, respectively. The majority of patients in this study (77%) underwent their operation after 1997 so that the distribution of each wrap type, over time, was similar. Baseline characteristics and operative details are shown in Table 1 for the three groups.

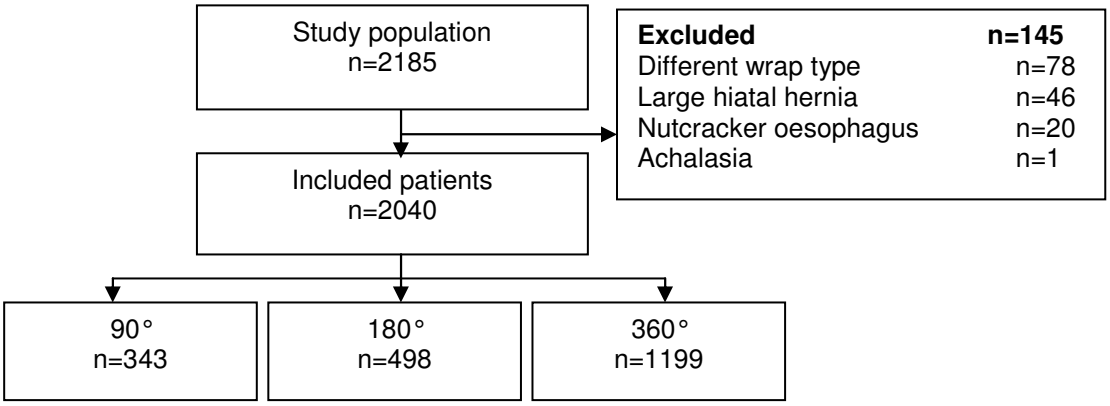
Mean age and percentage of female patients were higher in the 90° and 180° group, compared with the 360° group. Baseline characteristics for the subgroup of trial patients (n=287) were not different in the three groups. The number of patients with dysphagia scores recorded at 48 months (*n*=671) was significantly lower compared with 36 (*n*=1058) and 60 months (n=950), and therefore the 48-month data have not been reported in the subsequent analyses. Symptomatic follow-up beyond 72 months is not reported, since the number of patients was deemed too small to be representative. Symptomatic follow-up averaged 49.0 ± 0.55 months.

Table 1 Patient characteristics and operative details for laparoscopic fundoplication according to wrap type.

	90° (n=343)	180° (n=498)	360° (n=1199)
Age (range)	56.1 (19-94) ǂ	54.5 (18-95) ǂ	48.3 (18-91)
Male: Female	1:1.4 ǂ	1:1.2 ǂ	1:0.8
Body mass Index (kg/m^2) *	29.8±0.5	28.0±0.5	28.9±0.3
Hiatal repair	303/306 [99.0%]	485/495 [97.4%]	1003/1131 [88.7%]
Division short gastric vessels	6/213 [2.8%]	53/290 [18.3%]	157/996 [15.8%]
Use of bougie	52/343 [15.2%]	148/498 [29.7%]	1093/1199 [91.2%]

* Value given as mean ± SEM, ǂ P<0.001 vs. 360° fundoplication

Figure 1 Study profile



Predictive value of preoperative oesophageal manometry

Data were available for both preoperative manometry and clinical outcome in 1354 patients. There was no correlation between the preoperative percentage of successful primary peristaltic contractions and latest postoperative dysphagia scores (n=1354: Rs<0.001, P=0.657). There was a weak correlation between distal contraction amplitudes (n=1137: Rs=0.004, P=0.034) and latest postoperative dysphagia score. As expected there was a moderate correlation between preoperative percentage of peristaltic oesophageal contractions and distal contraction amplitudes (n=1363: Rs=0.133, P<0.001). Subgroup analysis of the trial patients and of the 360° fundoplication group yielded similar results.

Univariable binary logistic regression analysis demonstrated that the percentage of peristaltic contractions before surgery was a weak predictor of the need for endoscopic dilatation for dysphagia (OR per %: 1.009 [1.000-1.017], *P*=0.041, R^2=0.007) and did not predict reoperation for dysphagia (OR per %: 1.007 [0.996-1.017], *P*=0.201, R^2=0.004). Distal oesophageal contraction amplitude before surgery did not predict dilatation (OR per mm Hg: 1.000 [0.995-1.005], *P*=0.979, R^2=0.000) nor reoperation for dysphagia (OR per mm Hg: 0.999 [0.992-1.005], *P*=0.679, R^2=0.000). Subgroup analysis of the trial patients and of the 360° fundoplication group yielded similar results.

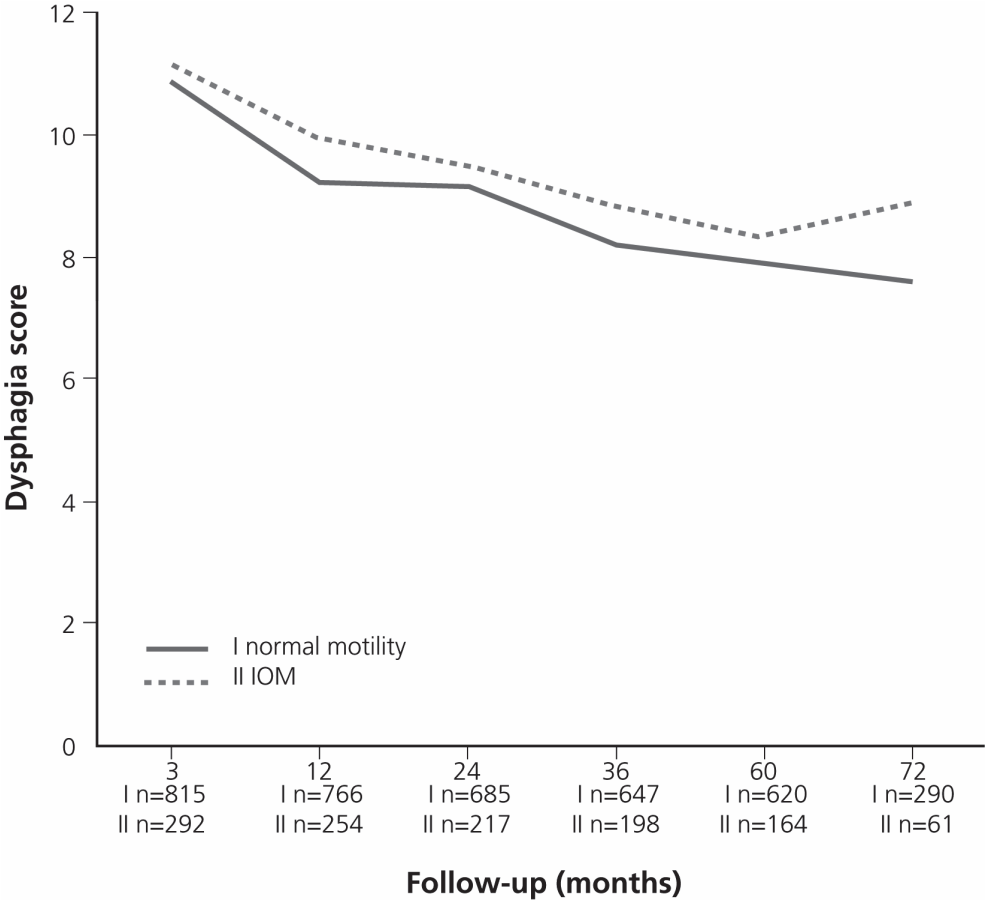
There was no significant association between preoperative standard motility parameters and postoperative dysphagia scores. The most appropriate cut-off value for ineffective motility with the highest predictive value for postoperative dysphagia could, therefore, not be determined. As a result patients were divided into two groups (normal motility, ineffective motility) using the percentage of peristaltic contractions according to the Castell classification system.[11]

Ineffective oesophageal motility and post-fundoplication dysphagia

Postoperative dysphagia scores were similar in patients with ineffective motility and normal motility (assessed preoperatively; Figure 2), with no significant differences at three months (11.1±0.7 vs. 10.9±0.4; *P*=0.943) and six years (8.9±1.2 vs. 7.6±0.5; *P*=0.315). The percentage of patients who underwent dilatation was similar in patients with ineffective motility and patients with normal motility (5.4% within 37.9±1.2 months vs. 8.2% within 40.6±0.7 months; *P*=0.066).

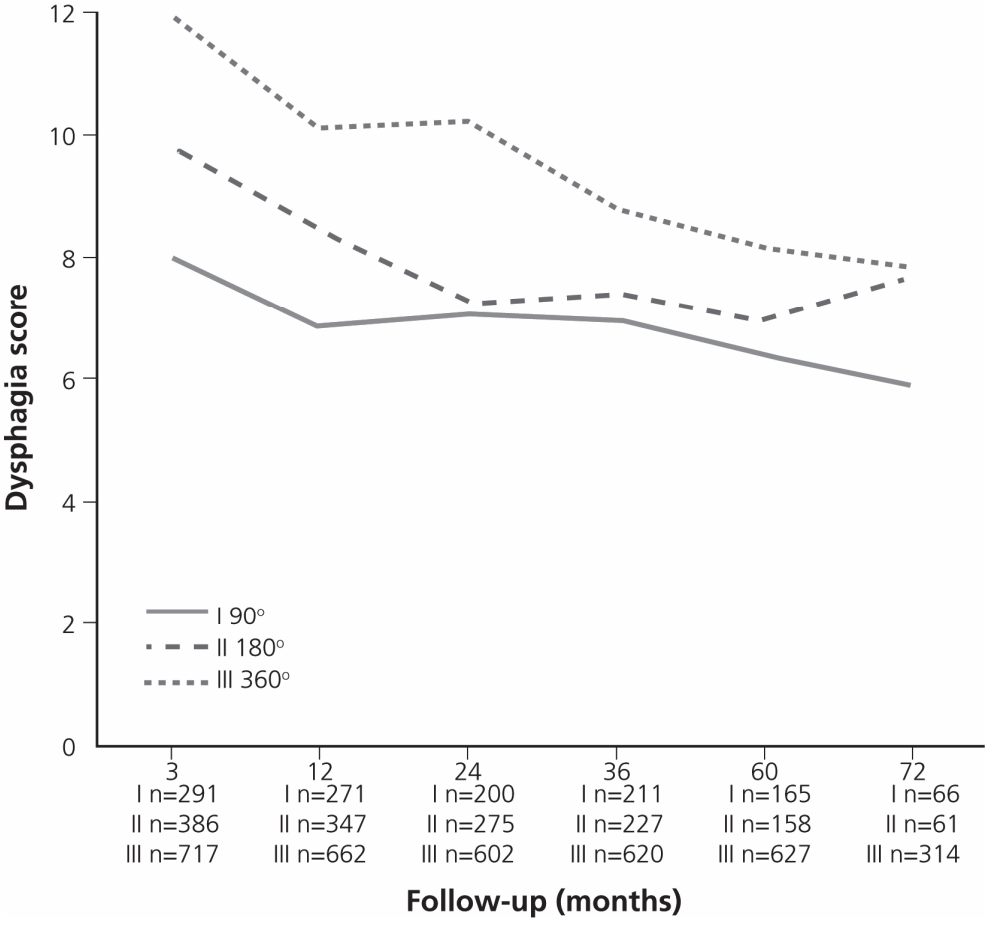
In addition, the percentage of patients who underwent reoperation for dysphagia was similar in patients with ineffective motility and patients with normal motility (3.1% within 37.9±1.2 months vs. 5.0% within 40.6±0.7 months; *P*=0.123). Subgroup analysis of the randomly allocated 360° fundoplication patients and the non-randomly allocated 360° fundoplication group yielded similar results. A secondary analysis based on the “new Castell criteria” yielded similar results.[13]

Figure 2 Postoperative dysphagia scores after laparoscopic fundoplication patients with normal preoperative oesophageal motility and ineffective oesophageal motility.



There were no significant differences at 3 months (P=0.943) and six years (P=0.315).

Figure 3 Postoperative dysphagia scores after laparoscopic fundoplication according to wrap type.



At 3 months, dysphagia scores were significantly lower after 90° compared with 360° fundoplication ($P<0.001$), and similarly, after 180° compared with 360° fundoplication ($P=0.003$). However, at 6 years, there were no significant differences between the different fundal wrap types.

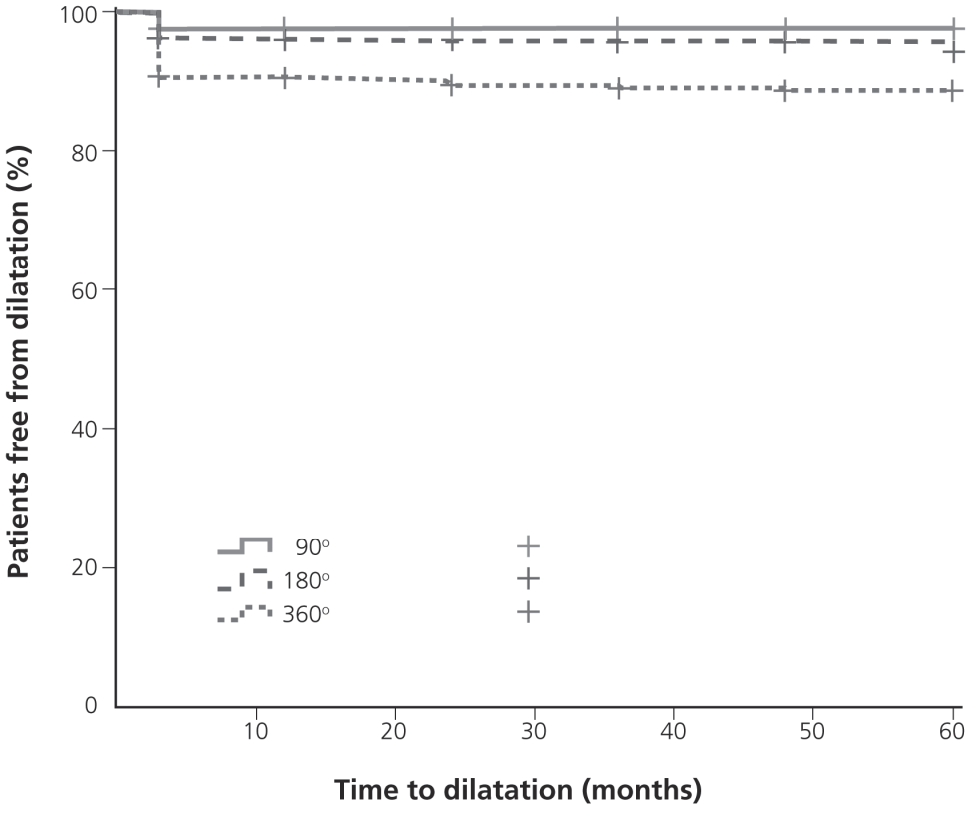
Wrap circumference and post-fundoplication dysphagia

There were no differences in primary and secondary outcomes between ineffective motility patients and patients with normal motility. Subsequent analyses compared the results of 90°, 180° and 360° fundoplication, irrespective of preoperative oesophageal motility. Postoperative dysphagia scores increased proportionately with increasing degree of wrap although this relationship weakened over time. At three months, dysphagia scores were lower after 90° (8.0±0.6; P<0.001 vs. 360°) and 180° fundoplication (9.8±0.5; P=0.003 vs.360°), compared with 360° fundoplication (11.9±0.4). However, dysphagia scores became similar over time and, at 6 years, there were no significant differences between 90° (5.9±1.1; P =0.068) and 180° (7.7±1.2; P =0.928), compared with 360° fundoplication (7.9±0.5: Figure 3).

Wrap circumference and dilatation or reoperation for dysphagia

The percentage of patients requiring postoperative dilatation for dysphagia increased proportionately with increasing degree of wrap (Figure 4). The incidence of dilatations was lower in the 90° (2.6% within 42.3±1.2 months, P<0.001 vs. 360°) and 180° group (4.4% within 33.6±1.1 months, P<0.001 vs. 360°), compared with the 360° group (9.8% within 40.4± 0.7 months). A total of 176 patients (8.6%) underwent surgical reintervention within 5 years of primary surgery. Eighty-nine (50.6%) of these reoperations were performed for dysphagia. The reoperation rate for dysphagia was lower after 90° (0.6% within 42.5±1.2 months, P<0.001 vs. 360°) and 180° fundoplication (1.0% within 33.8±1.1 months, P<0.001 vs. 360°), compared with 360° fundoplication (6.8% within 40.4±0.7 months; Figure 5). Forty reoperations were performed for recurrent reflux disease, with a higher rate after 90° (3.5%, P=0.002 vs. 360°) and 180° fundoplication (3.2%, P<0.001 vs. 360°), compared with 360° fundoplication (1.0%). There were no significant differences in 6-year dysphagia scores (9.8 (0.4) vs. 7.9 (0.9), P=0.116) or reoperations for dysphagia (7.5% vs. 5.5%, P=0.481) between patients who underwent 360° fundoplication with and without hiatal hernia repair. In contrast, the number of dilatations was higher in patients who underwent 360° fundoplication without hiatal hernia repair (9.7% vs. 15.6%, P=0.033).

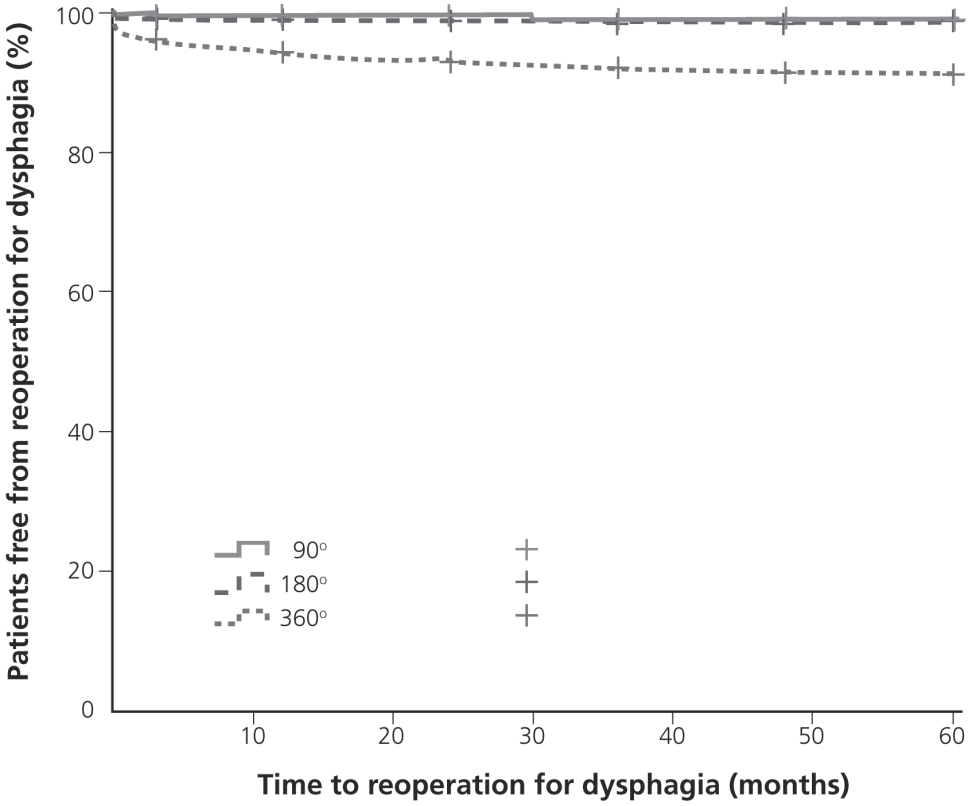
Figure 4 Time curve showing the percentage of patients free from dilatation after laparoscopic fundoplication according to wrap type.



Patients at risk	0	3	12	24	36	48	60
90°	343	324	303	275	239	206	183
180°	498	448	391	329	272	219	178
360°	1199	1062	927	862	790	741	688

The incidence of dilatations was lower in the 90° vs. 360° group (P<0.001), and in the 180° vs. 360° group (P<0.001).

Figure 5 Time curve showing the percentage of patients free from reoperation for dysphagia after laparoscopic fundoplication according to wrap type.



Patients at risk	0	3	12	24	36	48	60
90°	343	324	303	275	239	206	183
180°	498	448	391	329	272	219	178
360°	1199	1062	927	862	790	741	688

The reoperation rate for dysphagia was lower after 90° vs. 360° fundoplication (P<0.001), and after 180° vs. 360° fundoplication (P<0.001).

Discussion

This long-term cohort study demonstrates that preoperative oesophageal motility as assessed by standard manometric parameters does not predict postoperative dysphagia or reintervention for dysphagia after laparoscopic fundoplication. A threshold for ineffective oesophageal motility could not be identified above which a partial fundoplication should be considered.

Several studies have previously evaluated preoperative oesophageal motility and outcome after fundoplication. Subgroup analysis of two randomised trials failed to demonstrate that ineffective motility had an impact on outcome after fundoplication[18;19], although conservative cut-off values chosen for ineffective motility (mean distal amplitude < 40 mm Hg[19] and < 80% normal peristalsis[18]) have been suggested as reasons for the negative findings[20-22]. Short-term follow-up and limited sample size are other possible explanations. Three moderate sized comparative cohort studies[33-35] (n=761, n=420, n=617) have explored the relationship between motility and dysphagia and also found that preoperative oesophageal motility using standard manometric criteria cannot predict outcome after fundoplication. In contrast, three other studies[36,37;38] demonstrated that outcome after antireflux surgery is worse in ineffective motility patients. This discrepancy reflects different outcome measures as these three studies evaluated recurrent reflux.

A systematic review of studies that assessed the predictive value of ineffective oesophageal motility on outcome after fundoplication concluded that results between studies were inconsistent and recommended further studies with adequate sample size, improved methodological design, and validated outcome assessment[39]. The results of the current study meet all of these criteria because more than 2000 patients were evaluated prospectively using a validated score for dysphagia[32] and reintervention for dysphagia. The results demonstrate that postoperative dysphagia is similar in patients with normal motility and with ineffective motility, either after a partial or a total fundoplication. There is no evidence, therefore, for tailoring the wrap based on preoperative motility. This is in line with four randomised controlled trials that have demonstrated that the outcome of partial and total fundoplication is similar in patients with ineffective motility[18;19;40;41].

The second aim of the study was to assess the impact of wrap type on postoperative dysphagia. Patients with normal motility were pooled with patients with ineffective motility for this analysis, since this factor did not appear to influence outcome after fundoplication. Short-term dysphagia scores and reintervention rates for dysphagia were proportionately lower after 90° and 180° versus 360°

fundoplication. The mean dysphagia score was 8 after 90° fundoplication and 12 after 360° fundoplication. The clinical relevance of this short-term difference is illustrated by the fact that the dysphagia score is 9 points higher in patients who are able to eat an apple than in patiens who are able to eat a 40 gram steak as well. These results are supported by five randomised controlled trials, that showed that laparoscopic anterior fundoplication is associated with a significantly lower incidence of postoperative dysphagia[23;25;27;31;42]. Other trials have reported that dysphagia decreases during long-term follow[31;43-44]. The present study confirms this finding and demonstrates that proportionate differences in dysphagia scores between the different wrap types diminish over time. This decrease in dysphagia scores over time was not the result of dilatations nor reoperations for dysphagia, since follow-up data after reintervention were excluded.

The aim of antireflux surgery is to control reflux symptoms with minimal complications. The current results illustrate that 360° fundoplication should not necessarily be withheld from patients with ineffective motility. Although short-term dysphagia scores are higher after 360° fundoplication, these scores approach those of 90° and 180° fundoplication over time. A randomised controlled trial has demonstrated that mid-term reflux control seems inferior after 90°, compared with 360° fundoplication[45]. In contrast, the 10-year durability of reflux control after 180° fundoplication was similar in a randomised comparison with 360° fundoplication[43]. One-hundred-and-eighty degree and 360° fundoplication are therefore appropriate surgical treatments for GORD with similar long-term reflux control and dysphagia rates. The number of dilatations and reoperations for dysphagia are higher after 360° fundoplication, but this is counterbalanced by a lower rate of surgical reintervention for reflux compared with partial fundoplication.

The current study is limited by the fact that the majority of the patients were not randomised to undergo either partial or total fundoplication. The baseline differences between wrap types demonstrated that older and female patients were more likely to undergo a partial wrap to minimise postoperative gas bloating and flatulence. Some surgeons also tended to choose a partial wrap in patients with poor motility. In addition, patients with an adynamic or scleroderma oesophagus were excluded from the randomised trials. These choices introduced bias into our results even though subgroup analysis of the randomised patients for different wrap types did not alter our findings. Although the data indicate that tailoring the wrap is not helpful in minimising postoperative dysphagia, these biases must be acknowledged. Other limitations include the self-reported nature of the endpoint of postoperative dilatation. In addition, data were limited by the failure of some patients to return postal questionnaires and the absence of postoperative manometry as an objective endpoint after fundoplication.

Although there is no scientific evidence, a partial wrap remains the authors' wrap of choice for older, female patients and those with very poor or no peristaltic motility in whom the short-term side effects of bloating, increased flatulence and dysphagia can be troublesome.

Documentation of preoperative oesophageal function remains valuable as a benchmark in patients undergoing postoperative oesophageal motility testing for new or persisting symptoms[20]. While the current results demonstrate that ineffective motility as defined by conventional manometry does not predict dysphagia after fundoplication, high-resolution manometry and impedance monitoring in patients with and without dysphagia before and after fundoplication may disclose factors that influence outcome.

Acknowledgements

The authors thank Thomas Sullivan of the Discipline of Public Health of the University of Adelaide for statistical advice; and Lorelle Smith, Janet Sullivan and Nicky Carney for maintaining the prospective database.

References

(1) Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005; **54**(5):710-717.

(2) Bredenoord AJ, Dent J. Proton pump inhibitor-therapy refractory gastro-oesophageal reflux disease patients, who are they? *Gut* 2007; **56**(4):593-594.

(3) Spechler SJ, Lee E, Ahnen D, Goyal RK, Hirano I, Ramirez F et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. *JAMA* 2001; **285**(18):2331-2338.

(4) Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; **101**(8):1900-1920.

(5) Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. *Ann Surg* 2009; **250**(5):698-706.

(6) Broeders JA, Mauritz FA, Ahmed AU, Draaisma WA, Ruurda JP, Gooszen HG et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. *Br J Surg* 2010; **97**(9):1318-1330.

(7) Broeders JA, Broeders DJGH, Ahmed AU, Draaisma WA, Smout AJ, Hazebroek EJ. Laparoscopic anterior versus posterior fundoplication for gastroesophageal reflux disease - a meta-analysis of randomized trials. *Dis Esophagus* 2010; **23**(1):4A.

(8) Lamb PJ, Myers JC, Jamieson GG, Thompson SK, Devitt PG, Watson DI. Long-term outcomes of revisional surgery following laparoscopic fundoplication. *Br J Surg* 2009; **96**(4):391-397.

(9) Hunter JG, Trus TL, Branum GD, Waring JP, Wood WC. A physiologic approach to laparoscopic fundoplication for gastroesophageal reflux disease. *Ann Surg* 1996; **223**(6):673-685.

(10) Richter JE. Oesophageal motility disorders. *Lancet* 2001; **358**(9284):823-828.

(11) Spechler SJ, Castell DO. Classification of oesophageal motility abnormalities. *Gut* 2001; **49**(1):145-151.

(12) Bodger K, Trudgill N. Guidelines for oesophageal manometry and pH monitoring. 2006; *BSG Guidelines in Gastroenterology.* www.bsg.org.uk.

(13) Blonski W, Vela M, Safder A, Hila A, Castell DO. Revised criterion for diagnosis of ineffective esophageal motility is associated with more frequent dysphagia and greater bolus transit abnormalities. *Am J Gastroenterol* 2008; **103**(3):699-704.

(14) Kahrilas PJ, Dodds WJ, Hogan WJ, Kern M, Arndorfer RC, Reece A. Esophageal peristaltic dysfunction in peptic esophagitis. *Gastroenterology* 1986; **91**(4):897-904.

(15) Watson A, Jenkinson LR, Ball CS, Barlow AP, Norris TL. A more physiological alternative to total fundoplication for the surgical correction of resistant gastro-oesophageal reflux. *Br J Surg* 1991; **78**(9):1088-1094.

(16) Fuchs KH, Heimbucher J, Freys SM, Thiede A. Management of gastroesophageal reflux disease 1995: tailored concept of anti-reflux operations. *Dis Esophagus* 1995;(7):250-254.

(17) Kauer WK, Peters JH, DeMeester TR, Heimbucher J, Ireland AP, Bremner CG. A tailored approach to antireflux surgery. *J Thorac Cardiovasc Surg* 1995; **110**(1):141-146.

(18) Booth MI, Stratford J, Jones L, Dehn TC. Randomized clinical trial of laparoscopic total (Nissen) versus posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. *Br J Surg* 2008; **95**(1):57-63.

(19) Fibbe C, Layer P, Keller J, Strate U, Emmermann A, Zornig C. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized, clinical, and manometric study. *Gastroenterology* 2001; **121**(1):5-14.

(20) Castell DO. Esophageal manometry prior to antireflux surgery: required, preferred, or even needed? *Gastroenterology* 2001; **121**(1):214-216.

(21) Fang J, Bjorkman D. Prefundoplication testing: is manometry needed? *Am J Gastroenterol* 2002; **97**(4):1056-1058.

(22) Robertson AG, Dunn LJ, Shenfine J, Karat D, Griffin SM. Randomized clinical trial of laparoscopic total (Nissen) versus posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. *Br J Surg* 2008; **95**(6):799-800.

(23) Spence GM, Watson DI, Jamiesion GG, Lally CJ, Devitt PG. Single center prospective randomized trial of laparoscopic Nissen versus anterior 90 degrees fundoplication. *J Gastrointest Surg* 2006; **10**(5):698-705.

(24) Watson DI, Pike GK, Baigrie RJ, Mathew G, Devitt PG, Britten-Jones R et al. Prospective double-blind randomized trial of laparoscopic Nissen fundoplication with division and without division of short gastric vessels. *Ann Surg* 1997; **226**(5):642-652.

(25) Watson DI, Jamieson GG, Pike GK, Davies N, Richardson M, Devitt PG. Prospective randomized double-blind trial between laparoscopic Nissen fundoplication and anterior partial fundoplication. *Br J Surg* 1999; **86**(1):123-130.

(26) Watson DI, Jamieson GG, Devitt PG, Kennedy JA, Ellis T, Ackroyd R et al. A prospective randomized trial of laparoscopic Nissen fundoplication with anterior vs posterior hiatal repair. *Arch Surg* 2001; **136**(7):745-751.

(27) Watson DI, Jamieson GG, Lally C, Archer S, Bessell JR, Booth M et al. Multicenter, prospective, double-blind, randomized trial of laparoscopic nissen vs anterior 90 degrees partial fundoplication. *Arch Surg* 2004; **139**(11):1160-1167.

(28) Savary M, Miller G. The oesophagus. In *Handbook and atlas of endoscopy*, M Savary, G Miller (eds). Gossman: Solothurn, 1978: 135-142.

(29) Jamieson GG, Watson DI, Britten-Jones R, Mitchell PC, Anvari M. Laparoscopic Nissen fundoplication. *Ann Surg* 1994; **220**(2):137-145.

(30) Krysztopik RJ, Jamieson GG, Devitt PG, Watson DI. A further modification of fundoplication. 90 degrees anterior fundoplication. *Surg Endosc* 2002; **16**(10):1446-1451.

(31) Baigrie RJ, Cullis SN, Ndhluni AJ, Cariem A. Randomized double-blind trial of laparoscopic Nissen fundoplication versus anterior partial fundoplication. *Br J Surg* 2005; **92**(7):819-823.

(32) Dakkak M, Bennett JR. A new dysphagia score with objective validation. *J Clin Gastroenterol* 1992; **14**(2):99-100.

(33) Bessell JR, Finch R, Gotley DC, Smithers BM, Nathanson L, Menzies B. Chronic dysphagia following laparoscopic fundoplication. *Br J Surg* 2000; **87**(10):1341-1345.

(34) Pizza F, Rossetti G, Del GG, Maffettone V, Brusciano L, Del GA. Influence of esophageal motility on the outcome of laparoscopic total fundoplication. *Dis Esophagus* 2008; **21**(1):78-85.

(35) Bessell JR, Adair WD, Smithers BM, Martin I, Menzies B, Gotley DC. Early reoperation for acute dysphagia following laparoscopic fundoplication. *Br J Surg* 2002; **89**(6):783-786.

(36) Oelschlager BK, Quiroga E, Parra JD, Cahill M, Polissar N, Pellegrini CA. Long-term outcomes after laparoscopic antireflux surgery. *Am J Gastroenterol* 2008; **103**(2):280-287.

(37) Hafez J, Wrba F, Lenglinger J, Miholic J. Fundoplication for gastroesophageal reflux and factors associated with the outcome 6 to 10 years after the operation: multivariate analysis of prognostic factors using the propensity score. *Surg Endosc* 2008; **22**(8):1763-1768.

(38) Munitiz V, Ortiz A, Martinez de Haro LF, Molina J, Parrilla P. Ineffective oesophageal motility does not affect the clinical outcome of open Nissen fundoplication. *Br J Surg* 2004; **91**(8):1010-1014.

(39) Ip S, Tatsioni A, Conant A, Karagozian R, Fu L, Chew P et al. Predictors of clinical outcomes following fundoplication for gastroesophageal reflux disease remain insufficiently defined: a systematic review. *Am J Gastroenterol* 2009; **104**(3):752-758.

(40) Chrysos E, Tsiaoussis J, Zoras OJ, Athanasakis E, Mantides A, Katsamouris A et al. Laparoscopic surgery for gastroesophageal reflux disease patients with impaired esophageal peristalsis: total or partial fundoplication? *J Am Coll Surg* 2003; **197**(1):8-15.

(41) Rydberg L, Ruth M, Abrahamsson H, Lundell L. Tailoring antireflux surgery: A randomized clinical trial. *World J Surg* 1999; **23**(6):612-618.

(42) Ludemann R, Watson DI, Jamieson GG, Game PA, Devitt PG. Five-year follow-up of a randomized clinical trial of laparoscopic total versus anterior 180 degrees fundoplication. *Br J Surg* 2005; **92**(2):240-243.

(43) Cai W, Watson DI, Lally CJ, Devitt PG, Game PA, Jamieson GG. Ten-year clinical outcome of a prospective randomized clinical trial of laparoscopic Nissen versus anterior 180 (degrees) partial fundoplication. *Br J Surg* 2008; **95**(12):1501-1505.

(44) Engstrom C, Lonroth H, Mardani J, Lundell L. An anterior or posterior approach to partial fundoplication? Long-term results of a randomized trial. *World J Surg* 2007; **31**(6):1221-1225.

Part II

Techniques

8

Ten-year outcome of laparoscopic and conventional Nissen fundoplication: randomized clinical trial

J.A.J.L. Broeders[1]
H.G. Rijnhart-de Jong[1]
W.A. Draaisma[1]
A.J. Bredenoord[2]
A.J.P.M. Smout[3]
H.G. Gooszen[1]

[1]Dep. of Surgery, University Medical Center Utrecht
[2]Dep. of Gastroenterology, St. Antonius Hospital, Nieuwegein
[3]Dep.of Gastroenterology, University Medical Center Utrecht

16th annual meeting of the European Surgical Association
Vienna, Austria, April 2009
17th annual meeting of the European Association for Endoscopic Surgery
Prague, Czech Republic, June 2009
17th annual United European Gastroenterology Week
London, United Kingdom, November 2009

Annals of Surgery 2009; 250:698-706.

Abstract

Objective: To compare 10-year outcome of a multicenter RCT on laparoscopic (LNF) and conventional Nissen fundoplication (CNF), with focus on effectiveness and reoperation rate.

Summary of background data: LNF has replaced CNF as surgical treatment for GERD. Decisions are based on equal short-term effectiveness and reduced morbidity, but confirmation by long-term level 1 evidence is lacking.

Methods: From 1997 to 1999, 177 PPI-refractory GERD patients were randomized to undergo LNF or CNF. The ten-year results of surgery on reflux symptoms, general health, PPI use and reoperation rates, are described. High-resolution manometry, 24-h pH-impedance monitoring and barium swallow were performed in symptomatic patients only.

Results: A total of 148 patients (79 LNF, 69 CNF) participated in this ten-year follow-up study. GERD symptoms were relieved in 92.4% and 90.7% (NS) after LNF and CNF, respectively. Severity of heartburn and dysphagia were similar, but slightly more patients had relief of regurgitation after LNF (98.7 *vs* 91.0%; P=0.030). The percentage of patients using PPIs slowly increased with time in both groups to 26.6% for LNF and 22.4% for CNF (NS). General health (74.7% *vs* 72.7%; NS) and quality of life (VAS-score: 65.3 *vs* 61.4; NS) improved similarly in both groups. The percentage of patients that would have opted for surgery again was similar as well (78.5 *vs* 72.7%; NS). Twice as many patients underwent reoperation after CNF compared to LNF (12 [15.2%] *vs* 24 [34.8%]; *P*=0.006), including a higher number of incisional hernia corrections (2 *vs* 9; *P*=0.015). Mean interval between operation and reintervention was longer after CNF (22.9 *vs* 50.6 months; *P*=0.047). Of the patients who were dependent on daily PPI therapy at ten years (LNF 10, CNF 10), seven patients (LNF 3, CNF 4) had recurrent GERD on pH-impedance monitoring, five of them with some form of anatomical recurrence. A total of 13/20 [65.0%] patients did not have recurrent GERD. Fourteen patients had an abnormal high-resolution manometry.

Conclusions*:* CNF carries a higher risk for surgical reintervention compared to LNF, mainly due to incisional hernia corrections. The 10-year effectiveness of LNF and CNF is comparable in terms of improvement of GERD symptoms, PPI use, quality of life and objective reflux control. Consequently, the long-term results from this trial lend level 1 support to the use of LNF as the surgical procedure of choice for GERD.

Introduction

Laparoscopic Nissen fundoplication (LNF) rapidly replaced conventional Nissen fundoplication (CNF)[1] as surgical therapy of choice after the first report on this procedure in 1991.[2] As with the introduction of laparoscopic cholecystectomy, evidence from randomized studies that proved equivalent long-term effectiveness of the new approach is lacking, though. The need for long-term level 1 evidence is promoted by a large uncontrolled study[3] and a randomized study with 4-year follow-up,[4] reporting higher rates of failure and dissatisfaction after laparoscopic than after open antireflux surgery. There are eight randomized studies comparing laparoscopic with open Nissen fundoplication.[4-15] The follow-up of these studies is still too short to compare the relevant outcome measures of surgical therapy: long-term disease control and reoperation rate.

Recently, Nilsson et al. reported the 5-year outcome of a RCT (n = 60)[16] and Salminen et al. published the subjective symptomatic outcome and endoscopic assessment of the fundic wraps at 11 years after randomization to LNF or CNF (n = 110).[17] Our group has reported the 3-month[6] and 5-year[18] subjective outcome and data on objective reflux control of a RCT that was performed in the Netherlands between 1997 and 1999 in which 177 patients were included. In this study, we report the 10-year subjective and objective results of the largest RCT comparing LNF and CNF.

Methods

Study design and participants

From 1997 to 1999, 177 patients were included in a multicenter RCT to undergo Nissen fundoplication for PPI-refractory GERD in one of the participating tertiary care centers (n = 98, LNF; n = 79, CNF). Interim analysis at three months demonstrated that LNF carries a substantially higher risk for dysphagia necessitating esophageal dilation or surgical reintervention and the trial was prematurely terminated. At the time of the interim analysis, 57 patients underwent LNF and 46 patients CNF.[6] Four patients were never operated, six patients withdrew and another 64 patients were randomized during the interval of analyzing the first 100 patients and the process of decision making about how to continue. Consequently, 93 patients underwent laparoscopic and 74 patients underwent conventional 360° degree fundoplication and underwent evaluation of subjective outcome and esophageal manometry and 24-hour pH-metry at three months.

Of these patients, a total of 151 patients were eligible for prospectively evaluation of subjective outcome and results of esophageal manometry and 24-hour pH-metry at five years. Three patients refused all further follow-up at five years and

consequently 79 patients who underwent LNF were compared to 69 patients who underwent CNF.[18]
At ten years, surgical reinterventions were registered for the patients that participated in the 5-year follow-up study. In figure 1 and 2, the CONSORT analysis is described in detail.[19] All these patients were asked by mail to complete a questionnaire on reflux symptoms, general state of health (GsH), quality of life (QoL), patient satisfaction and use of antisecretory drugs. Only patients who used acid suppressing drugs for recurrent reflux symptoms were asked to undergo high-resolution manometry, 24-hour pH-impedance monitoring and barium swallow.

Surgical procedures
All primary operations were performed between January 1997 and August 1999. In both treatment arms a floppy 360° Nissen fundoplication of 2.5 to 3.0 cm was constructed after ligation and division of the short gastric vessels, full mobilization of the esophagus and posterior crural repair. Open surgery was performed through a standard upper midline incision.

Clinical outcome
Surgical reinterventions, time to reoperation and indication for and type of reintervention were registered up to ten years. Long-term clinical outcome was determined using a standardized questionnaire. The Visick score was applied to monitor the subjective effect of surgery as it correlates well to the most prominent symptom of GERD (heartburn)[20,21] and gives an over-all impression on the appreciation of antireflux surgery. Visick scores correlate well to a validated questionnaire[22] for reflux symptoms.[21] Patients were asked to rate the effect of surgery on their reflux symptoms by modified Visick grading as follows: complete resolution (Visick I), improvement (Visick II), no effect of surgery (Visick III) or deterioration (Visick IV), always in comparison with their preoperative state. The presence of heartburn, regurgitation and dysphagia were also assessed using a combined *frequency* and *severity* grading system resulting in a grade from 0 (symptom absent) to 3 (symptom frequent and severe).[23]
The effect of surgery on self-rated change in general health was measured on a 3-point scale that ranges from “improved” to “unchanged”, to “worsened”. A visual analogue scale (VAS), validated for quality of life assessment after esophageal surgery, was used to measure the impact on quality of life.[24] The scale ranged from 0 to 100, where zero represented worst possible health and 100 represented perfect health.[25] The effect of surgery on quality of life and use of antisecretory drugs was registered up to 10 years after surgery. Patients were asked whether they would opt for surgery again in retrospect as well. The same questionnaires

were used before surgery, at three months, five years and ten years, to make direct comparison of the outcomes possible.

Stationary esophageal high-resolution manometry

All studies were conducted after suspending medication that potentially affects gastrointestinal motility 7 days in advance and were performed by the same senior clinician of the gastrointestinal research center. Manometric recordings were performed using a solid state high-resolution catheter (Unisensor, Attikon, Switzerland). The catheter containing 36 micro-transducers with 1 cm interspaces was introduced transnasally. The manometric response to ten standardized wet swallows (5-ml water bolus) was recorded. The mean end-expiratory lower esophageal sphincter (LES) pressure and residual pressure of the LES during swallow-induced relaxation were determined. In addition, the 4-second integrated relaxation pressure (IRP 4-s) of the LES was determined to quantify LES relaxation.[26] The end-expiratory gastric baseline pressure served as the zero reference point. Mean amplitude and duration of the esophageal contractions in response to the wet swallows were determined 15 cm (proximal esophagus), 10 cm (mid esophagus) and 5 cm above the LES (distal esophagus). All studies were systematically evaluated by an independent gastroenterologist not aware of the patient's condition (A.J.B.).

Ambulatory 24-hour combined esophageal pH-impedance monitoring

Ambulatory 24-hour pH-impedance testing was conducted after cessation of at least 7 days of all medication that affects gastrointestinal motility and secretion and was performed by a senior clinician of the gastrointestinal research center (J.O.). A combined pH-impedance catheter (VersaFlex, Alpine Biomed, Fountain Valley, CA, USA) was introduced transnasally with the pH electrode positioned 5 cm above the manometrically determined upper margin of the LES. This catheter has a single antimony pH electrode and eight ring electrodes enabling impedance recording at 2–4, 4–6, 6–8, 8–10, 14–16 and 16–18 cm above the upper margin of the LES. The tracings were recorded in a digital data logger (Medical Measurements Systems, Enschede, The Netherlands) and patients were instructed to register body position, reflux symptoms, meals and beverages in a diary. In addition, they were asked to press a button on the digital data logger at the beginning of each symptom episode. After 24 hours, the pH recordings were analyzed automatically using a software program (MMS, Enschede, The Netherlands). If the patient experienced symptoms during the measurement, the symptom index (SI) and symptom association probability (SAP) were calculated.[27,28] The SI was considered to be indicative for positively reflux-related symptoms if it was equal to or higher

than 50%. The SAP had to be at least 95% to be positive. The upper limit for normal total esophageal acid exposure was two standard deviations above the mean value obtained in healthy volunteers during ambulatory 24-h pH monitoring.[29,30] Physiological esophageal acid exposure was defined as total acid exposure time < 5.8% and normal acid exposure time in upright (< 8.2 %) and supine (< 3.5 %) position. In addition, the DeMeester score was calculated. All 24-hr pH studies were systematically evaluated by an independent gastroenterologist not aware of the patient's condition (A.J.B.).

Barium swallow

Barium swallow was performed after an overnight fast. All studies were systematically evaluated by an independent senior radiologist not aware of the patient's condition (G.S.) for the presence of a hiatal hernia, slippage of the wrap into the thorax and telescoping of the LES through the wrap.

Statistical Analysis

The statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL). Data were analyzed according to the intention-to-treat principle. The number of patients for which data were available was determined for each parameter. Continuous variables were expressed as mean ± standard error of the mean (SEM). Differences in parametric data between the LNF and CNF group were analyzed using an independent *t*-test. The paired-samples *t*-test was used to determine significant effects of surgery on parametric data. The χ^2 test was used to compare groups for nominal variables and effects of surgery on these variables were analyzed using the McNemar-Bowker. Differences with a *P* value less than 0.05 were considered statistically significant.

Results

Overall responses and completeness of follow-up

The need for surgical reintervention, time to reintervention, indications and type of reintervention were registered for all patients at 10 years (n = 79, LNF; n = 69, CNF). Baseline characteristics were comparable for both groups (table 1). Conversion to an open procedure was required in 6 patients (7.6%). These patients were maintained in the LNF group according to the intention to treat principle. Mean time to follow-up was 9.8 (0.1) years after LNF and 9.6 (0.1) years after CNF. In the CNF group, one patient died of pancreatic cancer and one patient due to acute heart failure. All other patients participated in the follow-up study and as a result, clinical outcome was evaluated in 79 LNF patients and 67 CNF patients at

Figure 1 Study profile: CONSORT analysis five-year follow-up

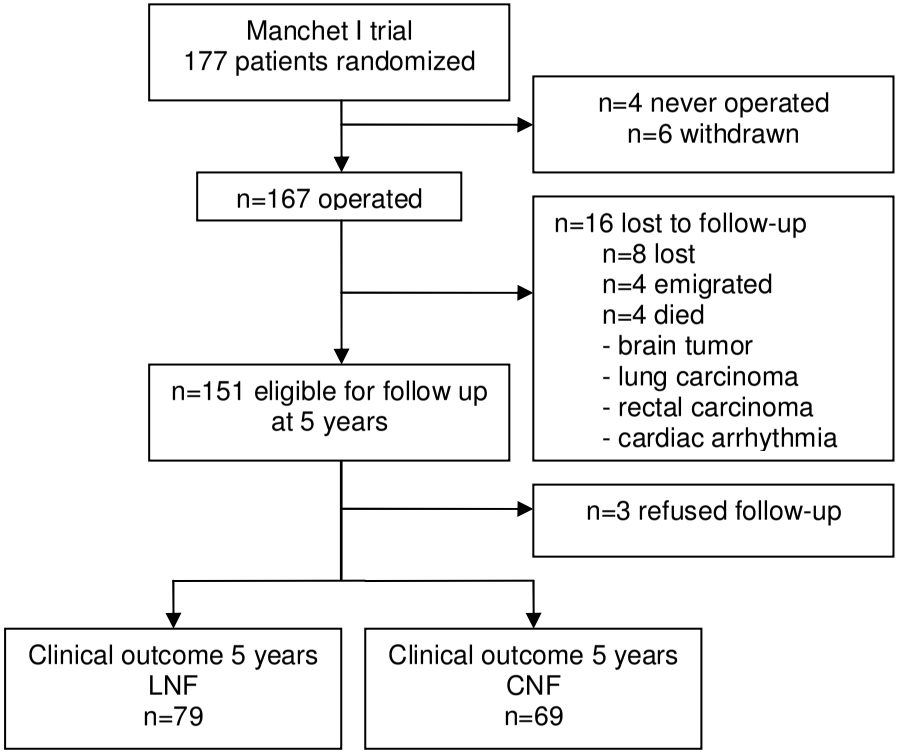


Figure 2 Study profile: CONSORT analysis ten-year follow-up

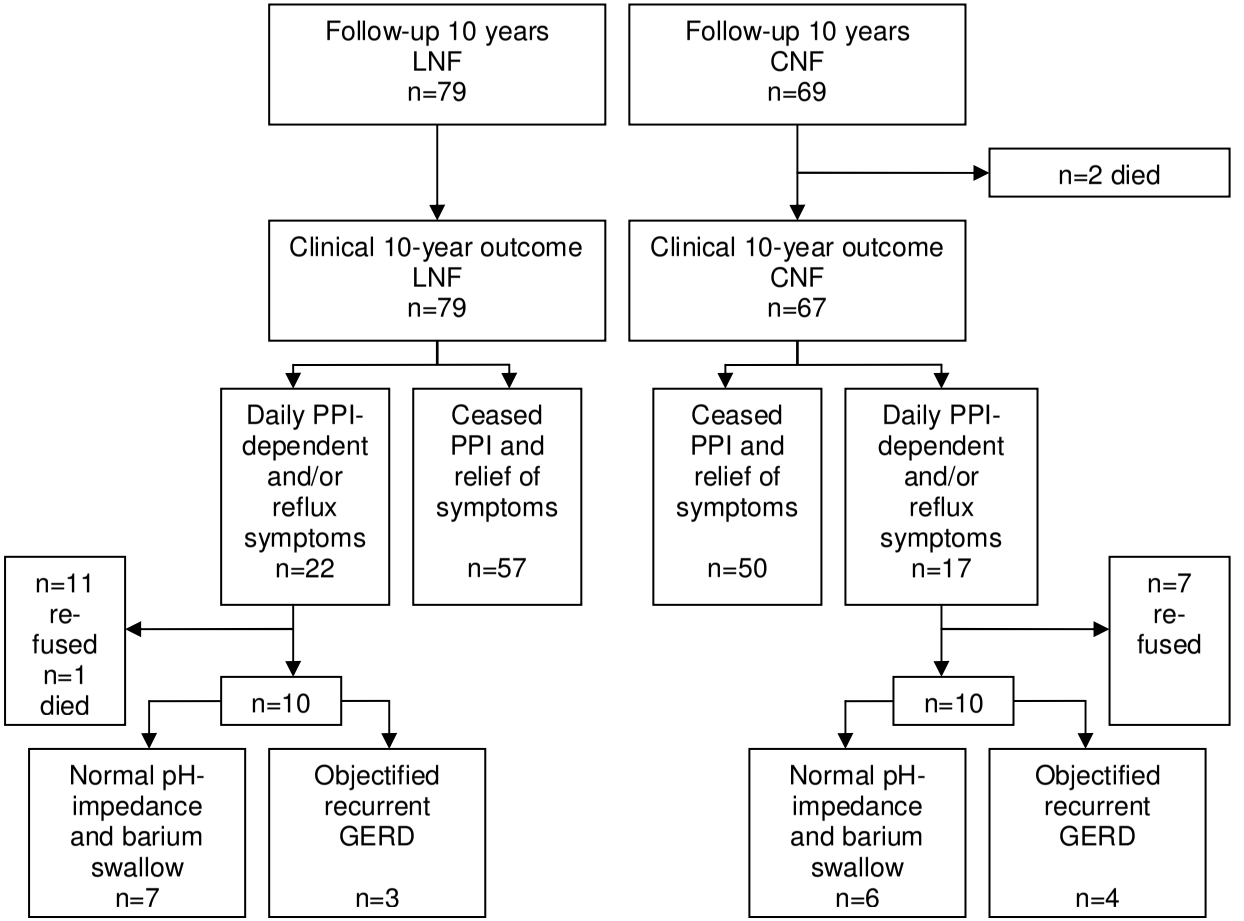


Table 1 Baseline characteristics of patients according to treatment group

	LNF	CNF
Patients (n)	79	69
Age (yr)	43.8 (17-79)	43.1 (19-75)
Male / female sex	43 / 36	45 / 24
Body mass index (BMI) *	26.0 (0.5)	26.8 (0.4)
Conversion rate	6 [7.6%]	
Follow-up interval (yr) *	9.8 (0.1)	9.6 (0.1)

* values are given as mean (SEM)

10 years (figure 2). In the LNF group, 57/79 [72.2%] patients ceased use of acid-suppressing drugs and had persistent relief of reflux symptoms. Twenty-one patients were dependent on daily acid-suppressing drug therapy in order to relieve heartburn and regurgitation and one patient did not use antisecretory drugs, but had aggravation of reflux symptoms compared to the preoperative state (Visick IV). Of these 22 patients, eleven patients refused to objectify disease at ten years and one patient suffered from liver cirrhosis and died of bleeding of esophageal varices during the analysis of clinical outcome. In the CNF group, the number of patients with persistent relief of reflux symptoms and independence of acid-suppressing drug use was similar compared to LNF (50/67 [74.6%]; NS). Fifteen patients were dependent on daily acid-suppressing drug therapy to relieve heartburn and regurgitation and two patients did not use antisecretory drugs, but had no relief or deterioration of reflux symptoms compared to the preoperative state (Visick III and IV). Seven of these seventeen patients refused to objectify these complaints at ten years. As a result, post-operative GERD symptoms were objectified in 10 patients in the LNF group and 10 patients in the CNF group (figure 2).

Clinical outcome

After LNF 73/79 [92.4%] patients scored their reflux symptoms as resolved or improved (Visick I and II) and 59/65 [90.7%] patients did so after CNF (NS). Improvement of reflux symptoms after surgery was similar in both groups (table 2). The percentage of patients with no or mild heartburn (94.9% *vs* 91.1%; NS) and dysphagia (92.4% *vs* 85.1%; NS) was similar in LNF and CNF. The percentage of patients with no or mild regurgitation was slightly higher after LNF (98.7% *vs* 91.0%; $P = 0.030$). See table 2. General state of health (table 3: 59/79 [74.7%] *vs* 48/66 [72.7%]; NS) and quality of life (table 3: VAS-score 65.3 (2.4) *vs* 61.4 (3.1); NS) improved similarly in both groups. Both after LNF and CNF quality of life significantly increased, compared to the preoperative state throughout the follow-up

Table 2 Self-rated change in reflux symptoms *versus* preoperative state and heartburn, regurgitation and dysphagia grades 10 years after LNF and CNF

	LNF	CNF
Self-rated change in reflux symptoms *versus* preoperative state (n [%])		
Visick I: Resolved	45 [57.0%]	29 [44.6%]
Visick II: Improved	28 [35.4%]	30 [46.2%]
Visick III: Unchanged	3 [3.8%]	1 [1.5%]
Visick IV: Worsened	3 [3.8%]	5 [7.7%]
Heartburn (n [%])		
Grade 0	47 [59.5%]	41 [61.2%]
Grade 1	28 [35.4%]	20 [29.9%]
Grade 2	4 [5.1%]	2 [3.0%]
Grade 3	-	4 [6.0%]
Regurgitation (n [%])		
Grade 0	56 [70.9%] ~	54 [80.6%]
Grade 1	22 [27.8%] ~	7 [10.4%]
Grade 2	1 [1.3%]	3 [4.5%]
Grade 3	-	3 [4.5%]
Dysphagia (n [%])		
Grade 0	36 [46.2%]	37 [55.2%]
Grade 1	36 [46.2%]	20 [29.9%]
Grade 2	5 [6.4%]	9 [13.4%]
Grade 3	1 [1.3%]	1 [1.4%]

~ combined percentage of patients with grade 0 & 1: $P < 0.05$ *vs* CNF

period (figure 3: both $P < 0.001$ *versus* pre-op). The percentage of patients that would have opted for surgery again in retrospect (table 3: 62/79 [78.5%] *vs* 48/66 [72.7%]; NS) and the use of acid-suppressing drugs after ten years was similar in both groups (21/79 [26.6%] *vs* 15/67 [22.4%]; NS). The use of antisecretory drugs increased significantly with time in both groups (3 months post-op *versus* 10 years post-op: $P = 0.022$ and $P = 0.057$), but remained significantly reduced compare to the preoperative use (figure 4: both $P < 0.001$ *versus* pre-op).

Table 3 General state of health (GsH), quality of life (QoL), patient satisfaction and use of acid-suppressing drugs 10 years after LNF and CNF

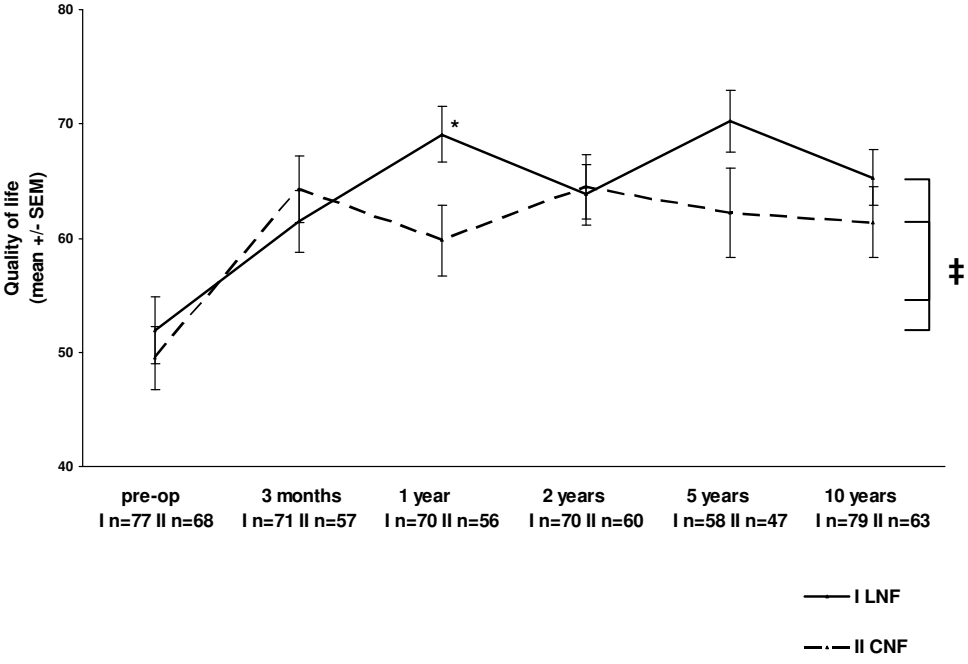
	LNF	CNF
General state of health (n [%])		
Improved	59 [74.7%]	48 [72.7%]
Unchanged	11 [13.9%]	5 [7.6%]
Worsened	9 [11.4%]	13 [19.7%]
General QoL		
(VAS score 0-100)*	65.3 (2.4) ‡	61.4 (3.1) ‡
LNF n=79		
CNF n=63		
Mean increase in general QoL (% of preoperative)	25.8%	24.0%
Opt for surgery again in retrospect (n [%])		
Yes	62 [78.5%]	48 [72.7%]
No	7 [8.9%]	10 [15.2%]
No opinion	10 [12.7%]	8 [12.1%]
Use of acid-suppressing drugs (n [%])	21 [26.6%] ‡	15 [22.4%] ‡

* values are given as mean (SEM), ‡ $P < 0.001$ *vs* preoperative results

Stationary high-resolution esophageal manometry

To further investigate a subgroup of twenty patients who used antisecretory drugs at ten years, high resolution manometry was performed (table 4); fourteen (8 LNF and 6 CNF), had some abnormal finding, not present on preoperative manometry. Eight patients had ineffective esophageal motility (5 LNF and 3 CNF), the patient with the most severely impaired esophageal motility, had the highest acid exposure time. Seven out of the eight patients with LES dysrelaxation reported moderate or severe retrosternal pain. No other relations between manometric and symptomatic outcome could be identified.

Figure 3 Mean quality of life (VAS score 0-100) up to ten years after CNF and LNF



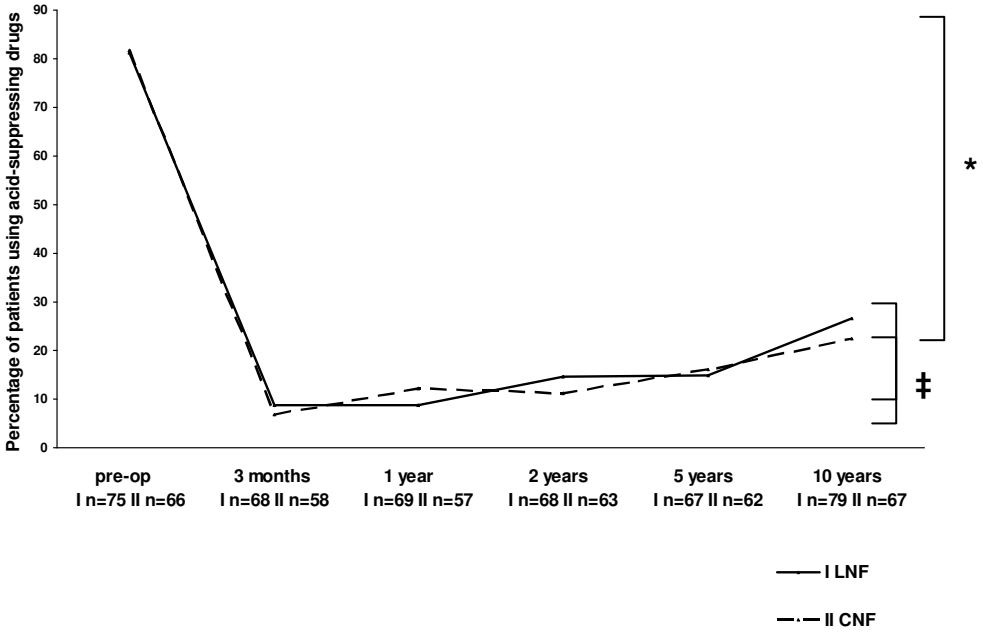
‡ P < 0.001 *vs* preoperative results for both groups at 10 years,
* P < 0.05 *vs* CNF group

Table 4 Results of esophageal high-resolution manometry in patients who were dependent on daily PPI therapy 10 years after LNF and CNF

	LNF (n=10)	CNF (n=10)
High-resolution manometry diagnosis (n)		
Normal	2	4
Hypertensive LES	2 *	1
Dysrelaxation LES	5	3
Ineffective esophageal motility	5 *	3 ♦

* including two patients that have also been reported with dysrelaxation LES, ♦ including a patient that has also been reported with dysrelaxation LES

Figure 4 Percentage of patients using acid-suppressing drugs up to ten years after LNF and CNF



* P < 0.001 *vs* preoperative results for both groups at ten years, ‡ P < 0.05 *vs* 3-month results for both groups at 10 years

24-hour combined pH-impedance monitoring and barium swallow

Recurrent GERD on pH-impedance monitoring was present in seven patients (LNF 3, CNF 4), in the subgroup of twenty patients who used acid suppressing drugs for recurrent reflux symptoms. Six patients had pathological acid exposure time and a positive DeMeester score. Four of them also had some form of anatomical recurrence on barium swallow. There was no correlation between manometric results and acid exposure time. One patient had the combination of physiological acid exposure with positive symptom-reflux correlation (esophageal acid-hypersensitivity) and anatomical recurrence. There were no differences in objective recurrence of GERD between LNF and CNF (table 5). The number of patients using antisecretory drugs with recurrent pathological reflux on pH-impedance monitoring was similar after LNF and CNF (3/79 [3.8%] *vs* 4/67 [6.0%]; NS). Thirteen out of the 20 [65.0%] symptomatic patients, had even an infra-physiological esophageal acid exposure (total acid exposure <1.0%), a negative

symptom-reflux correlation for both acid and non-acid reflux and no anatomical recurrence. In this group, six out of thirteen patients had LES dysrelaxation on manometry. Five out of these six patients with infra-physiologic acid exposure and LES dysrelaxation reported moderate or severe retrosternal pain.

Table 5 Results of esophageal 24-hr pH-impedance monitoring and barium swallow in patients who were dependent on daily PPI therapy 10 years after LNF and CNF

	LNF (n=10)	**CNF (n=10)**
24-hr esophageal pH recording (n)		
<5.8% acid exposure for total time	8	7
≥5.8% acid exposure for total time	2	3
<8.2% acid exposure in upright position	8	9
≥8.2% acid exposure in upright position	2	1
<3.5% acid exposure in supine position	9	7
≥3.5% acid exposure in supine position	2	3
DeMeester score		
<14.7	7	7
≥14.7	3	3
Symptom-reflux correlation (n)		
SI <50 % and SAP <95%	10	7
SI ≥50% and SAP ≥95%	-	3
Barium swallow diagnosis (n)		
Normal	8	7
Sliding hiatal hernia	1	3
Mixed hiatal hernia	1	-
Intrathoracical fundoplication	2 *♦	1 *
Telescoping fundoplication	-	1 *

* including a patient that has also been reported with a sliding hiatal hernia, ♦ including a patient that has also been reported with a mixed hiatal hernia

Surgical reintervention

Twelve out of 79 [15.2%] patients after LNF and 24/69 [34.8%] patients after CNF underwent reintervention (*P* = 0.006). According to the intention to treat principle, these patients were analyzed in their original group. The difference between the reintervention rate was mainly due to the high number of incisional hernia corrections in CNF patients (9 *vs* 2; *P* = 0.015). One of the two patients with an incisional hernia after LNF, underwent conversion to CNF during the primary procedure and had an incisional hernia of the upper midline incision. Other indications for reintervention and details of the procedure were similar in both groups (table 6). In contrast to the CNF group, all reinterventions were performed within the first 5 years after LNF.

Table 6 Surgical reintervention 10 years after LNF and CNF

	LNF (n=79)	**CNF (n=69)**
Surgical reintervention	12 [15.2%]	24 [34.8%] †
Mean time to reintervention (mo)*	22.9 (10.1)	50.6 (8.7) ~
Indication for reintervention (n)		
Recurrent GERD	4 ♦	7
Persistent dysphagia	3	2
Recurrent GERD and persistent dysphagia	1	3
Incisional hernia	2 ♦	9 ‡
Abdominal pain	1	2
Paraesophageal hernia	0	1
Gastric perforation	1	0
Reoperation (n)		
Re-Nissen	5	9
Belsey Mark IV	3 ♦	3
Correction incisional hernia	2 ♦	9 ‡
Adhesiolysis	1	1
Other	1	2

* values are given as mean (SEM), † *P* = 0.006 *vs* LNF, ~ *P* = 0.047 *vs* LNF, ‡ *P* = 0.015 *vs* LNF, ♦ including one patient that underwent conversion to CNF during primary procedure

Mean interval between operation and reintervention was significantly longer after CNF (22.9 (10.1) *vs* 50.6 (8.7) months; $P = 0.047$). Of the 39 patients who used antisecretory drugs for recurrent reflux symptoms at 10 years, fifteen patients [38.5%] had undergone surgical reintervention during the follow-up period. In this subgroup, more patients underwent surgery for recurrence of GERD compared to the asymptomatic group: seven for recurrent reflux, two for both recurrent reflux and dysphagia, two for dysphagia and four for an incisional hernia.

Discussion

Laparoscopic Nissen fundoplication has almost completely replaced conventional Nissen fundoplication, despite the lack of level 1evidence of its superiority in terms of effectiveness, reoperation rate or the combination. This is a report on the subjective and objective 10-year outcome of the largest RCT focusing on the overall reoperation rate and long-term effectiveness. In the LNF group, no patients did undergo surgical reintervention after 5 years of follow-up. In contrast, in the CNF group a substantial number underwent reoperation between 5 and 10 years of follow-up. Since there was no significant difference in reinterventions at five years, the difference became significant between 5 and 10 years after surgery, mainly due to a higher rate of incisional hernia corrections. Recently, Salminen's group reported the 11-year outcome of a RCT, which showed a similar difference between CNF and LNF, however in the Finnish study all incisional hernias were small and asymptomatic and did not require surgery.[17] Correction of an incisional hernia of an upper midline incision requires hospitalization and carries a substantial risk for recurrence. A reduced incidence of incisional hernias is recommended as a major long-term benefit of laparoscopic surgery compared to open surgery, in general. Recently, this has been shown after obesity surgery.[31,32] However thus far, the follow-up of randomized studies on cholecystectomy, appendectomy, colectomy and fundoplication has been too short to identify differences in the incidence of incisional hernias and the number of cicatricial hernia corrections. The current study is the first randomized controlled trial to demonstrate that laparoscopic antireflux surgery reduces the incidence of incisional hernias and the number of cicatricial hernia corrections compared to upper midline incision in non-obese patients.

The reoperation rates of the current study are high compared to literature, especially in the CNF group. However, reoperation rates of case series from single, usually expert, centers differ considerably from those of population based studies and randomized controlled trials.[33] Publication bias, selection bias and referral bias probably help to explain the difference in these results. A recent meta-analysis of

randomized controlled trials demonstrated that 9.6% of the patients needed surgical reintervention at a mean follow-up of two-and-a-half years after open or laparoscopic fundoplication.[33] The reoperation rate of the LNF group of the present study (15.2% at ten years) is largely in line with these results, considering the extended length of follow-up. The higher reintervention rate in the CNF group is mainly caused by the higher incidence of incisional hernias that developed during long-term follow-up. The conversion rate of the current study (7.6%) was the same as the pooled data from the meta-analysis by Catarci et al. (7.3%).[33] We therefore feel that the present reoperation rates are representative for surgical results in experienced, not necessarily expert, units.

The high rate of troublesome dysphagia necessitating reintervention at three months, was no longer observed at five and ten years of follow-up. In retrospect, the high percentage of dysphagia was most likely caused by the relative lack of experience with the laparoscopic approach of the participating surgeons at the start of the study.[18] Other RCTs initially reported a higher incidence of early dysphagia after LNF than after CNF,[9,12,15] but they also have observed that dysphagia resolves with extension of follow-up.[10,12,16]

In line with the 5-year results,[18] effectiveness of LNF and CNF was similar in terms of improvement of GERD symptoms, use of acid-suppressing drugs and quality of life at 10 years. All but one[4] of the other RCTs comparing LNF with CNF, report no differences in subjective and objective reflux control, beit at short-term follow-up.[5-15] Nilsson's 5-year[16] and Salminen's 11-year report[17], confirmed that CNF and LNF are equally effective in controlling heartburn, regurgitation and dysphagia, with similar use of acid-suppressing drugs and patient satisfaction after surgery.

Just like Salminen, the present study's percentage of patients using acid-suppressing drugs slowly increased with time to over 20% in both groups. The percentage of patients using antisecretory drugs 10-years after other large randomized controlled trials on antireflux surgery published last year are comparable: 15%[34], 17%[35] and 22%[36]. However, it has been demonstrated that only a small portion of the patients using antireflux medication postoperatively, has abnormal esophageal acid exposure on 24-hour pH monitoring[18,37,38] or endoscopic fundoplication disruption.[17] At five years, no correlation could be identified between use of acid-suppressing drugs and acid exposure and between medication use and the symptom correlation scores in the patients participating in the current study.[18] Similarly, at ten years, sixty-five percent of the patients who reported to be dependent on daily PPI therapy because of heartburn and regurgitation, had no objective evidence of recurrent GERD, esophageal acid-hypersensitivity or non-acid reflux. Obviously, these patients do not need their PPIs and consequently they can not be regarded as objective failures.

High-resolution manometry, pH-impedance monitoring and barium swallow were performed in patients using antisecretory drugs for recurrent reflux symptoms only. Therefore, the 10-year objective outcome is not representative for the whole group. To provide a complete picture of objective results at ten years, these examinations should have been repeated at 10 years in all patients, so in that respect, this study has a limitation. However, esophageal function tests were repeated at five years in 44 LNF patients and 47 CNF patients and showed durable favorable results on acid exposure, without differences between LNF and CNF. Since the *a priori* chance for recurrent pathological reflux in asymptomatic patients is low, esophageal function tests were only proposed to symptomatic patients at ten years. The completeness of the objective follow-up for this group was reasonable with 20/39 patients undergoing high-resolution manometry, 24-hr pH-impedance monitoring and barium swallow. There was no relation between manometric results and acid exposure time nor between manometric and symptomatic outcome, except for an association between LES dysrelaxation and retrosternal pain. Maybe misinterpretation by the general practitioner of these symptoms as related to reflux led to resumption of PPI treatment and partly explains for our observation of PPI treatment in non-reflux patients at ten years. There was a good correlation between the results of barium swallow and 24-hr pH-impedance monitoring: all patients with anatomical recurrence had recurrent GERD on pH-impedance monitoring. The internal validity of the results of the study is also augmented by the fact that investigations were performed and evaluated systematically by the same independent physician for all patients.

In conclusion, the 10-year outcome of this randomized controlled trial of LNF *versus* CNF provides valuable data concerning the long-term reoperation rate and effectiveness. The hypothesis at the time of the introduction of LNF: a lower reoperation rate for incisional hernia and similar effectiveness, is strongly supported by this study and this trial lends level 1 support to the use of laparoscopic Nissen fundoplication as the procedure of choice for the surgical treatment of gastroesophageal reflux disease. However, the majority of patients who use acid suppressing drugs at ten years after surgery, do not have recurrent reflux disease.

Acknowledgements

The authors thank J. Oors for performing the high-resolution manometries and 24-hour pH-impedance metries and dr. G. Stapper for the evaluation of the barium swallows.

Discussions

PROFESSOR M. GRIFFIN: This represents the largest randomized controlled trial certainly in the last 10 years and these conclusions are both important and interesting. However, we need to look at this article in the context of the previous articles that you produced, first in *The Lancet* when you reported 3 months data, then in the BJS at a year and subsequently in the *Annals of Surgery* at 5 years. I think that in the 3 month article you stopped the study because of dysphagia in the laparoscopic Nissen group, and then you showed no difference in the 1 year data and the 5-year data. I assume that is exactly what you found at 10 years, apart from this incisional hernia data.

I would like to ask about the methodology and your interpretation of the results. Regarding the tools you used to assess the general state of health; your dysphagia grading, your satisfaction questionnaire, and of course your quality of life, the only significant difference you found was in your quality of life assessment based on a visual analog score, which of course is a validated tool. The other tools you used were not validated and so I would ask why you selected those tools to assess the difference between laparoscopic and open Nissen fundoplication. Also, in terms of what you report in the abstract, you suggested that there is perhaps an overstating of the results of those questionnaires and validated tools. I would like to know why you chose those tools.

I would also like to ask about the intention to treat, because when some operations were converted in this series, using only the intention to treat may obscure any potential differences between techniques. Would you be prepared to sub-analyze those groups, because you did mention that one of the patients in the laparoscopic Nissen group in fact developed a hernia as it was converted to the open technique?

DR. J. BROEDERS: We did indeed observe a difference in dysphagia at 3 months and that was the reason for prematurely terminating the trial. However, 4 of the 8 randomized studies that have been published so far, report a difference in dysphagia at early follow-up in favor of the open fundoplication, but after 1, 2, or 5 years of follow-up, all those 4 randomized studies report that dysphagia resolves, as well. This is probably partly due to surgical reintervention or endoscopic dilatation for dysphagia. Another explanation may be that all patients experience some dysphagia after Nissen fundoplication, which gradually decreases with extended follow-up. For subjective follow-up, we used the same questionnaires at all intervals to make direct comparison possible. At the start of the study in 1997, there were no preferred validated questionnaires for gastroesophageal reflux

symptoms. Symptoms were assessed using a combination of symptom severity and frequency, a grading system described by our group in previous publications on the results of Belsey Mark IV fundoplication (Horbach, Gut 1994). The Visick score was applied to monitor the subjective effect of surgery as it correlates well to heartburn, and we and others have published validation studies (Rijnhart-de Jong, Scan J Gastroenterol 2008; Zeman, Surg Endosc 2005). The van Lanschot group validated the visual analog scale for quality of life assessment after esophageal surgery (de Boer, Qual Life Res 2004). Indeed there was a trend toward a higher quality of life and also a higher general state of health after laparoscopic surgery but this was not significant. A trend toward a more favorable outcome after laparoscopic surgery has been demonstrated. Regarding your third comment; even if we apply an intention-to-treat analysis and ascribe the patients who needed conversion in their original group, significant differences were demonstrated. If per-protocol analysis would have been chosen,the differences in the number of reinterventions would increase. In addition, the difference in the number of incisional hernia corrections reported after intention-to-treat analysis would increase if per-protocol analysis was applied. Intention-to-treat analysis is the way to analyze a randomized study and if per-protocol analysis had been applied, this would increase the differences reported. Thus, the results of this trial are actually in favor of the laparoscopic arm, irrespective of the type of analysis.

PROFESSOR P. SCHNEIDER: Reflux symptoms resolve briefly after surgery and dysphagia, even in your open group, resolved after 1 year. Do you have a logical explanation for the improvement of quality of life after 1 year? Second, in regards to your methodology section, you said that you used high-resolution manometry after 10 years of follow-up; however, you did not present the data. What
were your conclusions from the high resolution manometry results; a technique that was not available when you started the study?

DR. J. BROEDERS: In both groups, there was a significant increase in quality of life already 3 months after surgery. Afterwards quality of life remained on the same level and as a result there was no increase in quality of life between 3 months and 10 years of follow-up. In summary, there is an immediate and stable increase in quality of life. Regarding the results of high resolution manometry, 14 of the 20 patients that underwent high-resolution manometry had some form of abnormal manometric finding with no differences between the laparoscopic and the open group. High-resolution manometry was performed to analyze potential differences between symptomatic patients after laparoscopic and open fundoplication. Although the numbers are small, the most important finding is that there are no

differences in long-term effects on esophageal motility after laparoscopic and open Nissen fundoplication.

PROFESSOR T. LERUT: Your conclusion is that this surgery effectively controls acid reflux. To make that statement I think you should have done the same objective reevaluation in the asymptomatic patients. Not doing so somewhat weakens your conclusion. Also, in the symptomatic patients that were re-evaluated, I saw that there was a withdrawal of about half of the patients in each arm and that is a very high number. What is the reason was for this withdrawal? Second, why are asymptomatic patients continuing to take PPI or restarting to take PPI? Did they have non-acid reflux or, for instance, a hypersensitive esophagus? Did you perform, for instance, a Bernstein test with acid infusion to evaluate this?

DR. J. BROEDERS: Regarding your first comment, in fact we objectively reevaluated all patients, not only those who were symptomatic at 5 years and demonstrated that there were no differences between the 2 groups. It also became clear that less than 10% of the patients experienced recurrent acid reflux. We decided to limit the 10-year objective outcome assessment to patients that used PPIs as the a priori chance of the presence of recurrent reflux in asymptomatic patients is very low. At 10 years a substantial number of patients realized that they would not benefit from further invasive testing and many refused further participation in the objective assessment. Second, we know that patients used PPIs because their general practitioners tend to conclude, without further investigation, that recurrent reflux is the cause of symptoms and treat these patients accordingly. We have now demonstrated by impedance monitoring that their reflux symptoms were not correlated to both acidic and non-acidic reflux.

References

(1) NISSEN R. [A simple operation for control of reflux esophagitis.]. Laparoscopic Nissen fundoplication: preliminary report. Surg Laparosc Endosc 1991; 1:138-143.

(2) Dallemagne B, Weerts JM, Jehaes C, et al. Laparoscopic Nissen fundoplication preliminary report. Surg Laparosc Endosc. 1991;1:138 –143.

(3) Sandbu R, Khamis H, Gustavsson S et al. Long-term results of antireflux surgery indicate the need for a randomized clinical trial. Br J Surg 2002; 89:225-230.

(4) Franzen T, Anderberg B, Wiren M et al. Long-term outcome is worse after laparoscopic than after conventional Nissen fundoplication. Scand J Gastroenterol 2005; 40:1261-1268.

(5) Ackroyd R, Watson DI, Majeed AW et al. Randomized clinical trial of laparoscopic versus open fundoplication for gastro-oesophageal reflux disease. Br J Surg 2004; 91:975-982.

(6) Bais JE, Bartelsman JF, Bonjer HJ et al. Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. Lancet 2000; 355:170-174.

(7) Chrysos E, Tsiaoussis J, Athanasakis E et al. Laparoscopic vs open approach for Nissen fundoplication. A comparative study. Surg Endosc 2002; 16:1679-1684.

(8) Draaisma WA, Buskens E, Bais JE et al. Randomized clinical trial and follow-up study of cost-effectiveness of laparoscopic versus conventional Nissen fundoplication. Br J Surg 2006; 93:690-697.

(9) Heikkinen TJ, Haukipuro K, Koivukangas P et al. Comparison of costs between laparoscopic and open Nissen fundoplication: a prospective randomized study with a 3-month followup. J Am Coll Surg 1999; 188:368-376.

(10) Heikkinen TJ, Haukipuro K, Bringman S et al. Comparison of laparoscopic and open Nissen fundoplication 2 years after operation. A prospective randomized trial. Surg Endosc 2000; 14:1019-1023.

(11) Laine S, Rantala A, Gullichsen R et al. Laparoscopic vs conventional Nissen fundoplication. A prospective randomized study. Surg Endosc 1997; 11:441-444.

(12) Luostarinen M, Virtanen J, Koskinen M et al. Dysphagia and oesophageal clearance after laparoscopic versus open Nissen fundoplication. A randomized, prospective trial. Scand J Gastroenterol 2001; 36:565-571.

(13) Nilsson G, Larsson S, Johnsson F. Randomized clinical trial of laparoscopic versus open fundoplication: blind evaluation of recovery and discharge period. Br J Surg 2000; 87:873-878.

(14) Nilsson G, Larsson S, Johnsson F. Randomized clinical trial of laparoscopic versus open fundoplication: evaluation of psychological well-being and changes in everyday life from a patient perspective. Scand J Gastroenterol 2002; 37:385-391.

(15) Wenner J, Nilsson G, Oberg S et al. Short-term outcome after laparoscopic and open 360 degrees fundoplication. A prospective randomized trial. Surg Endosc 2001; 15:1124-1128.

(16) Nilsson G, Wenner J, Larsson S et al. Randomized clinical trial of laparoscopic versus open fundoplication for gastro-oesophageal reflux. Br J Surg 2004; 91:552-559.

(17) Salminen PT, Hiekkanen HI, Rantala AP et al. Comparison of long-term outcome of laparoscopic and conventional nissen fundoplication: a prospective randomized study with an 11-year follow-up. Ann Surg 2007; 246:201-206.

(18) Draaisma WA, Rijnhart-de Jong HG, Broeders IA et al. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. Ann Surg 2006; 244:34-41.

(19) Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001; 285:1987-1991.

(20) Rijnhart-de Jong HG, Draaisma WA, Smout AJ et al. The Visick score: a good measure for the overall effect of antireflux surgery? Scand J Gastroenterol 2008; 43:787-793.

(21) Zeman Z, Rozsa S, Tihanyi T et al. Psychometric documentation of a quality-of-life questionnaire for patients undergoing antireflux surgery (QOLARS). Surg Endosc 2005; 19:257-261.

(22) Velanovich V, Karmy-Jones R. Measuring gastroesophageal reflux disease: relationship between the Health-Related Quality of Life score and physiologic parameters. Am Surg 1998; 64:649-653.

(23) Horbach JM, Masclee AA, Lamers CB et al. Prospective evaluation of 24 hour ambulatory pH metry in Belsey Mark IV antireflux surgery. Gut 1994; 35:1529-1535.

(24) de Boer AG, van Lanschot JJ, Stalmeier PF et al. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? Qual Life Res 2004; 13:311-320.

(25) Nord E. The validity of a visual analogue scale in determining social utility weights for health states. Int J Health Plann Manage 1991; 6:234-242.

(26) Ghosh SK, Pandolfino JE, Rice J et al. Impaired deglutitive EGJ relaxation in clinical esophageal manometry: a quantitative analysis of 400 patients and 75 controls. Am J Physiol Gastrointest Liver Physiol 2007; 293:G878-G885.

(27) Wiener GJ, Richter JE, Copper JB et al. The symptom index: a clinically important parameter of ambulatory 24-hour esophageal pH monitoring. Am J Gastroenterol 1988; 83:358-361.

(28) Weusten BL, Roelofs JM, Akkermans LM et al. The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. Gastroenterology 1994; 107:1741-1745.

(29) Jamieson JR, Stein HJ, DeMeester TR et al. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. Am J Gastroenterol 1992; 87:1102-1111.

(30) Richter JE, Bradley LA, DeMeester TR et al. Normal 24-hr ambulatory esophageal pH values. Influence of study center, pH electrode, age, and gender. Dig Dis Sci 1992; 37:849-856.

(31) Nguyen NT, Goldman C, Rosenquist CJ et al. Laparoscopic versus open gastric bypass: a randomized study of outcomes, quality of life, and costs. Ann Surg 2001; 234:279-289.

(32) Puzziferri N, ustrheim-Smith IT, Wolfe BM et al. Three-year follow-up of a prospective randomized trial comparing laparoscopic versus open gastric bypass. Ann Surg 2006; 243:181-188.

(33) Catarci M, Gentileschi P, Papi C et al. Evidence-based appraisal of antireflux fundoplication. Ann Surg 2004; 239:325-337.

(34) Yang H, Watson DI, Lally CJ et al. Randomized trial of division versus nondivision of the short gastric vessels during laparoscopic Nissen fundoplication: 10-year outcomes. Ann Surg 2008; 247:38-42.

(35) Mardani J, Lundell L, Lonroth H et al. Ten-year results of a randomized clinical trial of laparoscopic total fundoplication with or without division of the short gastric vessels. Br J Surg 2008; 96:61-65.

(36) Cai W, Watson DI, Lally CJ et al. Ten-year clinical outcome of a prospective randomized clinical trial of laparoscopic Nissen versus anterior 180(degrees) partial fundoplication. Br J Surg 2008; 95:1501-1505.

(37) Jenkinson AD, Kadirkamanathan SS, Scott SM et al. Relationship between symptom response and oesophageal acid exposure after medical and surgical treatment for gastro-oesophageal reflux disease. Br J Surg 2004; 91:1460-1465.

(38) Lord RV, Kaminski A, Oberg S et al. Absence of gastroesophageal reflux disease in a majority of patients taking acid suppression medications after Nissen fundoplication. J Gastrointest Surg 2002; 6:3-9.

9

Impact of surgeon experience on 5-year outcome of laparoscopic Nissen fundoplication

J.A.J.L. Broeders[1]
W.A. Draaisma[1]
H.G. Rijnhart-de Jong[1]
A.J.P.M. Smout[2]
J.J.B. van Lanschot[3]
I.A.J.M. Broeders[4]
H.G. Gooszen[1]

[1]Dep. of Surgery, University Medical Center Utrecht
[2]Dep.of Gastroenterology, University Medical Center Utrecht
[3]Dep. of Surgery, Erasmus Medical Center, Rotterdam
[4]Dep. of Surgery, Meander Medical Center, Amersfoort

16th annual meeting of the European Association for Endoscopic Surgery
Stockholm, Sweden, June 2008

Archives of Surgery 2011; 146:340-6.

Abstract

Objective: To investigate the 5-year effect of surgeon experience with laparoscopic Nissen fundoplication (LNF). In 2000, a randomized controlled trial (RCT) was prematurely terminated, because LNF for gastroesophageal reflux disease was associated with a higher risk to develop dysphagia than conventional Nissen fundoplication (CNF). Critisism focused on alleged bias caused by the relative lack of experience with the laparoscopic approach of the participating surgeons.

Design: Multicenter RCT and prospective cohort study.

Setting: University medical centers and tertiary teaching hospitals.

Patients: In the RCT, 74 patients underwent CNF and 93 patients underwent LNF (LNFI). The complete set-up of the cohort study (LNFII) (n=121) mirrored the RCT, except that surgeon experience increased from more than 5 to more than 30 LNFs per surgeon.

Interventions: Conventional Nissen fundoplication, LNFI and LNFII.

Main outcome measures: Intra-operative and in-hospital characteristics, objective reflux control and clinical outcome.

Results: In LNFII, operating time (110 *vs* 165 min; P<0.001), dysphagia (2.5 *vs* 12.3%; P=0.008), dilatations for dysphagia (0.8 vs 7.0%; P=0.020), and conversions (3.5% *vs* 7.7%; P=0.192) were reduced compared with LNFI. Moreover, in LNFII, hospitalization (4.2 *vs* 5.6 days; P=0.073 and 4.2 *vs* 7.6 days; P<0.001) and in-hospital complications (5.1 *vs* 13.5%; P=0.046 and 5.1 *vs* 19.3%; P=0.005) were reduced compared with LNFI and CNF, respectively. In LNFII, the 6-month reintervention rate was reduced compared with LNFI (0.8 *vs* 10.1%; P=0.002). Esophagitis and esophageal acid exposure at 3 months and reflux symptoms, proton pump inhibitor use and quality of life at 5 years improved similarly.

Conclusions: Operating time, complications, hospitalization, early dysphagia, dilatations for dysphagia and reintervention rate after LNF, improve significantly when surgeon experience increases from more than 5 to more than 30 LNFs. In contrast, short-term objective reflux control and 5-year clinical outcome do not improve with experience. In experienced hands, LNF reduces in-hospital complications and hospitalization compared with CNF, with similar 5-year effectiveness and reoperation rate.

Introduction

Laparoscopic Nissen fundoplication (LNF) rapidly replaced conventional Nissen fundoplication (CNF) as surgical therapy for gastroesophageal reflux disease (GERD) after its first report in 1991.[1] As with the introduction of laparoscopic cholecystectomy, evidence from randomized studies that proved equivalence of the new approach was lacking at that time. Therefore, in 1997 a multicenter randomized clinical trial (RCT) was initiated in the Netherlands to compare the effectiveness of LNF (LNFI) with CNF. Interim analysis demonstrated that LNF carries a substantially higher risk to develop dysphagia needing dilatation or reoperation (LNF I 7 *vs* CNF 0; P = 0.016) than its open counterpart, and consequently, the trial was prematurely terminated.[2] The harsh criticism in response to the publication of these results[3-8] focussed on alleged bias caused by the relative lack of experience with the laparoscopic approach of the participating surgeons.

We responded by initiating a second, cohort study on LNF only (LNF II) to investigate the effect of experience on long-term outcome. In the cohort study, the complete set-up was the same as in the RCT, except that surgeon experience had grown from a minimum of 5 LNFs[9] to more than 30 LNFs per surgeon in accordance with new insights.[10-13] Participating surgeons, indications for surgery, techniques and patient management were identical to those in the RCT. As a result, the effect of surgical skill was the only new variable in this second study. The Achilles' heel of studies that have so far evaluated the effect of surgeon experience on the outcome of LNF is that surgical techniques have been changed during the course of the study.[9;14-17] These studies are biased because improvement of surgical technique, as well as increased experience, accounts for the better outcome in the latter patients. The purpose of this prospective study was thus to determine the isolated effect of surgeon experience on intra-operative and in-hospital characteristics, short-term objective reflux control, and 5-year outcome of LNF. These results were compared with the outcome after the initial LNF experience and CNF.

Methods

Study design and participants

From 1997 to 1999, 177 patients were included in a multicenter RCT to undergo Nissen fundoplication for refractory GERD. Surgical treatment was proposed to patients with heartburn and regurgitation, insufficiently responding to at least 40 mg of omeprazole daily. If 40 mg of omeprazole was insufficient to suppress symptoms, the dosage was raised to 40 mg 2 or 3 times daily. If symptoms

recurred after return to 40 mg daily, patients were classified as having proton pump inhibitor-refractory GERD. At the time of the interim analysis, 46 patients underwent CNF and 57 patients LNF. Four patients were never operated on, 6 patients withdrew; and, in the period needed for conducting and discussing the interim analysis, another 64 patients were randomized. Consequently, 74 patients underwent CNF and 93 patients underwent laparoscopic 360° fundoplication (LNFI). All participating surgeons had completed the learning curve of more than 5 LNFs for experienced laparoscopic surgeons and more than 20 for less experienced laparoscopic surgeons, defined by Watson et al.[9] The short-[2] and long-term[18] results of the RCT have been published previously. The operations of the second, cohort study, were performed by surgeons who participated in the initial RCT, after extension of the learning curve to a minimum of 30 LNFs in accordance with new insights.[10-13] The surgical techniques in the RCT included standardized mobilization of the esophagus over 5 to 7 cm in length, division of the short gastric vessels, posterior crural repair and creation of a floppy 360° fundoplication of 3 to 3.5 cm and were identical for the cohort study. The cranial fundoplication suture was also stitched to the diaphragm and the caudal suture was fixed to the esophagus at the level of the lower esophageal sphincter ("3-point fixation"). A total of 121 patients were included in the cohort study (LNFII).
Surgical techniques, operating time, blood loss, conversions, splenectomy rate, in-hospital complications and hospitalization were registered on case record forms. All patients were asked to fill out a questionnaire on quality of life (QoL), GERD symptoms and use of acid-suppressing drugs before surgery and at 3 months and 5 years after surgery. In addition, all patients were asked to rate the change in their reflux symptoms (Visick score) and general health status compared with the preoperative state. At 5 five years, patients were asked whether they would choose surgery again in retrospect. Surgical reinterventions, indications for reintervention and surgical procedures performed were recorded up to 5 years after initial surgery. For objective evaluation, all patients were asked to undergo upper endoscopy and 24-hour pH monitoring both before and at 3 months after surgery. These data and subjective outcome data were collected prospectively in consecutive patients.

Clinical outcome

The Visick score, the only "overall – score" available and validated, correlates well to the most prominent symptom of GERD (heartburn)[19] and to a validated questionnaire[20] for reflux symptoms[21] and was used in this study to score the effect of surgery on symptoms in 4 grades: complete resolution (grade I), improvement (grade II), no effect of surgery (grade III) or deterioration (grade IV), always in

comparison with their preoperative state. In addition, the *frequency* of heartburn, regurgitation and dysphagia were scored from 0 to 5. The *severity* of these symptoms was scored from 0 to 3. For the final assessment of these symptoms a combined *frequency* and *severity* grading system was used resulting in a grade from 0 (symptom absent) to 3 (symptom frequent and severe).[22] The impact on quality of life was measured using a visual analogue scale (VAS), validated for quality of life assessment after esophageal surgery.[23] The scale of this instrument ranged from worst possible health to perfect health (0-100).[24]

Upper gastrointestinal endoscopy

Experienced gastroenterologists evaluated the presence of esophagitis and hiatal hernia size during endoscopy. Initially, the Savary-Miller classification[25] was used to grade esophagitis and later the Los Angeles classification[26] for esophagitis was applied.

24-hour esophageal pH monitoring

Ambulatory 24-h pH monitoring was performed according to previously described methods[27], after suspending medication that could affect the results at least 7 days beforehand.

Statistical analysis

For parameters that were scored before and after surgery, only those patients were included for whom both the preoperative data and the results at 3 months or 5 years after surgery were available. The number of patients for whom data were available was determined for each parameter. Continuous variables were expressed as mean and standard error of the mean (SEM) and were analyzed for differences between the 3 three groups using a 1-way ANOVA and Bonferroni post-hoc test. To determine significant effects of surgery on quantitive data, the paired-samples *t*-test was used. The χ^2 test was used to compare nominal variables between groups, and effects of surgery on these variables were analysed using the McNemar–Bowker test. Differences were considered statistically significant at a *P* value less than 0.05. Statistical analysis was performed using SPSS® version 15.0 (SPSS, Chicago, Illinois).

Results

Patient population

The study population comprised 288 patients (74 CNF, 93 LNFI and 121 LNFII). Patient characteristics and mean hiatal hernia size were similar at baseline (table 1).

Procedural characteristics

All but 3 surgical procedures included mobilization of the fundus with division of the short gastric vessels. Mean length of the fundoplication and the percentage of patients with crural repair and 3-point fixation of the fundoplication were similar in CNF, LNFI and CNFII (table 2). In the second LNF cohort, skin-to-skin time was reduced compared with the first LNF group (110 (3.7) vs 165 (5.3) min; $P < 0.001$)

Table 1 Patient characteristics

	CNF	**LNF I**	**LNF II**
Patients (*n*)	74	93	121
Age (yr)	42.6 (20-77)	42.5 (17-85)	41.0 (16-64)
Male / female	49 / 25	42 / 51	78 / 43
Body Mass Index (BMI) *	26.7 (0.4)	26.1 (0.5)	26.1 (0.5)
Hiatal hernia (cm) *	2.8 (0.3)	3.4 (0.4)	3.0 (0.3)

* values are given as mean (SEM)

Table 2 Surgical techniques of CNF, LNF I and LNF II

	CNF	**LNF I**	**LNF II**
Mobilization of the fundus and division of the short gastric vessels (n [%]) CNF n=68 LNF I n=91 LNF II n=113	67 [98.5]	89 [97.8]	113 [100]
Crural repair (n [%]) CNF n=64 LNF I n=89 LNF II n=111	51 [79.7]	67 [75.3]	111 [100]
Three-point fixation fundoplication (n [%]) CNF n=66 LNF I n=90 LNF II n=112	60 [90.9]	72 [80.0]	112 [100]
Fundoplication length (cm)* CNF n=52 LNF I n=52 LNF II n=105	3.4 (0.1)	3.4 (0.1)	3.1 (0.1)

* values are given as mean (SEM)

and approached the operating time of the open procedure (98 (4.3) min; *P* = 0.224). Blood loss was reduced in the LNFI and LNFII group compared with the CNF group (92 (19) vs 207 (41) mL; *P* = 0.035 and 107 (29) vs 207 (41) mL; *P* = 0.065). There were no differences in splenectomy rate between LNFI and LNFII (0.8 vs 1.8%; *P* = 0.584). In LNFII the conversion rate was substantially reduced compared with LNFI, but this difference did not reach statistical significance (3.5 vs 7.7%; *P* = 0.192). There was a non-significant trend towards a lower splenectomy rate in the LNF II cohort compared with the CNF cohort as well (0.8 vs 4.3%; *P* = 0.126) (table 3).

Table 3 Procedural characteristics

	CNF	LNF I	LNF II
Operating time (min)* CNF n=62 LNF I n=81 LNF II n=109	98 (4.3)	165 (5.3) ~	110 (3.7) †
Blood loss (ml)* CNF n=62 LNF I n=81 LNF II n=101	207 (41)	92 (19) ~	107 (29) ‡
Conversion rate (n [%]) LNF I n=91 LNF II n=113	-	7 [7.7]	4 [3.5]
Splenectomy (n [%]) CNF n=46 LNF I n=57 LNF II n=121	2 [4.3]	1 [1.8]	1 [0.8]

* values are given as mean (SEM), ~ *P* < 0.05 vs CNF, † *P* < 0.05 vs LNFI, ‡ *P* = 0.065 vs CNF

Hospital stay and in-hospital complications

Mean hospital stay was reduced from 7.6 (0.7) days after CNF to 5.6 (0.4) days after LNFI (*P* = 0.009). Hospitalization decreased even more after LNFII to 4.2 (0.4) days, both compared with CNF (*P* < 0.001) and LNFI (*P* = 0.073). In-hospital complications were significantly lower after LNFII, compared with CNF (5.1 vs 19.3%; *P* = 0.005) and LNFI (5.1 vs 13.5%; *P* = 0.046) (table 4).

Clinical outcome 3 months after surgery

The prevalence of dysphagia was higher after LNFI, compared with both CNF (12.3 vs 0%; *P* = 0.014) and LNFII (12.3 vs 2.5%; *P* = 0.008). Compared with CNF and LNF II the percentage of patients who underwent dilatation for dysphagia was

higher after LNFI as well (0 vs 7.0%; *P* = 0.067 and 0.8 vs 7.0%; *P* = 0.020) (table 4). Quality of life and the percentage of patients using acid suppressing drugs improved significantly at 3 months compared with preoperatively, with no differences between the groups (figure 1 and 2).

Objective outcome 3 months after surgery

The effectiveness of surgery in terms of controlling esophagitis and the esophageal acid exposure was high (all *P* < 0.001 vs preoperatively), without divergences in any of the 3 groups before or after surgery (figure 3 and 4).

Table 4 Hospital stay, in-hospital complications and (dilatations for) dysphagia 3 months after CNF, LNF I and LNF II.

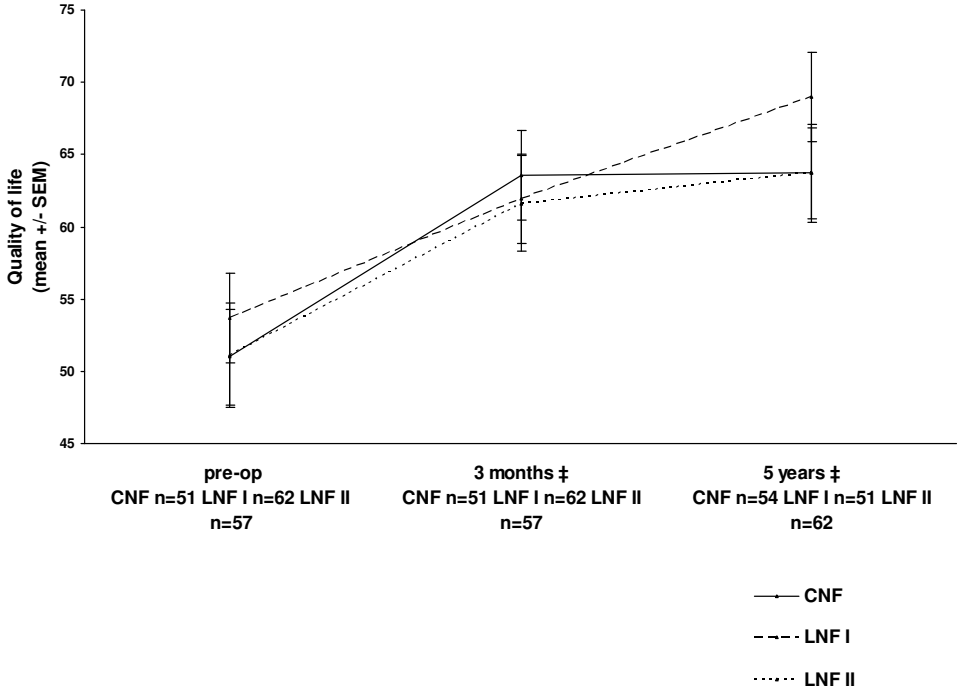
	CNF	**LNF I**	**LNF II**
Hospital stay (days)*	7.6 (0.7)	5.6 (0.4) ♦	4.2 (0.4) ♦ †
CNF n=59 LNF I n=89 LNF II n=102			
In-hospital complications (n [%])	11 [19.3]	12 [13.5]	5 [5.1] ♦ ‡
CNF n=57 LNF I n=89 LNF II n=98			
Ileus	2	-	-
Pneumothorax	1	3	-
Wound infection	2	1	1
Wound abscess	2	1	-
Subphrenic abscess	1	1	1
Intrathoracic herniation	1	1	-
Pleural effusion	-	2	-
Other complications	2	3	3
Dysphagia (n [%])	0 [0]	7 [12.3] ♦	3 [2.5] ‡
CNF n=46 LNF I n=57 LNF II n=121			
Dilatations for dysphagia (n [%])	0 [0]	4 [7.0]	1 [0.8] ‡
CNF n=46 LNF I n=57 LNF II n=121			

* values are given as mean (SEM), ♦ *P* < 0.05 vs CNF, ‡ *P* < 0.05 vs LNFI, † *P* = 0.073 vs LNFI

Clinical outcome 5 years after surgery

The self-rated effect of surgery on reflux symptoms was similar in the 3 groups. At 5 years, the 3 groups had similar heartburn, regurgitation and dysphagia grades. The self-rated change in general health and the percentage of patients who would choose surgery again in retrospect was similar as well (table 5). Quality of life and the percentage of patients using acid suppressing drugs remained significantly improved at 5 years compared with the preoperative values, without significant differences between the 3 groups (figure 1 and 2). However, the use of acid suppressing drugs increased with time in the 3 groups.

Figure 1 Quality of life (VAS) before surgery and 3 months and 5 years after CNF, LNF I and LNF II

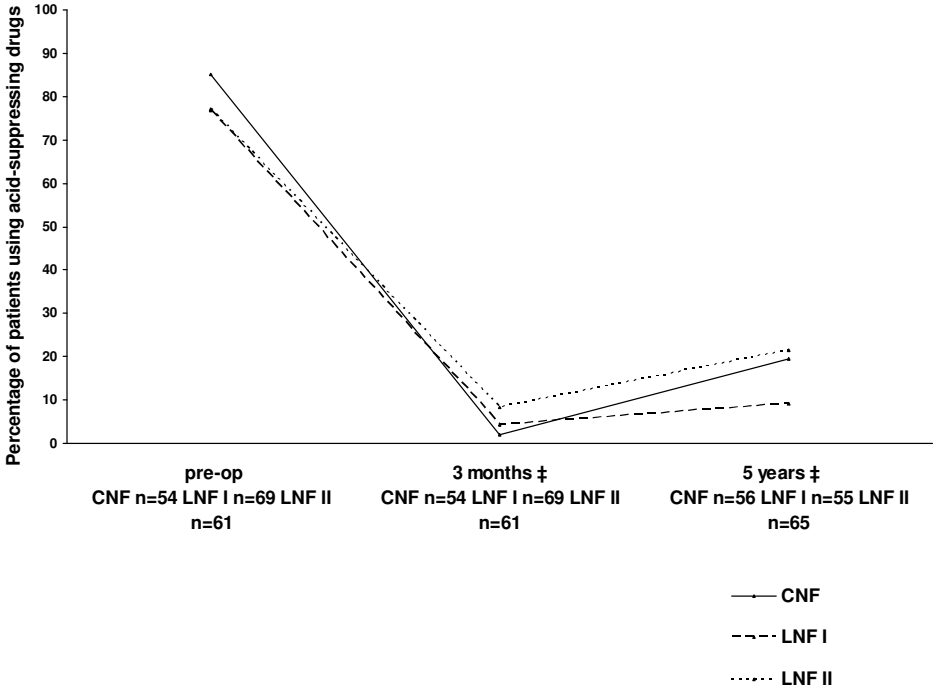


‡ $P < 0.05$ vs preoperative results for the three groups

Table 5 Clinical outcome 5 years after CNF, LNF I and LNF II.

	CNF	LNF I	LNF II
Change in reflux symptoms(n [%])			
CNF n=64 LNF I n=72 LNF II n=98			
Visick I: resolved	30 [46.9]	37 [51.4]	49 [50.0]
Visick II: improved	26 [40.6]	31 [43.1]	39 [39.8]
Visick III: unchanged	3 [4.7]	2 [2.8]	4 [4.1]
Visick IV: worsened	5 [7.8]	2 [2.8]	6 [6.1]
Heartburn (n [%])			
CNF n=66 LNF I n=74 LNF II n=96			
Grade 0	38 [57.6]	46 [62.2]	59 [61.5]
Grade 1	18 [27.3]	26 [35.1]	28 [29.2]
Grade 2	9 [13.6]	2 [2.7]	6 [6.3]
Grade 3	1 [1.5]	-	3 [3.1]
Regurgitation (n [%])			
CNF n=63 LNF I n=71 LNF II n=95			
Grade 0	41 [65.1]	54 [76.1]	70 [73.7]
Grade 1	13 [20.6]	15 [21.1]	19 [20.0]
Grade 2	8 [12.7]	2 [2.8]	4 [4.2]
Grade 3	1 [1.6]	-	2 [2.1]
Dysphagia (n [%])			
CNF n=63 LNF I n=71 LNF II n=96			
Grade 0	29 [46.0]	38 [53.5]	49 [51.0]
Grade 1	25 [39.7]	28 [39.4]	35 [36.5]
Grade 2	6 [9.5]	5 [7.0]	6 [6.3]
Grade 3	3 [4.8]	-	6 [6.3]
Change in general health (n [%])			
CNF n=65 LNF I n=74 LNF II n=98			
Improved	49 [75.4]	56 [75.7]	72 [73.5]
Unchanged	10 [15.4]	12 [16.2]	13 [13.3]
Worsened	6 [9.2]	6 [8.1]	13 [13.3]
Opt for surgery in retrospect (n [%])			
CNF n=65 LNF I n=72 LNF II n=96			
Yes	43 [66.2]	55 [76.4]	77 [80.2]
No	11 [16.9]	8 [11.1]	10 [10.4]
No opinion	11 [16.9]	9 [12.5]	9 [9.4]

Figure 2 Percentage of patients using acid-suppressing drugs before surgery and 5 years after CNF, LNF I and LNF II

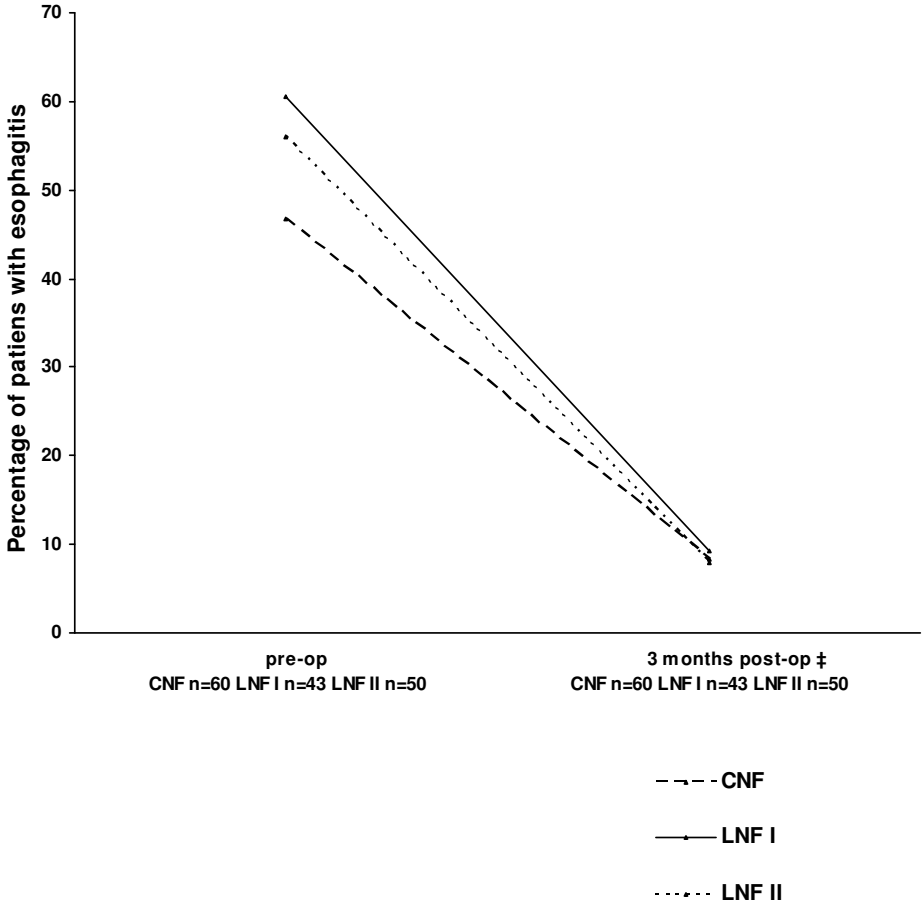


‡ $P < 0.001$ vs preoperative results for the three groups

Surgical reintervention

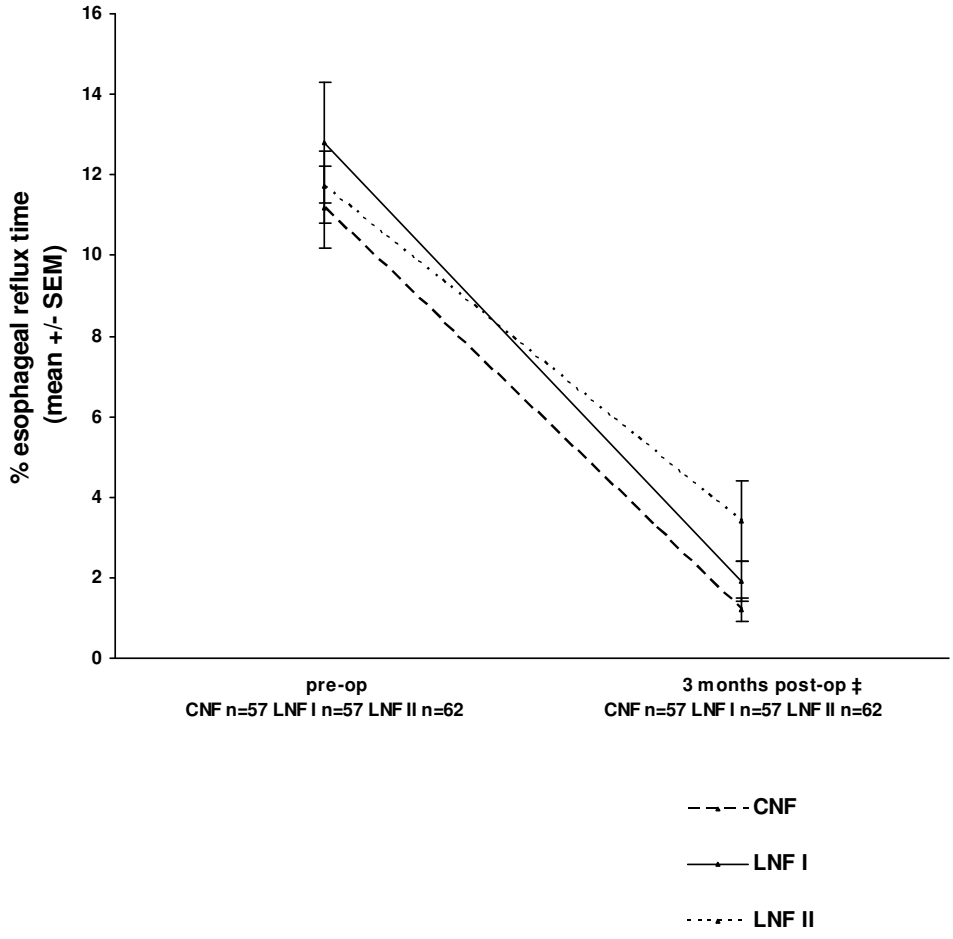
After LNFII, the high early reintervention rate that was observed in LNFI was no longer shown (figure 5). At 6 months, the reintervention rate was significantly higher after LNFI (10.1%), compared with CNF (1.4%; $P = 0.028$) and LNFII (0.8%; $P = 0.002$). In the LNFI group, most patients underwent reoperation for persistent dysphagia. The percentage of patients free from re-intervention stabilized after 12 months in the LNFI group, while in the CNF and LNFII groups, this took 2.5 years. As a result, the difference in reintervention rate after LNFI (15.2%) was reduced and lost significance at 5 years compared with CNF (11.6%; $P = 0.523$) and LNFII (11.6%; $P = 0.457$). The shift of the reintervention curve from LNF I to LNF II, illustrates the effect of surgeon experience on outcome (figure 5). The indications for surgical reintervention are presented in table 6.

Figure 3 Percentage of patients with esophagitis before surgery and 3 months after CNF, LNF I and LNF II



‡ $P < 0.05$ vs preoperative results for the three groups

Figure 4 Total esophageal acid exposure time before surgery and 3 months after CNF, LNF I and LNF II



‡ $P < 0.001$ vs preoperative results for the three groups

Figure 5 Time curve of percentage of patients free from reintervention after CNF, LNF I and LNF II

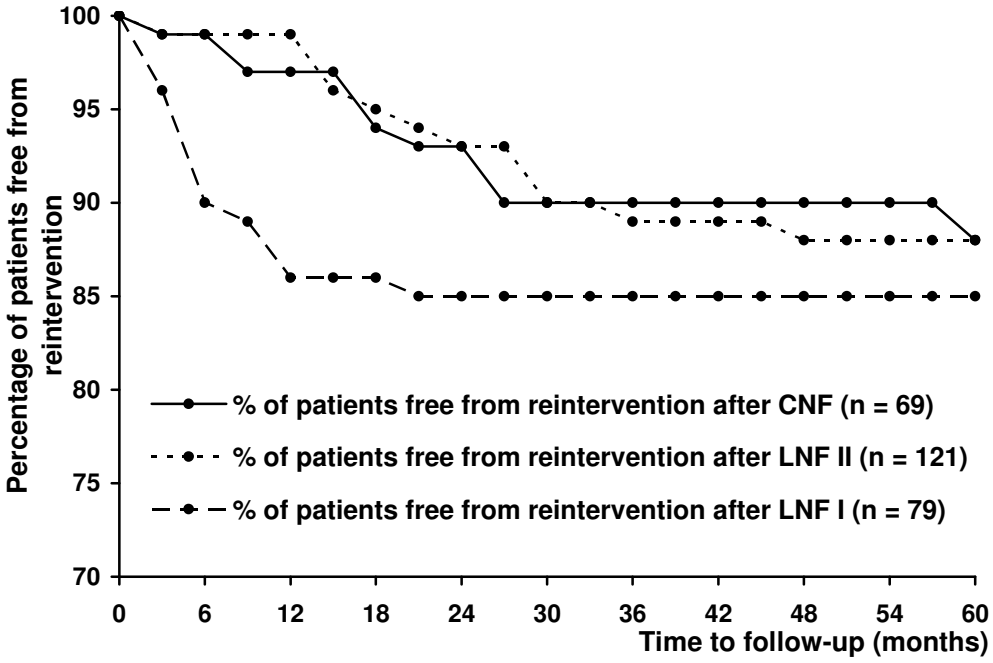


Table 6 Surgical reinterventions and reoperation indications 5 years after CNF, LNF I and LNF II.

	CNF n=69	LNF I n=79	LNF II n=121
Surgical reintervention (n [%])	8 [11.6]	12 [15.2]	14 [11.6]
Reoperation indication (n [%])			
Persistent dysphagia (> 3 months)	2 [2.9]	6 [7.6]	6 [5.0]
Recurrent reflux	3 [4.3]	2 [2.5]	5 [4.1]
Dysphagia and recurrent reflux	2 [2.9]	2 [2.5]	-
Intrathoracic migration	1 [1.4]	1 [1.3]	3 [2.5]*
Cicatricial hernia	-	1 [1.3]	-

* including a patient who needed reoperation for a para-esophageal hernia due to a car accident

Discussion

In 2000 an RCT was prematurely terminated at interim analysis, because LNF for GERD was associated with a higher risk to develop dysphagia than CNF.[2] The indication for surgery, construction of the fundoplication and potential bias caused by relative lack of laparoscopic experience were criticized after the publication of the trial.[3-8] The current study was designed to evaluate whether the unfavorable outcome after LNF was the result of relative inexperience with the laparoscopic approach. A long-term cohort study was initiated, mirroring the methods of the RCT, except for the laparoscopic experience that had grown to more than 30 LNFs per surgeon. Previous studies that evaluate the impact of surgeon experience on outcome are biased because surgical techniques changed during the study. In contrast, the present study further expands on the data currently available in the literature by showing the isolated effect of surgeon experience on long-term outcome of LNF. Operating time, conversion rate and complications are the most commonly used parameters to define the effect of experience on outcome of antireflux surgery.[9;14-16] However, objective reflux control and long-term subjective outcome would be more relevant in clinical practice. To our knowledge, the current study is the first to objectively document the effect of surgeon experience on 5-year outcome of LNF.

Studies that evaluate the impact of individual surgeon experience are scarce, but several studies have investigated the effect of institutional experience on outcome of LNF. In line with the results of the present study, these reports have demonstrated that experience reduces operating time[9;11-13;15;28-32], conversions[9-13;28;29;32], intra-operative complications[12;30], in-hospital complications[11;30;32], hospital stay[13;31], early dysphagia[10;11;15] and reinterventions.[9] In agreement with the present study, the only study that evaluated the effect on acid exposure during postoperative 24-h pH monitoring did not identify differences between the first 40 and subsequent institutional cases.[29] The current study did not focus on the effect of institutional expert experience, but on individual surgeon experience in a pragmatic trial with “all-day practice” applicability. It demonstrates significant improvement of highly comparable parameters.

The results of the current study should be compared with those of 6 earlier studies that report on the impact of individual surgeon experience.[9;14-17;33] The results of the studies that have previously addressed this issue are biased because changes in surgical techniques were introduced in the course of the study.[9;14-17] As a result, the effect of the increase in experience cannot be separated from the impact of changes in surgical technique. In the present study, surgical technique was deliberately left unchanged during the course of the study. The only previous study

free of modifications of surgical techniques, violated the intention-to-treat principle because patients with major complications were excluded from follow-up and this percentage was twice as high in the learning group.[33] Despite these sources of bias, the results of the previous studies are in line with the present report and demonstrate that individual surgeon experience reduces operating time[9;14;15;17], conversions[9;14;17], in-hospital complications[15;17], hospital stay[14], early dysphagia[15;17], dilatations for dysphagia[14;16;17] and surgical reinterventions[9;14] of LNF. In contrast, the current study and earlier reports show that objective reflux control[33] and long-term clinical outcome[17] are not correlated with experience. Once a good result is obtained, the effect lasts up to at least 5 years after surgery, as shown by postoperative reflux symptoms, proton pump inhbitor use and quality of life.

The current analysis confirms the criticism expressed in 2000 by showing that early outcome of LNF improves with experience increasing from 5 to a minimum of 30 procedures. Moreover, it shows a reduction of blood loss, splenectomy rate, in-hospital complications and duration of hospitalization, with similar long-term effectiveness and reoperation rate compared with CNF. Two recent meta-analyses comparing LNF and CNF confirm that the most important benefits of LNF are reduction of in-hospital complications and hospital stay, with similar efficacy compared with CNF.[34;35] The 10-year results of 2 RCTs comparing LNF and CNF have demonstrated that laparoscopic fundoplication reduces the incidence of incisional hernias[36] and incisional hernia corrections.[37] In contrast, the current study reports only 1 incisional hernia correction in the first laparoscopic cohort and none in the open group and the second laparoscopic cohort at 5 years. Our group has previously demonstrated that the higher rate of incisional hernias after open surgery is not present at 5 years[18] and becomes clinically relevant between 5 and 10 years of follow-up.[36;37]

In conclusion, this analysis clearly illustrates the effect of experience on the early outcome of laparoscopic antireflux surgery and represents a plea for centralization or concentration of expertise, even more so because the outcome after reoperation is inferior to that of the primary operation.[38;39]

References

(1) Dallemagne B, Weerts JM, Jehaes C, Markiewicz S, Lombard R. Laparoscopic Nissen fundoplication: preliminary report. Surg Laparosc Endosc 1991; 1(3):138-143.

(2) Bais JE, Bartelsman JF, Bonjer HJ, Cuesta MA, Go PM, Klinkenberg-Knol EC et al. Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. Lancet 2000; 355(9199):170-174.

(3) Bloechle C, Mann O, Gawad KA, Izbicki JR. Gastro-oesophageal reflux disease. Lancet 2000; 356(9223):69-3.

(4) Gorecki PJ, Hinder RA. Gastro-oesophageal reflux disease. Lancet 2000; 356(9223):70-73.

(5) Booth M, Dehn TC. Gastro-oesophageal reflux disease. Lancet 2000; 356(9223):70-71.

(6) Pellegrini CA. Gastro-oesophageal reflux disease. Lancet 2000; 356(9223):71-73.

(7) de Beaux AC, Watson DI, Jamieson GG. Gastro-oesophageal reflux disease. Lancet 2000; 356(9223):71-72.

(8) de Brauw LM, Beets GL. Gastro-oesophageal reflux disease. Lancet 2000; 356(9223):69-70.

(9) Watson DI, Baigrie RJ, Jamieson GG. A learning curve for laparoscopic fundoplication. Definable, avoidable, or a waste of time? Ann Surg 1996; 224(2):198-203.

(10) Voitk A, Joffe J, Alvarez C, Rosenthal G. Factors contributing to laparoscopic failure during the learning curve for laparoscopic Nissen fundoplication in a community hospital. J Laparoendosc Adv Surg Tech A 1999; 9(3):243-248.

(11) Champault GG, Barrat C, Rozon RC, Rizk N, Catheline JM. The effect of the learning curve on the outcome of laparoscopic treatment for gastroesophageal reflux. Surg Laparosc Endosc Percutan Tech 1999; 9(6):375-381.

(12) Soot SJ, Eshraghi N, Farahmand M, Sheppard BC, Deveney CW. Transition from open to laparoscopic fundoplication: the learning curve. Arch Surg 1999; 134(3):278-281.

(13) Deschamps C, Allen MS, Trastek VF, Johnson JO, Pairolero PC. Early experience and learning curve associated with laparoscopic Nissen fundoplication. J Thorac Cardiovasc Surg 1998; 115(2):281-284.

(14) Gill J, Booth MI, Stratford J, Dehn TC. The extended learning curve for laparoscopic fundoplication: a cohort analysis of 400 consecutive cases. J Gastrointest Surg 2007; 11(4):487-492.

(15) Hwang H, Turner LJ, Blair NP. Examining the learning curve of laparoscopic fundoplications at an urban community hospital. Am J Surg 2005; 189(5):522-526.

(16) Munro W, Brancatisano R, Adams IP, Falk GL. Complications of laparoscopic fundoplication: the first 100 patients. Surg Laparosc Endosc 1996; 6(6):421-423.

(17) Salminen P, Hiekkanen H, Laine S, Ovaska J. Surgeons' experience with laparoscopic fundoplication after the early personal experience: does it have an impact on the outcome? Surg Endosc 2007; 21(8):1377-1382.

(18) Draaisma WA, Rijnhart-de Jong HG, Broeders IA, Smout AJ, Furnee EJ, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. Ann Surg 2006; 244(1):34-41.

(19) Rijnhart-de Jong HG, Draaisma WA, Smout AJ, Broeders IA, Gooszen HG. The Visick score: a good measure for the overall effect of antireflux surgery? Scand J Gastroenterol 2008; 43(7):787-793.

(20) Velanovich V, Karmy-Jones R. Measuring gastroesophageal reflux disease: relationship between the Health-Related Quality of Life score and physiologic parameters. Am Surg 1998; 64(7):649-653.

(21) Zeman Z, Rozsa S, Tihanyi T, Tarko E. Psychometric documentation of a quality-of-life questionnaire for patients undergoing antireflux surgery (QOLARS). Surg Endosc 2005; 19(2):257-261.

(22) Horbach JM, Masclee AA, Lamers CB, Gooszen HG. Prospective evaluation of 24 hour ambulatory pH metry in Belsey Mark IV antireflux surgery. Gut 1994; 35(11):1529-1535.

(23) de Boer AG, van Lanschot JJ, Stalmeier PF, van Sandick JW, Hulscher JB, de Haes JC et al. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? Qual Life Res 2004; 13(2):311-320.

(24) Nord E. The validity of a visual analogue scale in determining social utility weights for health states. Int J Health Plann Manage 1991; 6(3):234-242.

(25) Savary M, Miller G. The esophagus. *ed Handbook and atlas of endoscopy Solothurn, Switzerland: Verlag Gossman*. ed. 1978.

(26) Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999; 45(2):172-180.

(27) Draaisma WA, Ruurda JP, Scheffer RC, Simmermacher RK, Gooszen HG, Rijnhart-de Jong HG et al. Randomized clinical trial of standard laparoscopic versus robot-assisted laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease. Br J Surg 2006; 93(11):1351-1359.

(28) Paluzzi MW. Laparoscopic Nissen fundoplication at a teaching center: prospective analysis of 103 consecutive patients. Surg Laparosc Endosc 1997; 7(5):363-368.

(29) Remzi M, Lenglinger J, Erne B, Bagmet N, Fugger R, Bischof G et al. [Effect of the learning phase on safety and efficiency of laparoscopic fundoplication]. Chirurg 2001; 72(3):261-265.

(30) Endzinas Z, Maleckas A, Mickevicius A, Kiudelis M. [Follow-up results and learning curve in laparoscopic gastrofundoplications]. Zentralbl Chir 2002; 127(11):939-943.

(31) Gotley DC, Smithers BM, Rhodes M, Menzies B, Branicki FJ, Nathanson L. Laparoscopic Nissen fundoplication--200 consecutive cases. Gut 1996; 38(4):487-491.

(32) Zacharoulis D, O'Boyle CJ, Sedman PC, Brough WA, Royston CM. Laparoscopic fundoplication: a 10-year learning curve. Surg Endosc 2006; 20(11):1662-1670.

(33) Contini S, Scarpignato C. Does the learning phase influence the late outcome of patients with gastroesophageal reflux disease after laparoscopic fundoplication? Surg Endosc 2004; 18(2):266-271.

(34) Catarci M, Gentileschi P, Papi C, Carrara A, Marrese R, Gaspari AL et al. Evidence-based appraisal of antireflux fundoplication. Ann Surg 2004; 239(3):325-337.

(35) Peters MJ, Mukhtar A, Yunus RM, Khan S, Pappalardo J, Memon B et al. Meta-analysis of randomized clinical trials comparing open and laparoscopic anti-reflux surgery. Am J Gastroenterol 2009; 104(6):1548-1561.

(36) Salminen PT, Hiekkanen HI, Rantala AP, Ovaska JT. Comparison of long-term outcome of laparoscopic and conventional nissen fundoplication: a prospective randomized study with an 11-year follow-up. Ann Surg 2007; 246(2):201-206.

(37) Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. Ann Surg 2009; 250(5):698-706.

(38) Furnee EJ, Draaisma WA, Broeders IA, Smout AJ, Gooszen HG. Surgical reintervention after antireflux surgery for gastroesophageal reflux disease: a prospective cohort study in 130 patients. Arch Surg 2008; 143(3):267-274.

(39) Furnee EJ, Draaisma WA, Broeders IA, Gooszen HG. Surgical reintervention after failed antireflux surgery: a systematic review of the literature. J Gastrointest Surg 2009; 13(8):1539-1549.

10

Systematic review and meta-analysis of laparoscopic Nissen (posterior total) *versus* Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease

J.A.J.L. Broeders[1]
F.A. Mauritz[1]
U. Ahmed Ali[1]
W.A. Draaisma[1]
J.P. Ruurda[1]
H.G. Gooszen[1]
A.J.P.M. Smout[2]
I.A.M.J. Broeders[3]
E.J. Hazebroek[1]

[1]Dep. of Surgery, University Medical Center Utrecht
[2]Dep.of Gastroenterology, University Medical Center Utrecht
[3]Dep. of Surgery, Meander Medical Center, Amersfoort

18th annual meeting of the European Association for Endoscopic Surgery
Geneva, Switzerland, June 2010
12th world congress of the International Society for Diseases of the Esophagus
Kagoshima, Japan, September 2010

British Journal of Surgery 2010; 97:1318-30.
Nederlands Tijdschrift voor Heelkunde 2011; in press.

Abstract

Background: Laparoscopic Nissen fundoplication (LNF) is currently considered the surgical therapy of choice for gastro-oesophageal reflux disease (GORD). Laparoscopic Toupet fundoplication (LTF) has been said to reduce troublesome dysphagia and gas-related symptoms. A systematic review and meta-analysis of randomized controlled trials (RCTs) was performed to compare outcome after LNF with that following LTF.

Methods: Four electronic databases (MEDLINE, Embase, Cochrane Library and ISI Web of Knowledge CPCI-S) were searched for RCTs comparing primary LNF with LTF for GORD. The methodological quality of all included trials was evaluated. Primary outcomes were recurrent pathological acid exposure, oesophagitis, dysphagia, dilatation for dysphagia and reoperation rate. Results were pooled in meta-analyses as risk ratios (RRs [95 per cent confidence interval]) and weighted mean differences.

Results: Seven eligible RCTs comparing LNF (n=404) with LTF (n=388) were identified. LNF was associated with a significantly higher prevalence of postoperative dysphagia (RR1.61 [1.06,2.44];P=0.02) and dilatation for dysphagia (RR2.45 [1.06,5.68]; P=0.04). The number of surgical reinterventions was higher after LNF (RR2.19 [1.09,4.40]; P=0.03). There were no differences regarding recurrent pathological acid exposure (RR1.26 [0.82,1.95]; P=0.29), oesophagitis (RR1.20 [0.78,1.85]; P=0.40), subjective reflux recurrence, patient satisfaction, operating time or in-hospital complications. The prevalence of inability to belch (RR2.04 [1.19,3.49], P=0.009) and gas bloating (RR1.58, [1.21,2.05]; P<0.001) was higher after LNF.

Conclusion: LTF reduces postoperative dysphagia and dilatation for dysphagia compared with LNF. Reoperation rate and prevalence of gas-related symptoms were lower after LTF with similar reflux control. These results provide level 1a support for the use of LTF as the posterior fundoplication of choice for GORD.

Introduction

Laparoscopic Nissen fundoplication (LNF) is the most frequently performed operation for gastro-oesophageal reflux disease (GORD). Accepted indications for antireflux surgery are persistent regurgitation despite adequate medical therapy, incomplete response to acid-suppressing drugs in patients with proven reflux, and unwillingness to take lifelong medication[1–3]. Several randomized studies have demonstrated that LNF has similar 5-year[4] and 10-year[5] rates for disease control, and fewer wound-related problems, compared with open fundoplication. LNF has been recommended as the surgical therapy of choice by the European Study Group for Antireflux Surgery[6] and the Society of American Gastrointestinal Endoscopic Surgeons[7].

Although LNF ensures long-term reflux control, postfundoplication symptoms may occur[8–11]. Some 8–12 per cent of patients develop severe dysphagia[12–15] and 19 per cent suffer from gas-related symptoms[16]. Laparoscopic Toupet fundoplication (LTF) has been proposed as an alternative operation. LTF differs from LNF by a partial posterior instead of a circumferential posterior fundoplication, with a different method of fixation[17]. It has been suggested that LTF reduces the prevalence of postoperative dysphagia[18,19] and bloating[20,21] compared with LNF. Despite these potential benefits, LTF is not widely used, probably because uncontrolled studies have reported less effective reflux control compared with LNF[22–27]. Partial fundoplication was then proposed as potentially the better procedure for patients with preoperative oesophageal motility disorders to minimize postfundoplication complaints, until randomized clinical trials (RCTs) demonstrated no increase in symptoms following total fundoplication in these patients[28–31].

In the last 2 years, large RCTs comparing LNF with LTF have been published. Results of these individual RCTs have not provided a definitive answer. Most trials do not show significant differences. The present study aimed systematically to review and perform meta-analyses of all RCTs comparing LNF with LTF for GORD, and to generate the highest level of evidence to determine which procedure should be regarded as the surgical therapy of choice.

Methods

Study selection

A systematic literature search with predefined search terms was carried out in MEDLINE (1960 to 2009)[32], Embase (from 1980)[33], Cochrane Library (issue 1, 2009) and the ISI Web of Knowledge Conference Proceedings Citation Index – Science (CPCI-S; from 1990) databases for articles published to 30 December

2009 (*Fig. 1*). All identified articles were screened for cross-references. Language restrictions were not applied.

Inclusion criteria

Titles and abstracts of all identified articles were screened for the following inclusion criteria: study population – adult patients with established GORD undergoing primary antireflux surgery; intervention – clearly documented surgical technique of LNF as laparoscopic Nissen or posterior total (360°) fundoplication, irrespective of division of the short gastric vessels[16], and of LTF as laparoscopic Toupet or posterior partial fundoplication covering the oesophagus 200–270°; study outcomes – at least one of the outcome measures reported below; study design – patients assigned to either LNF or LTF by random allocation; publication – published as an article in a peer-reviewed journal.

Exclusion criteria

Studies were excluded from analysis if they did not meet the inclusion criteria, or if it was impossible to extract or calculate appropriate data from the published results and the corresponding author was not able to provide data requested. Abstracts of RCTs were excluded as the methodological quality and risk of bias of these studies could not be assessed.

Outcomes of interest and definitions

Outcome measures examined were: recurrent or persistent pathological acid exposure on pH monitoring, endoscopic oesophagitis, dysphagia, postoperative dilatation for dysphagia, reoperation rate, inability to belch, gas bloating, hyperflatulence, subjective reflux persistence and/or recurrence (defined as postoperative heartburn on a dichotomous scale or unchanged to worsened reflux symptoms compared with the preoperative state[34]), satisfaction with the intervention, mean lower oesophageal sphincter (LOS) pressure on manometry, operating time, mortality and in-hospital complications, and length of hospital stay. Short-term clinical outcomes were excluded and results acquired after at least 1 year of follow-up were pooled.

Data extraction

Titles and abstracts of all retrieved records, and subsequently full-text articles, were examined independently by two authors (J.A.J.L.B., F.A.M.) according to the Quality of Reporting of Meta-analyses (QUOROM) guidelines[35]. The following data were extracted separately by the same two authors for all studies meeting the inclusion criteria: reference of study, study population characteristics, study design,

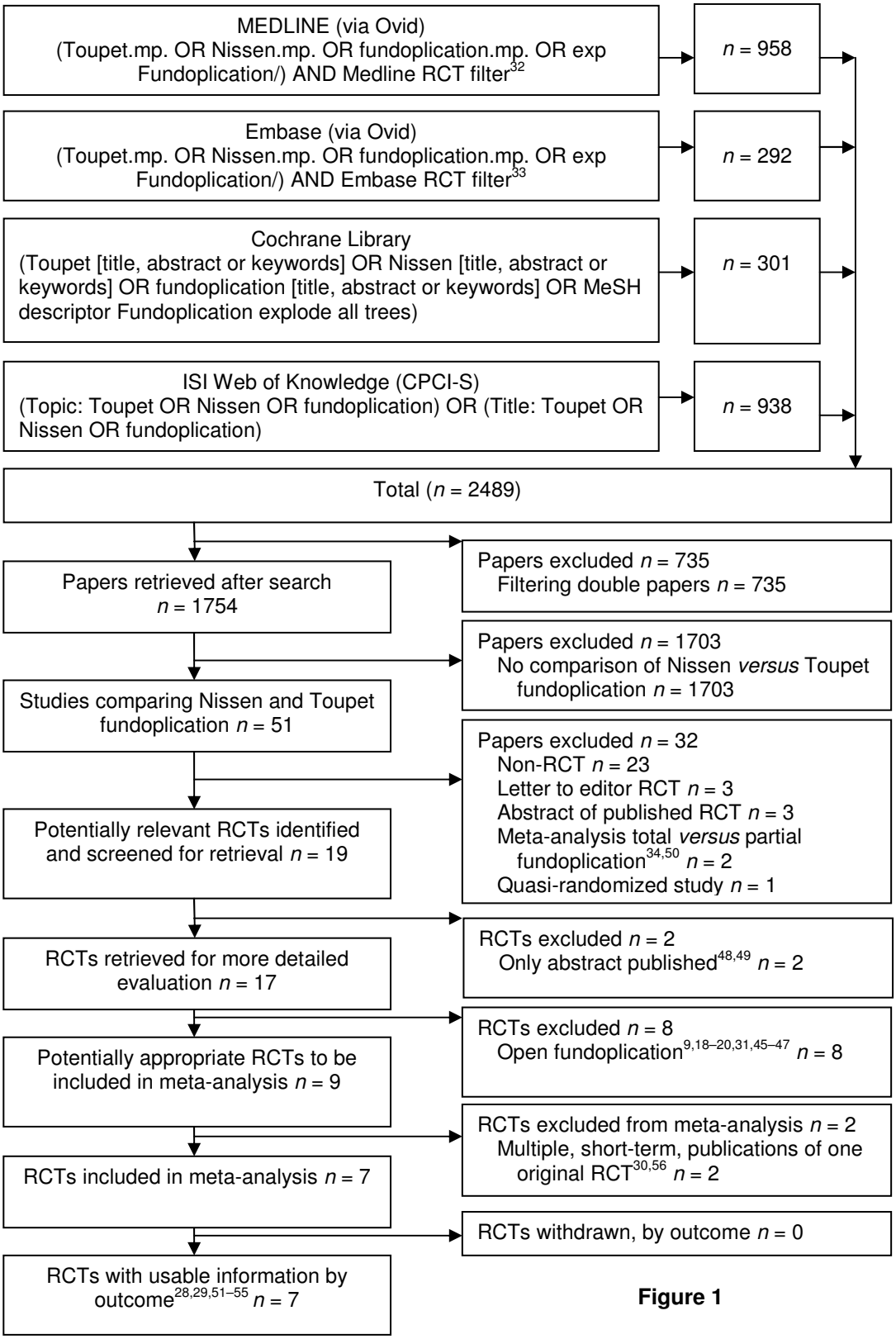

MEDLINE (via Ovid)
(Toupet.mp. OR Nissen.mp. OR fundoplication.mp. OR exp Fundoplication/) AND Medline RCT filter[32]
n = 958
Embase (via Ovid)
(Toupet.mp. OR Nissen.mp. OR fundoplication.mp. OR exp Fundoplication/) AND Embase RCT filter[33]
n = 292
Cochrane Library
(Toupet [title, abstract or keywords] OR Nissen [title, abstract or keywords] OR fundoplication [title, abstract or keywords] OR MeSH descriptor Fundoplication explode all trees)
n = 301
ISI Web of Knowledge (CPCI-S)
(Topic: Toupet OR Nissen OR fundoplication) OR (Title: Toupet OR Nissen OR fundoplication)
n = 938
Total (n = 2489)
Papers excluded n = 735
Filtering double papers n = 735
Papers retrieved after search n = 1754
Papers excluded n = 1703
No comparison of Nissen versus Toupet fundoplication n = 1703
Studies comparing Nissen and Toupet fundoplication n = 51
Papers excluded n = 32
Non-RCT n = 23
Letter to editor RCT n = 3
Abstract of published RCT n = 3
Meta-analysis total versus partial fundoplication[34,50] n = 2
Quasi-randomized study n = 1
Potentially relevant RCTs identified and screened for retrieval n = 19
RCTs excluded n = 2
Only abstract published[48,49] n = 2
RCTs retrieved for more detailed evaluation n = 17
RCTs excluded n = 8
Open fundoplication[9,18–20,31,45–47] n = 8
Potentially appropriate RCTs to be included in meta-analysis n = 9
RCTs excluded from meta-analysis n = 2
Multiple, short-term, publications of one original RCT[30,56] n = 2
RCTs included in meta-analysis n = 7
RCTs withdrawn, by outcome n = 0
RCTs with usable information by outcome[28,29,51–55] n = 7

Figure 1

inclusion and exclusion criteria, number of participating subjects and events for each endpoint. In case of discrepancies, a third author (U.A.A.) was consulted and agreement reached by consensus. Authors of the original RCTs were contacted to provide missing data; total numbers of patients for each outcome parameter and standard deviations of continuous outcomes were determined.

Risk of bias assessment

Risk of bias was assessed of all articles using both the Cochrane Collaboration's tool for assessing risk of bias[32] and the Jadad scoring system[36].

Statistical analysis

Statistical analyses were performed following the recommendations of the Cochrane Collaboration and QUOROM guidelines[35,37,38]. Outcomes reported by two or more studies were pooled in meta-analyses. Dichotomous and continuous outcomes were presented as risk ratios (RRs) and weighted mean differences (WMD) respectively. Data were pooled using the Mantel–Haenszel and the inverse variance method for dichotomous and continuous outcomes respectively. Trials with zero events in one arm were included in the analysis by adding a continuity correction of 0.5 to all cells in the two by two table for that study. Trials with zero events in both arms were excluded from meta-analysis. For all analyses the 95 per cent confidence interval (c.i.) was calculated.

The fixed-effects model was used if no heterogeneity was present (χ^2 *P* value greater than 0.100 and I^2 less than 50 per cent); otherwise the DerSimonian random-effects model was used[39]. Heterogeneity was calculated using Higgins χ^2 test[40], and inconsistency in study effects was quantified by the I^2 [32,41]. If excessive heterogeneity was present, data were first rechecked. When heterogeneity persisted, subgroup or sensitivity analyses were used to explore its causes. Funnel plots were used to help identify the presence of publication or other types of bias[42–44]. Data management and statistical analyses were conducted using the Review Manager software (RevMan© version 5.0.16) provided by the Cochrane Collaboration.

Results

Description of studies

A total of 2489 potential relevant publications were identified. *Fig. 1* outlines the search strategy. Fifty-one relevant papers were identified. Twenty-four studies did not randomly allocate patients. Eight RCTs[9,18,19,21,31,45–47] were excluded because an open surgical approach had been used, and two trials[48,49] were published only

Table 1 Details of included randomized clinical trials comparing laparoscopic Nissen and Toupet fundoplication

	Period	Method	*n*	Circum-ference	Crural repair	Bougie (Fr)	DSGV	Fixation to oesophagus*	Wrap length	Follow-up (mo)
Booth 08[28]	98–01	Nissen	64		Yes	56	Yes	Yes	2	12
		Toupet	63	270	Yes	56	Yes	Yes	2	
Chrysos 03[29]	NR	Nissen	14		Yes	None	No	Yes	3–4	12
		Toupet	19	270	Yes	None	No	Yes	3–4	
Guérin 07[51]	98–02	Nissen	77		NR	34	Yes	Yes	3	12
		Toupet	63	270	NR	NR	Yes	Yes	NR	
Laws 97[52]	NR	Nissen	23		Yes	30–40	Yes	Yes	2.2	27
		Toupet	16	200–70	No	NR	Yes	Yes	NR	
Mickevicius 08[53]	00–03	Nissen	76		Yes	52	Yes	Yes	1.5/3	12
		Toupet	77	200–270	Yes	52	Yes	Yes	1.5/3	
Shaw 10[54]	97–01	Nissen	50		Yes	52	Yes	Yes	1	60
		Toupet	50	270	Yes	52	Yes	Yes	2	
Strate 08[30,55,56]	99–00	Nissen	100		Yes	36	Yes	No	2	24
		Toupet	100	270	Yes	NR	Yes	Yes	NR	

Table 2 Patient characteristics

	Method	Mean age (years)	Sex ratio (M : F)	Oesophageal dysmotility	Indication for surgical treatment
Booth[28]	Nissen	45.3	41 : 23	26 of 64	GORD proven on 24-h pH monitoring; refractory to PPI therapy (n=94) or patient preference (n=33)
	Toupet	44.2	43 : 20	26 of 63	
Chrysos[29]	Nissen	59.2	7 : 7	14 of 14	GORD requiring daily PPI therapy, proven on 24-h pH monitoring
	Toupet	61.7	11 : 8	19 of 19	
Guérin[51]	Nissen	NR	54 : 23	0 of 77	GORD requiring daily PPI therapy, proven on upper endoscopy
	Toupet	NR	32 : 31	0 of 63	
Laws[52]	Nissen	45.5	10 : 13	0 of 23	GORD proven on upper endoscopy
	Toupet	55.5	9 : 7	0 of 16	
Mickevicius[53]	Nissen	51.5	34 : 42	NR	GORD requiring daily PPI therapy, proven on upper endoscopy
	Toupet	53.6	40 : 37	NR	
Shaw[54]	Nissen	45.2	31 : 19	14 of 50	GORD proven on upper endoscopy
	Toupet	45.6	29 : 21	11 of 50	
Strate[30,55,56]	Nissen	56.0	121 : 79	50 of 100	GORD requiring daily PPI therapy, proven on 24-h pH monitoring or upper endoscopy
	Toupet			50 of 100	

as abstracts. Two papers reported meta-analyses comparing both laparoscopic and open, as well as total *versus* various types of anterior and posterior partial fundoplication[16,50]. Finally, seven original randomized trials[28,29,51–55] comparing laparoscopic Nissen with Toupet fundoplication were identified (*Fig. 1*).

Included trials were published between 1997 and 2009. They presented outcomes after different times but with at least 12 months of follow-up. In total, 792 antireflux operations (404 LNF; 388 LTF) were performed. In all patients, a standardized total (360°) LNF or a LTF with a circumferential range of 200–270° was created. In all trials the length of the fundoplication was similar in both arms, but the fundoplication length differed from 1 to 4 cm between trials. The only exception was the study by Shaw and colleagues[54], who performed a 1-cm LNF wrap and a 2-cm LTF wrap. Laws and co-workers[52] did not perform routine posterior crural repair in the LTF group, and Strate *et al.*[30,55,56] did not suture the wrap to the oesophagus in the LNF group (*Table 1*). The trials enrolled patients with and without oesophageal dysmotility, with no differences between the arms of each trial. Patient characteristics and indications for surgical treatment are listed in *Table 2*.

Methodological quality of included studies

The methodological quality of the included trials ranged from poor to excellent, with a median Jadad score of 2 (range 1–5) (*Table 3*). This resulted from poor description of randomization methods, lack of double-blinding, and absence of explanation for withdrawals and dropouts. In addition, none of the RCTs reported a sample size calculation. In the study of Booth and colleagues[28] there was a significantly higher preoperative prevalence of moderate dysphagia in the LNF group compared with the LTF group. Therefore, new-onset dysphagia or worsening of dysphagia was used to compare this study in a meta-analysis. Five of seven authors of original trials agreed to share missing data[28,29,53–55]. Outcome measures that were missing and completed by the authors were reoperation rate (n=1), recurrent reflux symptoms (n=2), inability to belch (n=1), gas bloating (n=2), patient satisfaction (n=2) and operating time (n=1). Outcome measures that were missing and could not be completed by the authors were recurrent pathological acid exposure (n=2), oesophagitis (n=1), inability to belch (n=2), gas bloating (n=1) and satisfaction with the intervention (n=1).

Table 3 Risk of bias summary

	Booth[28]	Chrysos[29]	Guérin[51]	Laws[52]	Mickevicius[53]	Shaw[54]	Strate[30,55,56]
Adequate sequence generation	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Allocation concealment	Yes	Yes	NR	NR	Yes	Yes	Yes
Blinding (observer)	NR	Yes	NR	Yes	Yes	Yes	Yes
Blinding (patient)	Yes	No	No	No	No	Yes	No
Adequate report loss follow-up	No	Yes	No	No	No	Yes	No
No other sources of bias	No*	Yes	Yes	No†	Yes	Yes	NR
Jadad score[36]	2	3	1	1	2	5	2

* baseline imbalance in dysphagia between the two arms; † no crural repair in laparoscopic Toupet fundoplication group.NR, not reported

Results of outcomes

All primary outcomes and all but two secondary outcomes were reported by two or more studies. There were no differences in the percentage of patients with recurrent pathological acid exposure (RR 1.26, 95 per cent c.i. 0.82 to 1.95; P = 0.29) (*Fig. 2*) or oesophagitis (RR 1.20, 95 per cent c.i. 0.78 to 1.85; P = 0.40) (*Fig. 3*) in LNF and LTF groups.

Figure 2 Meta-analysis of recurrent pathological acid exposure following laparoscopic Nissen and Toupet fundoplication for gastro-oesophageal reflux disease. Risk ratios are shown with 95 per cent confidence intervals (Mantel–Haenszel fixed-effects model)

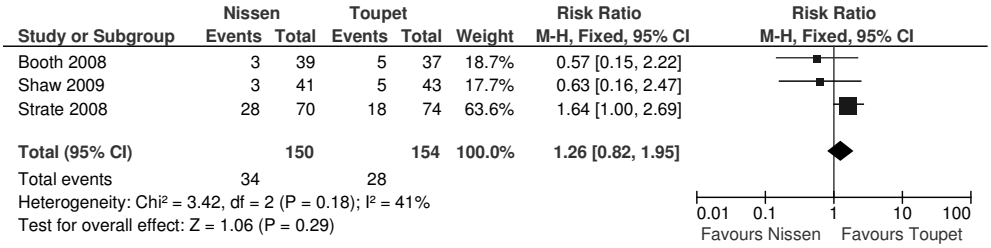
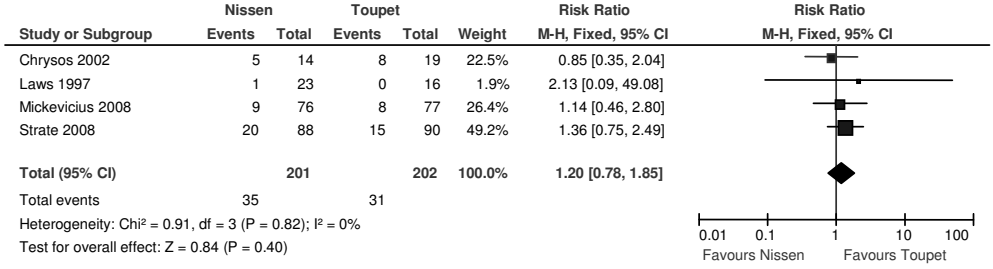


Figure 3 Meta-analysis of oesophagitis following laparoscopic Nissen and Toupet fundoplication for gastro-oesophageal reflux disease. Risk ratios are shown with 95 per cent confidence intervals (Mantel–Haenszel fixed-effects model)



LNF was associated with a significantly higher prevalence of postoperative dysphagia (13.5 *versus* 8.6 per cent; RR 1.61, 95 per cent c.i. 1.06 to 2.44; P = 0.02) (*Fig. 4*), or in the percentage that underwent postoperative dilatation for dysphagia (6.9 *versus* 2.7 per cent; RR 2.45, 95 per cent c.i. 1.06 to 5.68; P = 0.04) (*Fig. 5*). The number of surgical reinterventions was also higher after LNF (7.0 *versus* 3.1 per cent; RR 2.19, 95 per cent c.i. 1.09 to 4.40; P = 0.03) (*Fig. 6*).

Figure 4 Meta-analysis of dysphagia following laparoscopic Nissen and Toupet fundoplication for gastro-oesophageal reflux disease. Risk ratios are shown with 95 per cent confidence intervals (Mantel–Haenszel fixed-effects model)

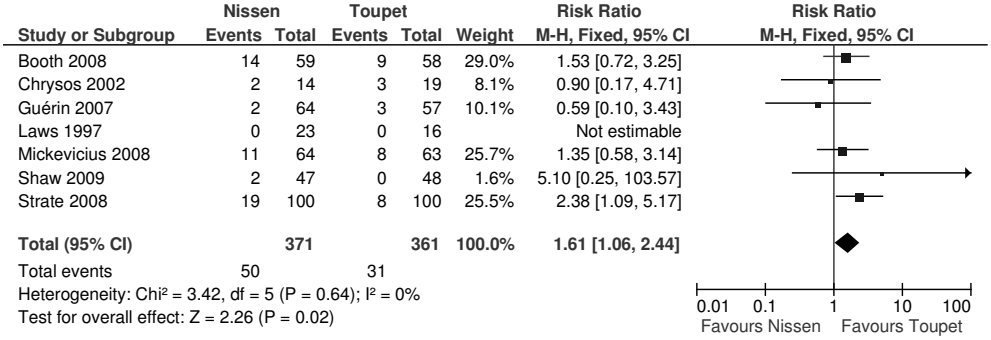


Figure 5 Meta-analysis of postoperative dilatation for dysphagia following laparoscopic Nissen and Toupet fundoplication for gastro-oesophageal reflux disease. Risk ratios are shown with 95 per cent confidence intervals (Mantel–Haenszel fixed-effects model)

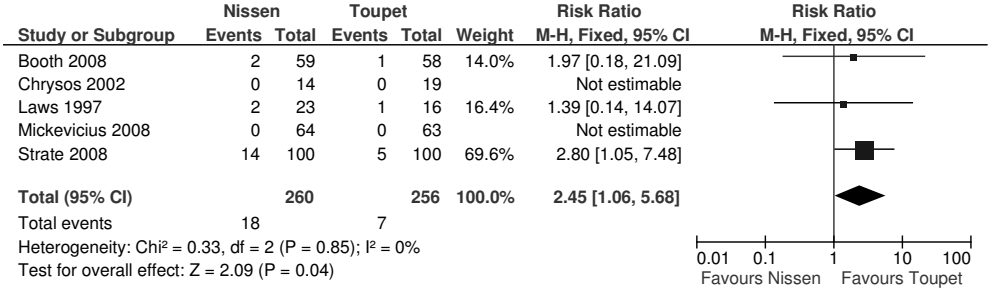
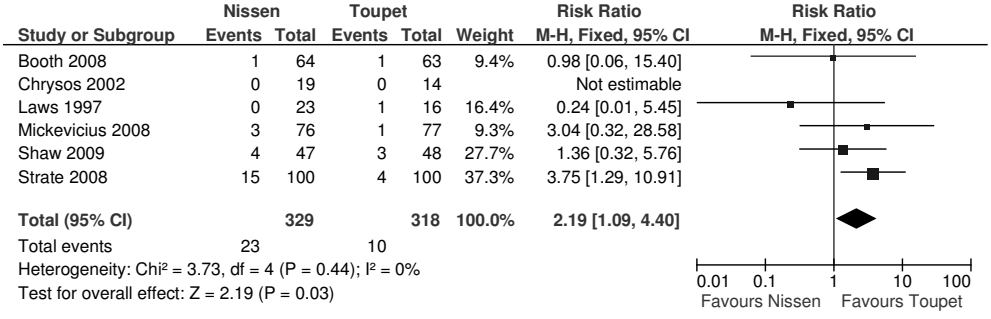


Figure 6 Meta-analysis of reoperation rate following laparoscopic Nissen and Toupet fundoplication for gastro-oesophageal reflux disease. Risk ratios are shown with 95 per cent confidence intervals (Mantel–Haenszel fixed-effects model)



Gas-related symptoms were more common after LNF. A higher prevalence of inability to belch (RR 2.04, 95 per cent c.i. 1.19 to 3.49; $P = 0.009$) (*Fig. 7*) and gas bloating (RR 1.58, 95 per cent c.i. 1.21 to 2.05; $P < 0.001$) (*Fig. 8*) was found after LNF. Subjective reflux recurrence (RR 1.11, 95 per cent c.i. 0.75 to 1.63; $P = 0.61$) (*Fig. 9*) and satisfaction with the intervention (RR 1.01, 95 per cent c.i. 0.95 to 1.06; $P = 0.77$) (*Fig. 10*) were similar for both groups.

Figure 7 Meta-analysis of inability to belch following laparoscopic Nissen and Toupet fundoplication for gastro-oesophageal reflux disease. Risk ratios are shown with 95 per cent confidence intervals (Mantel–Haenszel fixed-effects model)

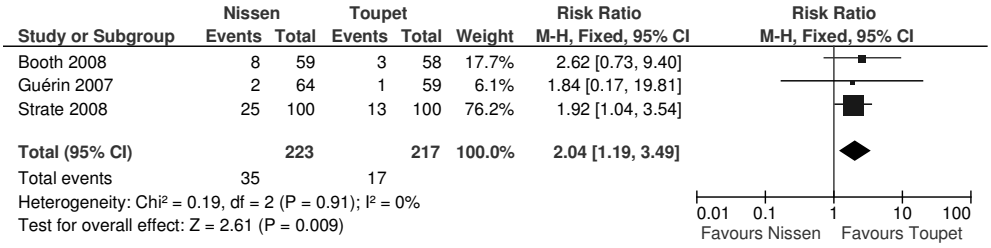


Figure 8 Meta-analysis of gas bloating following laparoscopic Nissen and Toupet fundoplication for gastro-oesophageal reflux disease. Risk ratios are shown with 95 per cent confidence intervals (Mantel–Haenszel fixed-effects model)

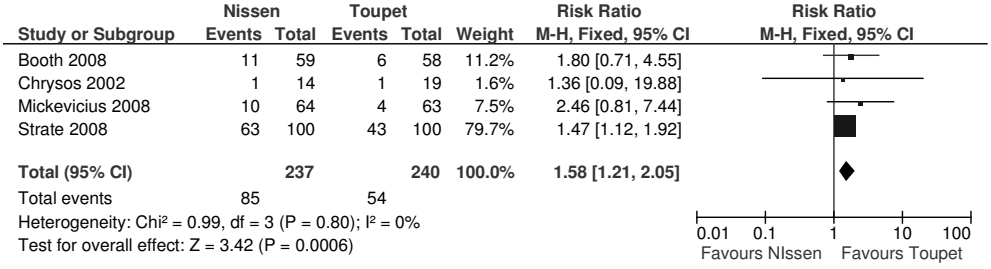


Figure 9 Meta-analysis of subjective reflux recurrence following laparoscopic Nissen and Toupet fundoplication for gastro-oesophageal reflux disease. Risk ratios are shown with 95 per cent confidence intervals (Mantel–Haenszel fixed-effects model)

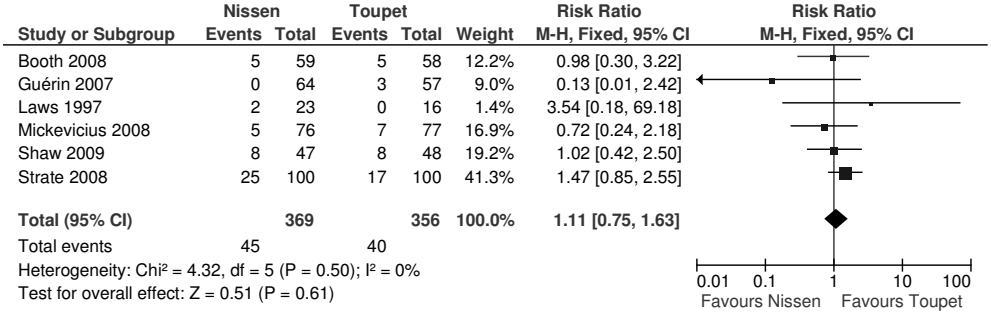


Figure 10 Meta-analysis of satisfaction with laparoscopic Nissen and Toupet fundoplication for gastro-oesophageal reflux disease. Risk ratios are shown with 95 per cent confidence intervals (Mantel–Haenszel fixed-effects model)

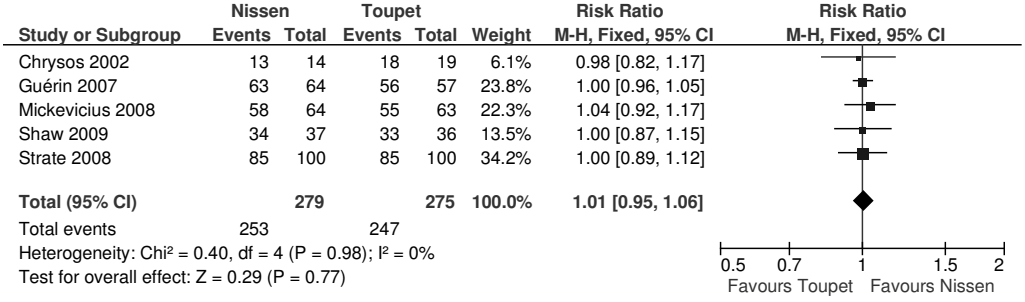
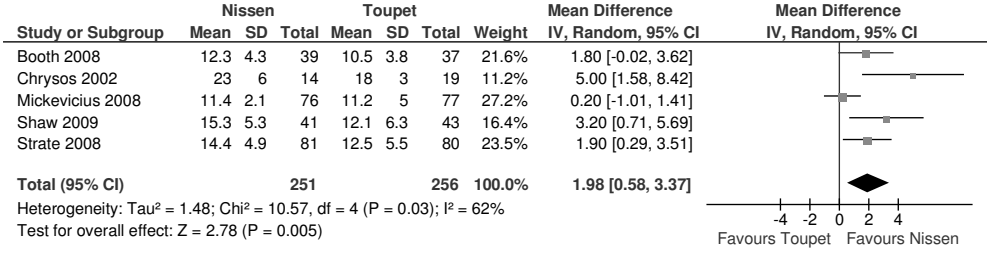


Figure 11 Meta-analysis of mean(s.d.) lower oesophageal sphincter (LOS) pressure in mm Hg following laparoscopic Nissen and Toupet fundoplication for gastro-oesophageal reflux disease. Risk ratios are shown with 95 per cent confidence intervals (inverse variance random-effects model)



Meta-analysis of LOS pressure and operating time showed excessive heterogeneity. Therefore, the random-effects model was used for pooling data. This showed a slightly higher mean LOS pressure after LNF (WMD 1.98 (95 per cent c.i. 0.58 to 3.37) mmHg; $P = 0.005$, χ^2 $P = 0.03$, $I^2 = 62$ per cent) (*Fig. 11*) and no significant difference in operating time between the two techniques (WMD −7.31 (95 per cent c.i. −15.28 to 0.66) min; $P = 0.07$, χ^2 $P < 0.001$, $I^2 = 80$ per cent) (*Fig. 12*). Exploring possible causes of heterogeneity, taking into account variations in technique concerning division of the short gastric vessels, reduced the heterogeneity of operating time significantly (4 trials with short gastric vessel division: WMD −2.07 (95 per cent c.i. −4.81 to 0.66) min; $P = 0.14$, χ^2 $P = 0.41$, $I^2 = 0$ per cent) (*Fig. 12*). One postoperative death occurred after oesophageal perforation during LTF[53]. In-hospital complications (postoperative bleeding, oesophageal and gastric perforation, gastric dilatation, subphrenic abscess, pneumothorax, pneumonia, atelectasis, minor pleural effusion, wound infection, cardiac arrhythmia and thrombophlebitis) were similar for both operations (RR 0.62, 95 per cent c.i. 0.29 to 1.32; $P = 0.22$) (*Fig. 13*). Funnel plots did not demonstrate clear evidence of publication bias.

Figure 12 Meta-analysis of mean(s.d.) operating time for laparoscopic Nissen and Toupet fundoplication for gastro-oesophageal reflux disease. Risk ratios are shown with 95 per cent confidence intervals (inverse variance random-effects model). DSGV, division of short gastric vessels

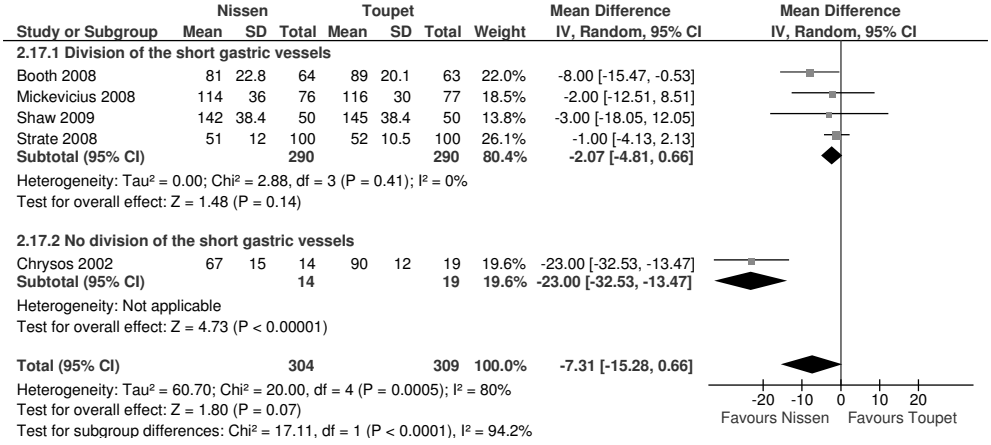
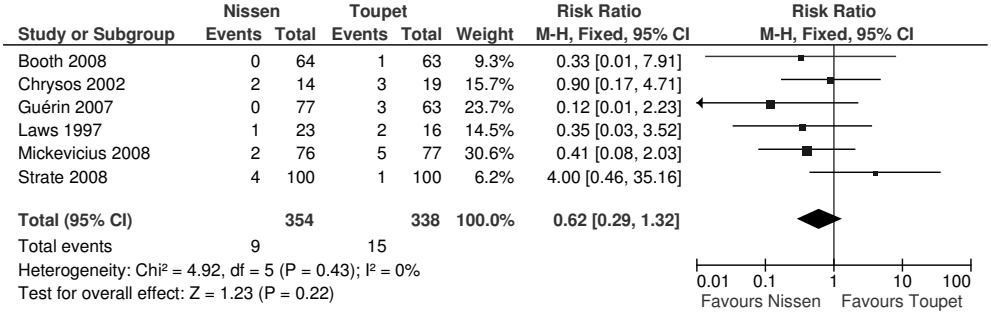


Figure 13 Meta-analysis of in-hospital complications following laparoscopic Nissen and Toupet fundoplication for gastro-oesophageal reflux disease. Risk ratios are shown with 95 per cent confidence intervals (Mantel–Haenszel fixed-effects model)



Discussion

Between 2007 and 2009, five large RCTs were published comparing LTF and LNF[28,51,53–55]. These individual trials were inconclusive in establishing clear differences in outcomes between the two procedures and have not been subjected to meta-analysis.

The methodological quality of the seven RCTs included in the present meta-analysis ranged from poor to excellent. Surgical techniques of the included trials were standardized and generally similar. All patients underwent laparoscopic 360° total or 200–270° partial fundoplication, with all but one trial involving routine use of a bougie, crural repair or fixation of the wrap to the oesophagus. One trial did not routinely divide short gastric vessels, but was included in this review because it has already been shown that there is no difference in outcome after fundoplication with routine *versus* no division of short gastric vessels[16]. The fundoplication length was similar in both arms of all except one trial[54], although the length of fundoplication varied from 1 to 4 cm in the included RCTs. The present meta-analysis included RCTs that enrolled patients with normal and abnormal oesophageal motility as all four RCTs addressing this issue showed that the outcome of Nissen and Toupet fundoplication was similar in patients with normal and abnormal motility[28–31].

The absence of standard crural repair in the LTF group in one study represented a clear difference between the surgical techniques in the two arms and a potential threat to the validity of this RCT[52]. This difference between the arms probably did not cause bias as postoperative subjective and objective reflux recurrence and reoperation rates were not higher in the LTF group. Another potential threat to validity was a significantly higher prevalence of moderate dysphagia in the LNF

group at baseline in one study[28]. To exclude this potential source of bias from the meta-analysis, new-onset or worsening dysphagia was analysed for this RCT.

LTF was associated with a significant and clinically relevant reduction in postoperative dysphagia, dilatations for dysphagia, and surgical reinterventions compared with LNF. The lower reoperation rate after LTF was caused partially by the lower prevalence of dysphagia after this procedure, resulting in a lower number of surgical reinterventions to relieve this symptom. LTF significantly reduced inability to belch and gas bloating compared with LNF. In contrast to previous uncontrolled studies[22–27], the present analysis showed that rates of recurrent pathological acid exposure, oesophagitis and reflux symptoms after LTF and LNF were similar. In-hospital complication rates were similar for the two operations. The techniques of LNF and LTF are identical, except for construction of the wrap. In-hospital complications of both techniques might therefore be expected to be similar, except for an increased theoretical risk of perforation due to the greater number of oesophageal and wrap sutures during LTF. The three studies [28,52,53] that specified complications reported one wrap and two oesophageal perforations after LTF, and none after LNF.

Two related meta-analyses have been published previously[16,50]. These reports pooled various types of partial fundoplication, both anterior and posterior with various circumferences, and compared these techniques with total fundoplication. They also included both open and laparoscopic fundoplication techniques. Pooling of these data is questionable, as RCTs have demonstrated important differences in reflux control and reoperation rates between anterior and posterior partial fundoplication techniques[57,58]. Inclusion of open techniques also undermines the generalizability, because laparoscopic fundoplication has become the surgical approach of choice for primary antireflux surgery[5]. In contrast to previous reviews that combined short- and long-term outcomes (range 4–138 months), short-term clinical outcomes were excluded in the present analysis. Outcome was evaluated after at least 12 (range 12–60) months' follow-up, and additional missing data were obtained. Only nine of 59 outcome measures were missing and completed by the authors and seven outcome measures could not be completed by the authors. Therefore, it is unlikely that addition of the unpublished results would affect the results.

The present study is limited by the methodological quality of the included studies and by the fact that follow-up was restricted to 1, 2 or 5 years. Long-term results of RCTs comparing open Nissen and Toupet fundoplication have, however, demonstrated that short-term reflux control is durable throughout 5-year[19] and 10-year[45] follow-up. As there were no differences in short-term[15] and long-term[5] reflux

control between open and laparoscopic fundoplication, it seems unlikely that differences in reflux control after LNF and LTF will develop with longer follow-up.
LTF is associated with less postoperative dysphagia and need for dilatation for dysphagia compared with LNF, with similar reflux control. The reoperation rate and the prevalence of inability to belch and gas bloating are lower after LTF. There is now level 1a support for the use of LTF as the posterior fundoplication of choice for patients with GORD.

Acknowledgements

The authors thank Professor E. Xynos, U. Straate, M. I. Booth, J. M. Shaw and A. Mickevičius for providing additional data on their trials.

Commentary

Sir

We have read the article by Broeders and colleagues, reviewing laparoscopic Nissen and Toupet fundoplication for the treatment of gastro-oesophageal reflux disease, with great pleasure, but would like to discuss the final conclusion.
The authors concluded that they had reached level 1a evidence in favour of the Toupet fundoplication with their meta-analysis, particularly with respect to dysphagia and detection of dysphagia. However, when considering the results, it seems that the total risk ratios were all comparable with those in the study by Strate and co-workers, disregarding the risk ratios of the other studies in this analysis. They did grade the included studies with Jadad scores but, based on this article, the Strate trial had a Jadad score of only 2, which was not sufficient to allow such high weighting of this study. Therefore, this metaanalysis of laparoscopic Nissen *versus* Toupet fundoplication may be heavily skewed by a low-quality randomized clinical trial, and thus in our opinion does not provide level 1a evidence that the Toupet procedure is superior.
Another issue in the comparison of postoperative dysphagia between these operative techniques is dissection of the short gastric vessels. In this metaanalysis there was no separate analysis of no or minimal dissection of the short gastric vessels *versus* total dissection (with proper dissection of the point of His), in either the Nissen or Toupet fundoplication. This part of the procedure could, however, be important in the prevention of postoperative dysphagia[1–3].Another deficiency of most of the studies included in the meta-analysis is that no objective 24-h pH measurement showed the effectiveness of either operative treatment. Finally, it is probably not correct for the authors of a paper to judge the level of evidence themselves; this is up to the external assessor of the next meta-analysis.

S. M. B. I. Botden and N. D. Bouvy
Department of Surgery, Maastricht
University Medical Centre, Maastricht,
The Netherlands

(1) Rantanen TK, Oksala NK, Oksala AK,Salo JA, Sihvo EI. Complications in antireflux surgery: national-based analysis of laparoscopic and open fundoplications. *Arch Surg* 2008; **143**: 359–365.
(2) Catarci M, Gentileschi P, Papi C, Carrara A, Marrese R, Gaspari AL *et al*. Evidence-based appraisal of antireflux fundoplication. *Ann Surg* 2004; **239**: 325–337.
(3) Soper NJ. Fundoplication and the short gastric vessels: divide and conquer. *Ann Surg* 2002; **235**: 171–173.

Sir

We appreciate the interest shown by Botden and colleagues. Their main comment challenges the levels of evidence for evidence-based medicine and the methodology of meta-analyses in general. Level 1a evidence is defined as a homogeneous systematic review[1], with weights of individual randomized trials based on sample sizes and event rates[2]. The study by Strate and coworkers was twice the size of the other trials and consequently had a weight of more than 50 per cent in four of 12 outcome measures. Botden and colleagues suggest that the methodological quality of this trial was not sufficient to allow this weight. The Jadad score (range 0–5) allocates two points for doubleblinding, rendering a maximum of only 3 points for single-blinded surgical trials[3]. Consequently, the Jadad score of 2 is similar to the median of the trials included in this meta-analysis, 25 trials on antireflux surgery[4] and 202 surgical trials[5]. The low Jadad score resulted from lack of blinding patients and report of dropouts, and is not a valid reason for exclusion. Moreover, all meta-analyseswere homogeneous, demonstrating that the effects of this trial are similar those in the other studies.

In the discussion we explain that one trial which did not routinely divide short gastric vessels was included, because level 1a evidence demonstrated absence of impact on dysphagia and recurrence4. This trial contributed just 4 per cent of the patients and did not cause heterogeneity in any of the outcome measures, except for operating time. Consequently, subgroup analysis after exclusion of this trial yielded a similar difference in dysphagia rate (13·4 *versus* 8·2 per cent; risk ratio (RR) 1·67, 95 per cent confidence interval 1·09 to 2·57; $P = 0·02$). There were no dilatations or reoperations in either arm of this trial.

The fact that only three of seven studies performed pH measurement is indeed a limitation. However, six trials demonstrated no difference in objective reflux recurrence, defined as the presence of oesophagitis or recurrent pathological acid exposure (14·6 *versus* 14·5 per cent;RR1·05, 0·71 to 1·56; $P = 0·80$).The level of evidence of our study has recently been confirmed by two external assessors[6].

J. A. J. L. Broeders and E. J. Hazebroek
Department of Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

(1) Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B *et al*. *Levels of Evidence and Grades of Recommendations*. Oxford Centre for Evidence-based Medicine. http://www.cebm.net/index.aspx?o=1025 [accessed 01 November 2010].

(2) Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. JohnWiley: Chichester, 2008.
(3) Jadad AR, Enkin MW. *Randomized Controlled Trials: Questions, Answers and Musings* (2nd edn). Blackwell Publishing: Oxford, 2007.
(4) Catarci M, Gentileschi P, Papi C, Carrara A, Marrese R, Gaspari AL *et al*. Evidence-based appraisal of antireflux fundoplication. *Ann Surg* 2004; **239**: 325–337.
(5) Solomon MJ, Laxamana A, Devore L, McLeod RS. Randomized controlled trials in surgery. *Surgery* 1994; **115**: 707–712.
(6) Rahden von BH, Germer CT. Superiority of Toupet compared to Nissen fundoplication: new evidence level from meta-analysis. *Chirurg* 2010; **81**: 1031–1032.

References

(1) Bredenoord AJ, Dent J. Proton pump inhibitor-therapy refractory gastro-oesophageal reflux disease patients, who are they? *Gut* 2007; **56**: 593–594.

(2) Spechler SJ, Lee E, Ahnen D, Goyal RK, Hirano I, Ramirez F *et al*. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. *JAMA* 2001; **285**: 2331–2338.

(3) Vakil N. Review article: The role of surgery in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2007; **25**: 1365–1372.

(4) Draaisma WA, Rijnhart-de Jong HG, Broeders IA, Smout AJ, Furnee EJ, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. *Ann Surg* 2006; **244**: 34–41.

(5) Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. Ten-year outcome of laparoscopic and conventional Nissen fundoplication: randomized clinical trial. *Ann Surg* 2009; **250**: 698–706.

(6) Fuchs KH, Feussner H, Bonavina L, Collard JM, Coosemans W. Current status and trends in laparoscopic antireflux surgery: results of a consensus meeting. The European Study Group for Antireflux Surgery (ESGARS). *Endoscopy* 1997; **29**: 298–308.

(7) Society of American Gastrointestinal Endoscopic Surgeons (SAGES). Guidelines for surgical treatment of gastroesophageal reflux disease (GERD). *Surg Endosc* 1998; **12**: 186–188.

(8) Lundell L. Complications after anti-reflux surgery. Best Pract Res Clin Gastroenterol 2004; **18**: 935–945.

(9) Rydberg L, Ruth M, Lundell L. Does oesophageal motor function improve with time after successful antireflux surgery? Results of a prospective, randomised clinical study. *Gut* 1997; **41**: 82–86.

(10) Watson A. Surgical management of gastro-oesophageal reflux disease. *Br J Surg* 1996; **83**: 1313–1315.

(11) Zaninotto G, Costantini M, Anselmino M, Boccù C, Bagolin F, Polo R *et al*. Excessive competence of the lower oesophageal sphincter after Nissen fundoplication: evaluation by three-dimensional computerised imaging. *Eur J Surg* 1995; **161**: 241–246.

(12) McKenzie D, Grayson T, Polk HC Jr. The impact of omeprazole and laparoscopy upon hiatal hernia and reflux esophagitis. *J Am Coll Surg* 1996; **183**: 413–418.

(13) Klaus A, Hinder RA, DeVault KR, Achem SR. Bowel dysfunction after laparoscopic antireflux surgery: incidence, severity, and clinical course. *Am J Med* 2003; **114**: 6–9.

(14) Spechler SJ. Comparison of medical and surgical therapy for complicated gastroesophageal reflux disease in veterans. The Department of Veterans Affairs Gastroesophageal Reflux Disease Study Group. *N Engl J Med* 1992; **326**: 786–792.

(15) Bais JE, Bartelsman JF, Bonjer HJ, Cuesta MA, Go PM, Klinkenberg-Knol EC *et al*. Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. *Lancet* 2000; **355**: 170–174.

(16) Catarci M, Gentileschi P, Papi C, Carrara A, Marrese R, Gaspari AL *et al*. Evidence-based appraisal of antireflux fundoplication. *Ann Surg* 2004; **239**: 325–337.

(17) Toupet A. Technique d'oesophago-gastroplastie avec phreno-gastropexie appliquée dans la cure radicale des hernies hiatales et comme complement de l'opération d'Heller dans les cardiospames. *Mem Acad Chir (Paris)* 1963; **89**: 384–389.

(18) Lundell L, Abrahamsson H, Ruth M, Rydberg L, Lönroth H, Olbe L. Long-term results of a prospective randomized comparison of total fundic wrap (Nissen–Rossetti) or semifundoplication (Toupet) for gastro-oesophageal reflux. *Br J Surg* 1996; **83**: 830–835.

(19) Thor KB, Silander T. A long-term randomized prospective trial of the Nissen procedure *versus* a modified Toupet technique. *Ann Surg* 1989; **210**: 719–724.

(20) Granderath FA, Kamolz T, Granderath UM, Pointner R. Gas-related symptoms after laparoscopic 360 degrees Nissen or 270 degrees Toupet fundoplication in gastrooesophageal reflux disease patients with aerophagia as comorbidity. *Dig Liver Dis* 2007; **39**: 312–318.

(21) Rydberg L, Ruth M, Lundell L. Mechanism of action of antireflux procedures. *Br J Surg* 1999; **86**: 405–410.

(22) Dallemagne B, Weerts J, Markiewicz S, Dewandre JM, Wahlen C, Monami B *et al*. Clinical results of laparoscopic fundoplication at ten years after surgery. *Surg Endosc* 2006; **20**: 159–165.

(23) Farrell TM, Archer SB, Galloway KD, Branum GD, Smith CD, Hunter JG. Heartburn is more likely to recur after Toupet fundoplication than Nissen fundoplication. *Am Surg* 2000; **66**: 229–236.

(24) Fein M, Bueter M, Thalheimer A, Pachmayr V, Heimbucher J, Freys SM *et al*. Ten-year outcome of laparoscopic antireflux surgery. *J Gastrointest Surg* 2008; **12**: 1893–1899.

(25) Fernando HC, Lucketich JD, Christie NA, Ikramuddin S, Schauer PR. Outcomes of laparoscopic Toupet compared to laparoscopic Nissen fundoplication. *Surg Endosc* 2002; **16**: 905–908.

(26) Horvath KD, Jobe BA, Herron DM, Swanstrom LL. Laparoscopic Toupet fundoplication is an inadequate procedure for patients with severe reflux disease. *J Gastrointest Surg* 1999; **3**: 583–591.

(27) Kamolz T, Granderath FA, Bammer T, Wykypiel H Jr, Pointner R. 'Floppy' Nissen *vs*. Toupet laparoscopic fundoplication: quality of life assessment in a 5-year follow-up (part 2). *Endoscopy* 2002; **34**: 917–922.

(28) Booth MI, Stratford J, Jones L, Dehn TC. Randomized clinical trial of l aparoscopic total (Nissen) *versus* posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. *Br J Surg* 2008; **95**: 57–63.

(29) Chrysos E, Tsiaoussis J, Zoras OJ, Athanasakis E, Mantides A, Katsamouris A *et al*. Laparoscopic surgery for gastroesophageal reflux disease patients with impaired esophageal peristalsis: total or partial fundoplication? *J Am Coll Surg* 2003; **197**: 8–15.

(30) Fibbe C, Layer P, Keller J, Strate U, Emmermann A, Zornig C. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized, clinical, and manometric study. *Gastroenterology* 2001; **121**: 5–14.

(31) Rydberg L, Ruth M, Abrahamsson H, Lundell L. Tailoring antireflux surgery: a randomized clinical trial. *World J Surg* 1999; **23**: 612–618.

(32) Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. John Wileys: Chichester, 2008.

(33) *BMJ* Clinical Evidence website. Search filters. http://clinicalevidence.bmj.com/ceweb/about/search_filters.jsp [accessed 28 May 2009].

(34) Rijnhart-de Jong HG, Draaisma WA, Smout AJ, Broeders IA, Gooszen HG. The Visick score: a good measure for the overall effect of antireflux surgery? *Scand J Gastroenterol* 2008; **43**: 787–793.

(35) Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999; **354**: 1896–1900.

(36) Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1–12.

(37) Clarke M, Horton R. Bringing it all together: Lancet–Cochrane collaborate on systematic reviews. *Lancet* 2001; **357**: 1728.

(38) Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008–2012.

(39) DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–188.

(40) Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539–1558.

(41) Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–560.

(42) Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; **50**: 1088–1101.

(43) Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–634.

(44) Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. *Stat Med* 2001; **20**: 641–654.

(45) Hagedorn C, Lönroth H, Rydberg L, Ruth M, Lundell L. Long-term efficacy of total (Nissen–Rossetti) and posterior partial (Toupet) fundoplication: results of a randomized clinical trial. *J Gastrointest Surg* 2002; **6**: 540–545.

(46) Lundell L, Abrahamsson H, Ruth M, Sandberg N, Olbe LC. Lower esophageal sphincter characteristics and esophageal acid exposure following partial or 360 degrees fundoplication: results of a prospective, randomized, clinical study. *World J Surg* 1991; **15**: 115–120.

(47) Segol P, Hay JM, Pottier D. [Surgical treatment of gastroesophageal reflux: which operation to choose: Nissen, Toupet or Lortat-Jacob? A multicenter randomized trial.] *Gastroenterol Clin Biol* 1989; **13**: 873–879.

(48) Bouillot JL, Alamowitch B, Aouad K, Gasne P, Gilbert T, Bloch F. [Laparoscopy cure of gastro-oesophageal reflux. Nissen *versus* Toupet: a prospective randomized study in 50 patients.] *Ann Chir* 1999; 53: 669.

(49) Ferulano GP, La Manna S, Dilillo S, Forgione A, Vanni L, Brunaccino R *et al.* Laparoscopic partial posterior *vs.* total fundoplication in gastro-oesophageal reflux disease (GERD) with oesophageal dismotility. Short term results of a prospective study. *Proceedings of the Eighth International Congress of the European Association for Endoscopic Surgery,* Nice, 2000; 315–320.

(50) Varin O, Velstra B, De Sutter S, Ceelen W. Total *vs* partial fundoplication in the treatment of gastroesophageal reflux disease: a meta-analysis. *Arch Surg* 2009; **144**: 273–278.

(51) Guérin E, Betroune K, Closset J, Mehdi A, Lefèbvre JC, Houben JJ *et al*. Nissen *versus* Toupet fundoplication: results of a randomized and multicenter trial. *Surg Endosc* 2007; **21**: 1985–1990.

(52) Laws HL, Clements RH, Swillie CM. A randomized, prospective comparison of the Nissen fundoplication *versus* the Toupet fundoplication for gastroesophageal reflux disease. *Ann Surg* 1997; **225**: 647–653.

(53) Mickevicius A, Endzinas Z, Kiudelis M, Jonaitis L, Kupcinskas L, Maleckas A *et al*. Influence of wrap length on the effectiveness of Nissen and Toupet fundoplication: a prospective randomized study. *Surg Endosc* 2008; **22**: 2269–2276.

(54) Shaw JM, Bornman PC, Callanan MD, Beckingham IJ, Metz DC. Long-term outcome of laparoscopic Nissen and laparoscopic Toupet fundoplication for gastroesophageal reflux disease: a prospective, randomized trial. *Surg Endosc* 2010; **24**: 924–932.

(55) Strate U, Emmermann A, Fibbe C, Layer P, Zornig C. Laparoscopic fundoplication: Nissen *versus* Toupet two-year outcome of a prospective randomized study of 200 patients regarding preoperative esophageal motility. *Surg Endosc* 2008; **22**: 21–30.

(56) Zornig C, Strate U, Fibbe C, Emmermann A, Layer P. Nissen *vs* Toupet laparoscopic fundoplication. *Surg Endosc* 2002; **16**: 758–766.

(57) Engström C, Lönroth H, Mardani J, Lundell L. An anterior or posterior approach to partial fundoplication? Long-term results of a randomized trial. *World J Surg* 2007; **31**: 1221–1225.

(58) Hagedorn C, Jönson C, Lönroth H, Ruth M, Thune A, Lundell L. Efficacy of an anterior as compared with a posterior laparoscopic partial fundoplication: results of a randomized, controlled clinical trial. *Ann Surg* 2003; **238**: 189–196.

11

Laparoscopic anterior *versus* posterior fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials

J.A.J.L. Broeders[1]
D.J.G.H. Roks[1]
U. Ahmed Ali[1]
W.A. Draaisma[1]
A.J.P.M. Smout[2]
E.J. Hazebroek[1]

[1]Dep. of Surgery, University Medical Center Utrecht
[2]Dep.of Gastroenterology, University Medical Center Utrecht

12th world congress of the International Society for Diseases of the Esophagus
Kagoshima, Japan, September 2010

Annals of Surgery 2011; in press.

Abstract

Objective: To compare short and long-term outcome after laparoscopic anterior fundoplication (LAF) *versus* posterior fundoplication (LPF) through a systematic review and meta-analysis of randomized clinical trials (RCTs).

Summary of background data: LPF is currently considered the surgical therapy of choice for GERD. Alternatively, LAF has been alleged to reduce troublesome dysphagia and gas-related symptoms.

Methods: Four electronic databases (MEDLINE, EMBASE, Cochrane Library and ISI web of Knowledge CPCI-S) were searched for RCTs comparing primary LAF *versus* LPF for GERD. The methodological quality was evaluated to assess bias risk. Primary outcomes were esophageal acid exposure time, heartburn, Dakkak dysphagia score [0-45] and reoperation rate. Short and long-term results were pooled separately in meta-analyses as relative risk (RRs) and weighted mean differences (WMDs).

Results: Eleven reports on 7 eligible RCTs (anterior *vs* posterior total[n=5];anterior *vs* posterior partial[n=2]) comparing LAF (n=345) *versus* LPF (n=338) were identified. Short-term (6-12months) esophageal acid exposure time (3.3 *vs* 0.8%: WMD2.04;95%CI [0.84,3.24];P<0.001), heartburn (21 *vs* 8%; RR2.71;95%CI[1.72,4.26];*P*<0.001) and reoperation rate (8 *vs* 4%; RR1.94;95%CI[0.97,3.87];*P*=0.06) were higher after LAF. In contrast, the Dakkak dysphagia score was lower after LAF (2.5 vs 5.7; WMD-2.87;95%CI[-3.88,-1.87];P<0.001). There were no short-term differences in prevalence of esophagitis, regurgitation and perioperative outcomes. The higher rate of heartburn after LAF persisted during long-term (2-10 years) follow-up (31 *vs* 14%; RR 2.15;95%CI[1.49,3.09];*P*<0.001) with more PPI use (25 *vs* 10%; RR2.53;95%CI[1.40,4.45];*P*=0.002). The long-term reoperation rate was twice as high after LAF (10 *vs* 5%; RR 2.12;95%CI[1.07,4.21];*P*=0.03). Long-term Dakkak dysphagia scores, inability to belch, gas bloating and satisfaction were not different.

Conclusions: Esophageal acid exposure time and the prevalence of heartburn are higher after LAF compared with LPF. In the short-term this is counterbalanced by less severe dysphagia. However, dysphagia scores become similar in the long-term, with a persistent substantial increase in prevalence of heartburn and PPI use after LAF. The reoperation rate is twice as high after LAF as well, mainly due to reinterventions for recurrent GERD. The prevalence of gas-related symptoms is similar. These results lend level 1a support for the use of LPF as the surgical treatment of choice for GERD.

Introduction

Laparoscopic fundoplication is the surgical approach of choice for gastroesophageal reflux disease (GERD). Three randomized clinical trials (RCTs) have recently demonstrated that the laparoscopic approach offers similar 5-year[1] and 10-year rates for disease control[2] compared with open fundoplication, with fewer incisional hernias[2,3].

A fundoplication is created by wrapping the fundus of the stomach anteriorly or posteriorly around the esophagus. Currently, laparoscopic posterior fundoplication (LPF) is widely considered the surgical therapy of choice for GERD[1-3]. In North America total posterior fundoplication is considered the gold standard[4-6], whereas partial posterior fundoplication is more common in Europe[7]. Generally, the aim of antireflux surgery is to control reflux symptoms with minimal postoperative dysphagia and gas-related symptoms. A recently published systematic review comparing posterior total to posterior partial fundoplication demonstrated that posterior fundoplication ensures excellent reflux control, although this is traded off against a high prevalence of postfundoplication symptoms[7]. Eleven percent of the patients develop dysphagia and 5 per cent require dilation for dysphagia after LPF[7]. In addition, 12 percent of the patients suffer from the inability to belch and 29 percent report gas bloating after posterior fundoplication[7]. Therefore, the development of dysphagia and gas-related symptoms seem to be clinically important drawbacks associated with LPF.

Laparoscopic anterior fundoplication (LAF) has been proposed as an alternative operation aiming to reduce postfundoplication symptoms. Several RCTs have demonstrated that LAF reduces dysphagia[8-13] and gas-related symptoms[10,11,13], when compared with LPF. Some RCTs suggest that this is offset by a higher reflux recurrence rate[8,10-12,14-16], though other RCTs report similar reflux control[9,13,17]. As a result, these individual RTCs comparing LAF to LPF have not provided a definitive answer.

Up to date, no systematic review of literature exists to address this question. The current study aims, therefore, to systematically review all RCTs comparing LAF to LPF for GERD. Short and long-term outcomes are analyzed separately, in order to generate the highest level of evidence to determine which procedure should be regarded as the surgical therapy of choice.

Methods

Study selection

A systematic literature search with predefined search terms (Figure 1) was carried out in MEDLINE (from 1960)[18], EMBASE (from 1980)[19], Cochrane Library (issue 1,

2010) and the ISI Web of Knowledge Conference Proceedings Citation Index - Science (CPCI-S; from 1990) databases for articles published to June 1st, 2010 (Figure 1). All identified articles were screened for cross-references. Language restrictions were not applied.

Inclusion criteria

Title and abstract of all identified articles were screened and selected according to the following inclusion criteria: study population - adult patients with established GERD undergoing primary antireflux surgery; intervention - clearly documented surgical technique of laparoscopic anterior fundoplication and laparoscopic posterior fundoplication, irrespective of division of the short gastric vessels[20]; study outcomes - at least one of the outcome measures reported below; study design - patients assigned to either LAF or LPF by random allocation; publication - published as a full article in a peer-reviewed journal.

Exclusion criteria

Studies were excluded from analysis if they did not meet the inclusion criteria, or if the corresponding author was not able to provide data requested and it was impossible to extract or calculate appropriate data from the published results. Abstracts of RCTs were excluded as the methodological quality and the risk of bias of these studies could not be assessed.

Outcomes of interest and definitions

Primary outcomes were: esophageal acid exposure time on pH monitoring, heartburn, the validated Dakkak dysphagia score (0, no dysphagia; 45, severe dysphagia)[21] and reoperation rate. Secondary outcomes included endoscopic esophagitis, regurgitation, PPI use, inability to belch, gas bloating, ability to relieve bloating, satisfaction with intervention, willingness to undergo surgery again, lower esophageal sphincter (LES) pressure and LES relaxation nadir pressure on manometry, operating time, conversion rate, in-hospital complications and length of hospital stay. Short (6-12 months) and long-term (2-10 years) results were pooled separately in meta-analysis. Subgroup analysis was performed after exclusion of RCTs with 90 degree anterior fundoplication, since short[10,11] and long-term[14] reflux control after this procedure is poor compared to short[9] and long-term[17] effectiveness of 180 degree fundoplication.

Data extraction

Titles and abstracts of all retrieved records, and subsequently full-text articles, were examined independently by two authors (JAB, DJR) according to the Quality of Reporting of Meta-analyses (QUOROM) guidelines[22-24]. The following data were extracted separately by the same two authors (JAB, DJR) for all studies meeting the inclusion criteria: reference of study, study population characteristics, study design, inclusion and exclusion criteria and number of participating subjects for each endpoint. For dichotomous outcomes, the number of events was recorded and for continuous outcomes means and standard deviations (SDs) were registered. In case of discrepancies, a third author (UAA) was consulted and agreement was reached by consensus.

Authors of all the original RCTs were contacted to provide missing data. When authors could not provide missing data, the following methods of handling missing data were applied. If the number of patients per arm was missing for an outcome, an equal distribution between both arms was assumed. Missing standard deviations (SDs) were either imputed based on ranges when available[25] or based on the average SDs reported by other RCTs for the same outcome[18]. If both means and SDs were missing, they were imputed based on the medians and ranges[25] or based on medians and interquartile ranges[18], according to availability.

Risk of bias assessment

Risk of bias was assessed of all articles using both the Cochrane Collaboration's tool for assessing risk of bias[18] and the Jadad scoring system[26].

Statistical analysis

Statistical analyses were performed following the recommendations of the Cochrane Collaboration and QUOROM guidelines[22-24]. Outcomes reported by three or more studies were pooled in meta-analyses. Short and long-term results were analyzed separately. Dichotomous and continuous outcomes were presented as risk ratios (RRs) and weighted mean differences (WMDs), respectively. Data were pooled using the Mantel-Haenszel and the inverse-variance method for dichotomous outcomes and for continuous outcomes, respectively. Trials with zero events in both arms were excluded from meta-analysis. Trials with zero events in one arm were included in the analysis by adding a continuity correction of 0.5 to all cells in the 2x2 table of that study. As a robustness assessment, meta-analyses with RCTs with zero events in one arm were also performed using risk differences in a sensitivity analyses. For all analyses the 95% confidence interval (CI) was calculated.

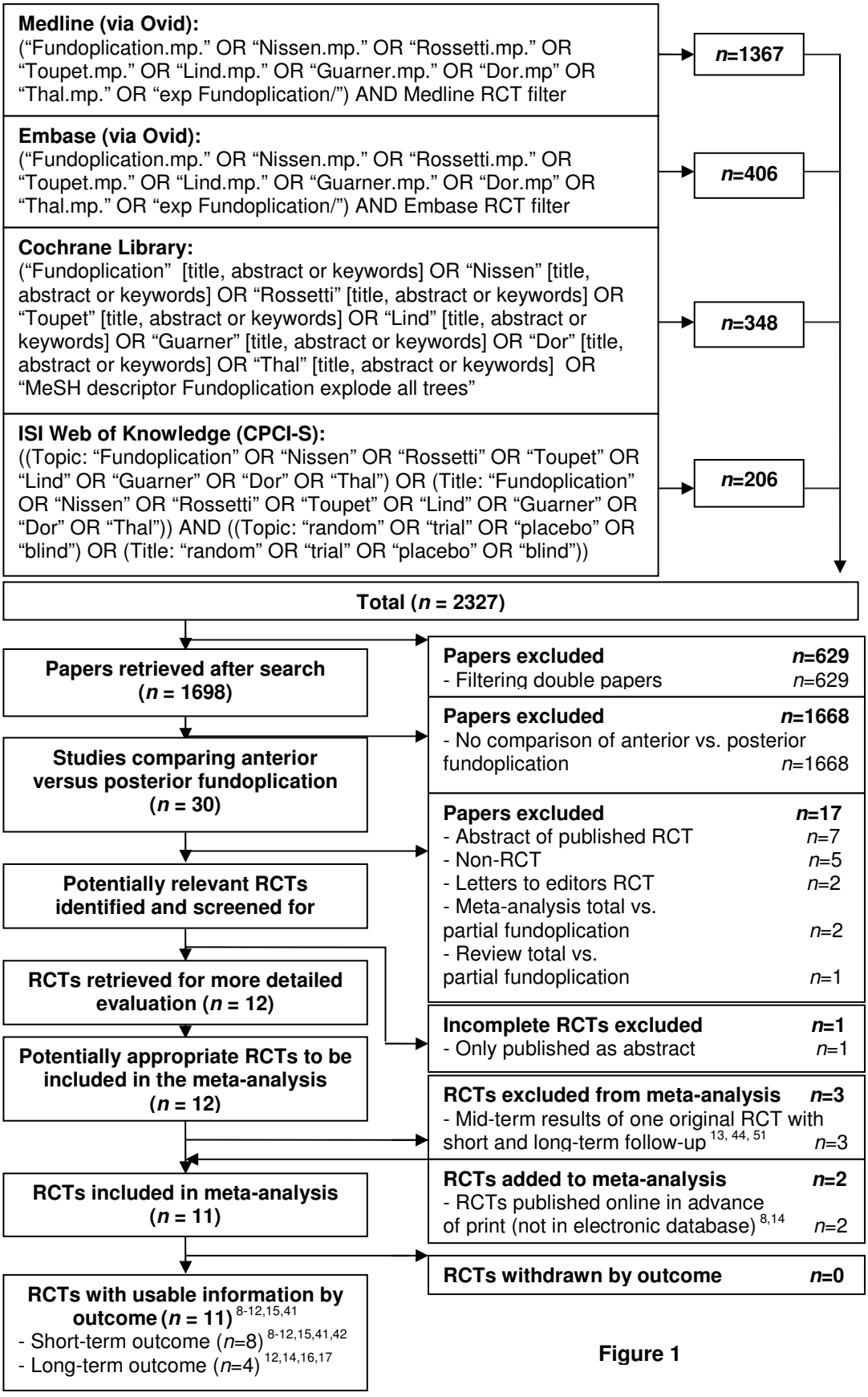

Medline (via Ovid):
("Fundoplication.mp." OR "Nissen.mp." OR "Rossetti.mp." OR "Toupet.mp." OR "Lind.mp." OR "Guarner.mp." OR "Dor.mp" OR "Thal.mp." OR "exp Fundoplication/") AND Medline RCT filter
n=1367
Embase (via Ovid):
("Fundoplication.mp." OR "Nissen.mp." OR "Rossetti.mp." OR "Toupet.mp." OR "Lind.mp." OR "Guarner.mp." OR "Dor.mp" OR "Thal.mp." OR "exp Fundoplication/") AND Embase RCT filter
n=406
Cochrane Library:
("Fundoplication" [title, abstract or keywords] OR "Nissen" [title, abstract or keywords] OR "Rossetti" [title, abstract or keywords] OR "Toupet" [title, abstract or keywords] OR "Lind" [title, abstract or keywords] OR "Guarner" [title, abstract or keywords] OR "Dor" [title, abstract or keywords] OR "Thal" [title, abstract or keywords] OR "MeSH descriptor Fundoplication explode all trees"
n=348
ISI Web of Knowledge (CPCI-S):
((Topic: "Fundoplication" OR "Nissen" OR "Rossetti" OR "Toupet" OR "Lind" OR "Guarner" OR "Dor" OR "Thal") OR (Title: "Fundoplication" OR "Nissen" OR "Rossetti" OR "Toupet" OR "Lind" OR "Guarner" OR "Dor" OR "Thal")) AND ((Topic: "random" OR "trial" OR "placebo" OR "blind") OR (Title: "random" OR "trial" OR "placebo" OR "blind"))
n=206
Total (n = 2327)
Papers retrieved after search (n = 1698)
Papers excluded n=629
- Filtering double papers n=629
Studies comparing anterior versus posterior fundoplication (n = 30)
Papers excluded n=1668
- No comparison of anterior vs. posterior fundoplication n=1668
Potentially relevant RCTs identified and screened for
Papers excluded n=17
- Abstract of published RCT n=7
- Non-RCT n=5
- Letters to editors RCT n=2
- Meta-analysis total vs. partial fundoplication n=2
- Review total vs. partial fundoplication n=1
RCTs retrieved for more detailed evaluation (n = 12)
Incomplete RCTs excluded n=1
- Only published as abstract n=1
Potentially appropriate RCTs to be included in the meta-analysis (n = 12)
RCTs excluded from meta-analysis n=3
- Mid-term results of one original RCT with short and long-term follow-up [13, 44, 51] n=3
RCTs added to meta-analysis n=2
- RCTs published online in advance of print (not in electronic database) [8,14] n=2
RCTs included in meta-analysis (n = 11)
RCTs withdrawn by outcome n=0
RCTs with usable information by outcome (n = 11) [8-12,15,41]
- Short-term outcome (n=8) [8-12,15,41,42]
- Long-term outcome (n=4) [12,14,16,17]

Figure 1

Heterogeneity was calculated using Higgins χ^2 test[27], and inconsistency in study effects was quantified by I^2 values[18,28]. The fixed-effects model was used if no heterogeneity was present (χ^2 *P* value > 0.100 and I^2 < 50%). If excessive heterogeneity was present, data were first re-checked and the DerSimonian random-effects model was used when heterogeneity persisted[29]. Funnel plots were used to help identify the presence of publication or other types of bias[30-32]. Review Manager software (RevMan© v. 5.0.16) provided by The Cochrane Collaboration was used for data management and statistical analyses.

Results

Description of studies

A total of 2327 potential relevant publications were identified (Figure 1). Thirty papers comparing anterior versus posterior fundoplication were identified. Five studies did not randomly allocate patients[33-37]. Two meta-analyses[20,38], one review[39] and one German publication that was published as an abstract only without a peer-reviewed publication[40] were excluded. Two RCTs were added that had been published online in advance of print and were not listed in the electronic database[8,14]. Finally, 11 publications on seven original RCTs[8-12,15,41] comparing laparoscopic anterior *versus* posterior fundoplication were identified. Eight publications[8-12,15,41,42] reported short-term results and four publications evaluated long-term outcome[12,14,16,17] (Figure 1).

The seven included trials were published between 1999 and 2010, all with at least 6 months of follow-up. A total of 683 fundoplications (345 LAF; 338 LPF) were performed. In all patients, a standardized LAF with a circumferential range of 90-180° or a standardized LPF with a circumference of 180-360° was created after crural repair (Table 1). Two trials divided the short gastric vessels in the LPF group[10,14-16,42]. One trial enrolled patients with esophageal dysmotility and included 11 patients of this subgroup in both arms[9,17]. Patient characteristics and indications for surgical treatment are listed in Table 2.

Methodological quality of included studies

The trials had good methodological quality, with a mean Jadad score of 4 (range 1-5) (Table 3). Three trials lacked double blinding[8,15,16,41,42] and two trials did not conceal allocation[15,16,41,42]. One trial did not report the method of sequence generation[15,16,42] and another study did not report loss to follow-up[41]. Four trials reported a sample size calculation[8-11,14,17].

Table 1 Details of included RCTs comparing LAF *versus* LPF

	Year	Period	Method	*n*	°	Crural repair	DSGV	Bougie	Fixation to esophagus†	Short term FU	Long term FU
Baigrie[12]	'05	'99-'01	Anterior	79	180°	Yes	No	NR	No	12 [12]	24 [12]
			Posterior	84	360°	Yes	No	56 Fr	No		
Chrysos[41]	'04	NR	Anterior	12	180°	Yes	No	None	Yes	6 [41]	
		NR	Posterior	12	360°	Yes	No	None	No		
Khan[8]	'10	NR	Anterior	53	180°	Yes	No	None	Yes	12 [8]	
		NR	Posterior	50	180°	Yes	No	None	Yes		
Lundell[15,16,42]	'03/'07	NR	Anterior	47	120°	Yes	No	None	Yes	12 [15,42]	65 [16]
			Posterior	48	180-200°	Yes	Yes	None	Yes		
Spence[11]	'06	'99-'03	Anterior	40	90°	Yes	No	None	Yes	12 [11]	
			Posterior	39	360°	Yes	No	52 Fr	No		
Watson '99[9,17]	'99/'04/'08	'95-'97	Anterior	54	180°	Yes	No	None	Yes	6 [9]	120 [17]
			Posterior	53	360°	Yes	No	52 Fr	No		
Watson '04[10,14]	'04/"10	'00-'03	Anterior	60	90°	Yes	No	None	Yes	6 [10]	60 [14]
			Posterior	52	360°	Yes	Yes	52-60 Fr	No		

°, Circumference of the wrap; DSGV, Division of the short gastric vessels; †Fixation of the fundoplication to the esophagus; FU, Follow-up (months); NR, Not reported; Fr, French

Table 2 Patient characteristics

	Method	Age (yr)	Male / female sex	Esophageal dysmotility / total	Indication for surgical treatment
Baigrie[12]	Anterior	NR	45/34	NR	pH or endoscopically proven GERD
	Posterior	NR	49/34	NR	
Chrysos[41]	Anterior	58	4/8	0/12	pH or endoscopically proven GERD
	Posterior	52	9/3	0/12	
Khan[8]	Anterior	43	36/17	0/53	pH or endoscopically proven GERD
	Posterior	43	38/12	0/50	
Lundell[5,16,42]	Anterior	47	34/13	NR	chronic GERD
	Posterior	46	38/18	NR	
Spence[11]	Anterior	46	24/16	0/40	pH or endoscopically proven GERD
	Posterior	47	19/20	0/39	
Watson 1999[9,17]	Anterior	NR	NR	11/54	pH or endoscopically proven GERD
	Posterior	NR	NR	11/53	
Watson 2004[10,14]	Anterior	47	35/25	0/60	pH or endoscopically proven GERD
	Posterior	49	33/19	0/52	

GERD, gastroesophageal reflux disease; pH or endoscopically proven GERD, GERD proven on endoscopy or 24h pH-metry

Table 3 Risk of bias summary

	Baigrie[12]	Chrysos[41]	Khan[8]	Lundell[15,16,42]	Spence[11]	Watson 1999[9,17]	Watson 2004[10,14]
Adequate sequence generation	Yes	Yes	Yes	No	Yes	Yes	Yes
Allocation concealment	Yes	No	Yes	No	Yes	Yes	Yes
Blinding (observer)	Yes	No	No	No	Yes	Yes	Yes
Blinding (patient)	Yes	No	NR	No	Yes	Yes	Yes
Adequate report on loss to follow-up	Yes	No	Yes	Yes	Yes	Yes	Yes
Free of other sources of bias	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jadad score	5	2	3	1	5	5	5

NR, Not reported

Short-term outcomes

PPI use was the only short-term outcome that was not reported by three or more studies. Mean esophageal acid exposure time on 24-h pH monitoring was higher after LAF (3.3% *vs* 0.8%; WMD 2.04%; 95% CI [0.84, 3.24]; P<0.001; Figure 2). The percentage of patients with heartburn was higher after LAF as well (21% *vs* 8%; RR 2.71; 95% CI [1.72, 4.26]; *P*<0.001; Figure 3). In contrast, the mean Dakkak dysphagia score was lower after LAF (2.5 *vs* 5.7; WMD -2.87; 95% CI [-3.88, -1.87]; P<0.001; Figure 4) and this was accompanied by a lower LES relaxation nadir pressure (4.3 *vs* 8.0 mm Hg; WMD -3.12 mm Hg; 95% CI [-6.04, -0.21]; *P*=0.04; Figure 6). The number of surgical reinterventions was twice as high after LAF compared with LPF, although this difference did not reach statistical significance (8% *vs* 4%; RR 1.94; 95% CI [0.97, 3.87]; *P*=0.06; Figure 5). In the LAF group, 18 out of 22 reoperations were performed for recurrent GERD and 1 for dysphagia. In contrast, 2 out of 11 surgical reinterventions after LPF were for recurrent GERD and 8 for dypshagia. There were no differences in the prevalence of esophagitis and regurgitation (Table 4). The prevalence of inability to belch and gas bloating were similar as well (Table 4). The ability to relieve bloating was higher after LAF (77% *vs* 60%; RR 1.30; 95% CI [1.12, 1.50]; *P*<0.001; Figure 7).

Figure 2 Short-term acid exposure

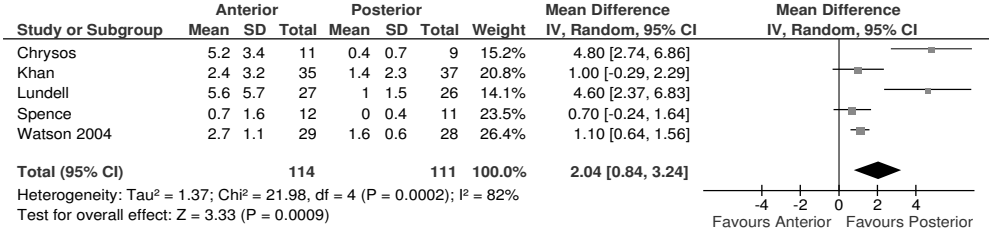


Figure 3 Short-term heartburn

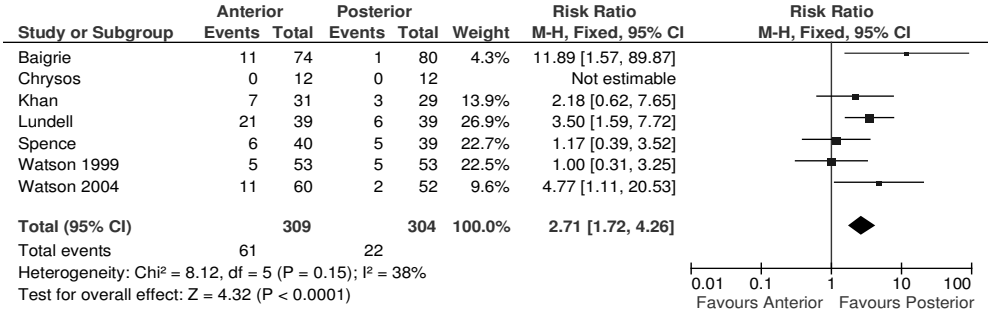


Figure 4 Short-term Dakkak dysphagia score

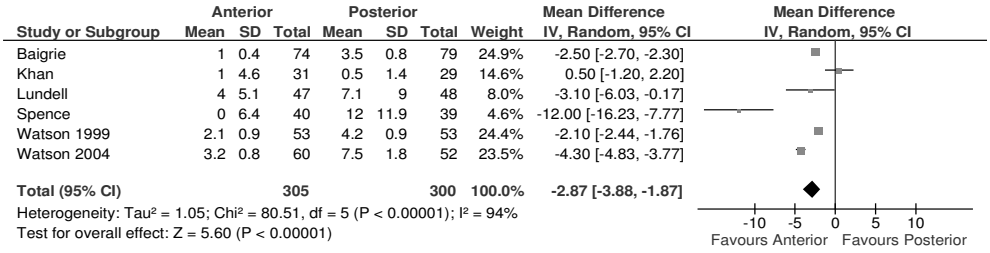


Figure 5 Short-term reoperation rate

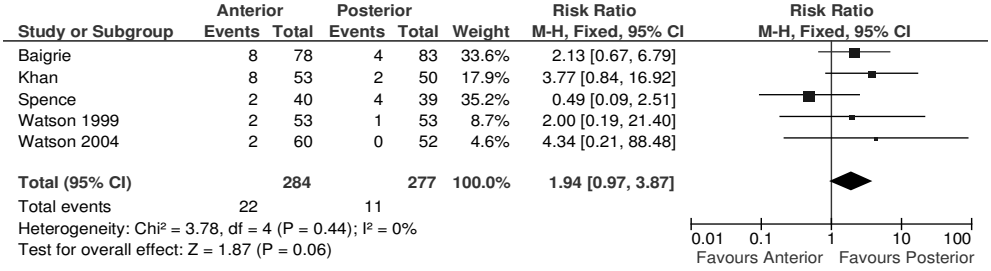


Figure 6 Short-term LES relaxation nadir pressure (mm Hg)

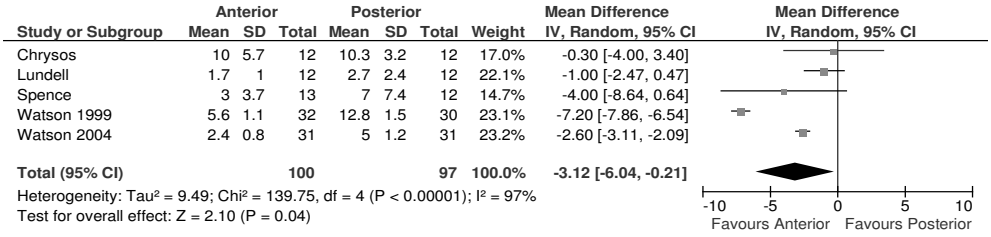
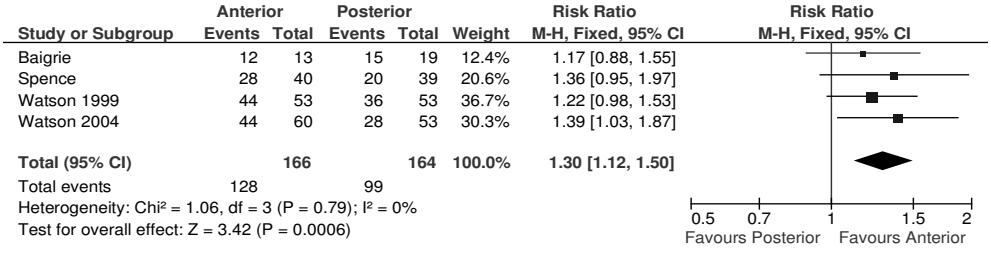


Figure 7 Short-term ability to relieve bloating



Satisfaction with intervention, willingness to undergo surgery again and LES pressure were not different (Table 4). Operating time, conversion rate, in-hospital complications and length of hospital stay were similar for both groups (Table 4). The included trials reported no mortality. Sensitivity analysis of outcomes with zero

events in one arm (heartburn, gas bloating and conversion) yielded similar results. Funnel plots did not demonstrate evidence of publication bias (Figure 13).
Subgroup analysis after exclusion of two RCTs[10,11] that performed 90 degree LAF yielded similar results: mean esophageal acid exposure time (4.0% *vs* 1.1%; WMD 3.36%; 95% CI [0.61, 6.10]; *P*=0.02), heartburn (21% *vs* 7%; RR 2.93; 95% CI [1.72, 5.02]; *P*<0.001), Dakkak dysphagia score (2.0 *vs* 4.1; WMD -2.03; 95% CI [-2.68, -1.39]; *P*<0.001) and ability to relieve bloating (85% *vs* 71%; RR 1.21; 95%CI [1.01, 1.45]; *P*=0.04). The only discrepancies compared with the main analysis were that the difference in surgical reintervention (9.8% *vs* 3.8%; RR 2.60; 95%CI [1.11, 6.08]; *P*=0.03), regurgitation (13% *vs* 7%; RR 3.61; 95% CI [1.79, 7.25]; *P*<0.001) and LES pressure (18.7 *vs* 25.5 mm Hg; WMD -5.65 mmHg; 95% CI [-10.74, -0.56]; *P*=0.03) were significant and the difference in LES relaxation nadir pressure was not significant in the subgroup (5.7 *vs* 10 mm Hg; WMD
-2.99 mm Hg; 95% CI [-8.05, 2.08]; *P*=0.25).

Long-term outcomes

In the long-term, 3 out of 4 primary outcomes and 6 out of 10 secondary outcomes were reported by three or more studies. LAF resulted in a persistent two-fold higher rate of heartburn compared with LPF at long-term follow-up (31% *vs* 14%; RR 2.15; 95% CI [1.49, 3.09]; *P*<0.001; Figure 8). This was associated with more PPI use in the LAF group (25% *vs* 10%; RR 2.53; 95% CI [1.40, 4.45]; *P*=0.002; Figure 11). Dakkak dysphagia scores (4.6 *vs* 5.6; WMD -1.46; 95% CI [-3.16, 0.24]; *P*=0.09; Figure 9) and the ability to relieve bloating (56% *vs* 50%; RR 1.07; 95% CI [0.84, 1.35]; *P*=0.59; Figure 12) became similar in the LAF and LPF group with extension of follow-up. The reoperation rate remained twice as high after LAF in the long-term (10% *vs* 5%; RR 2.12; 95% CI [1.07, 4.21]; *P*=0.03; Figure 10). In the LAF group, 18 out of 22 reoperations were performed for recurrent GERD and 1 for dysphagia. In contrast, 2 out of 11 surgical reinterventions after LPF were for recurrent GERD and 8 for dysphagia.

Figure 8 Long-term heartburn

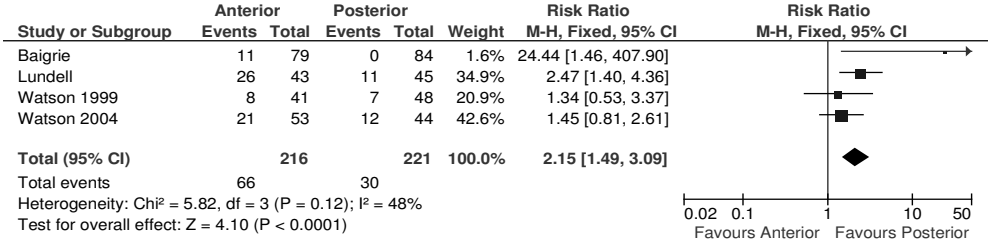


Figure 9 Long-term Dakkak dysphagia score

Study or Subgroup	Anterior Mean	SD	Total	Posterior Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Baigrie	0.2	0.1	68	1.1	0.3	78	37.4%	-0.90 [-0.97, -0.83]
Lundell	7.2	10.5	43	5.5	8	45	12.5%	1.70 [-2.21, 5.61]
Watson 1999	7.8	5.3	41	12	4.2	48	24.5%	-4.20 [-6.21, -2.19]
Watson 2004	5.5	5.3	53	6.7	4.2	44	25.6%	-1.20 [-3.09, 0.69]
Total (95% CI)			**205**			**215**	**100.0%**	**-1.46 [-3.16, 0.24]**

Heterogeneity: Tau² = 2.01; Chi² = 12.13, df = 3 (P = 0.007); I² = 75%
Test for overall effect: Z = 1.68 (P = 0.09)

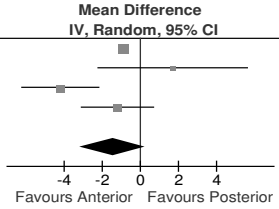


Figure 10 Long-term reoperation rate

Study or Subgroup	Anterior Events	Total	Posterior Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Baigrie	8	78	4	83	35.5%	2.13 [0.67, 6.79]
Lundell	5	43	1	45	8.9%	5.23 [0.64, 42.99]
Watson 1999	7	41	6	48	50.6%	1.37 [0.50, 3.74]
Watson 2004	2	53	0	44	5.0%	4.17 [0.21, 84.57]
Total (95% CI)		**215**		**220**	**100.0%**	**2.12 [1.07, 4.21]**
Total events	22		11			

Heterogeneity: Chi² = 1.63, df = 3 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.15 (P = 0.03)

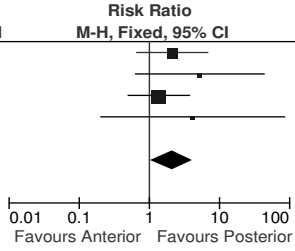


Figure 11 Long-term PPI use

Study or Subgroup	Anterior Events	Total	Posterior Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lundell	10	43	3	45	21.9%	3.49 [1.03, 11.82]
Watson 1999	11	41	9	48	61.8%	1.43 [0.66, 3.11]
Watson 2004	13	53	2	44	16.3%	5.40 [1.29, 22.64]
Total (95% CI)		**137**		**137**	**100.0%**	**2.53 [1.40, 4.55]**
Total events	34		14			

Heterogeneity: Chi² = 3.41, df = 2 (P = 0.18); I² = 41%
Test for overall effect: Z = 3.09 (P = 0.002)

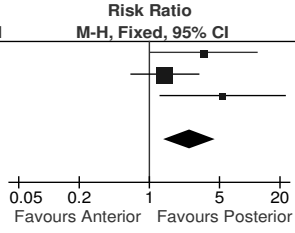
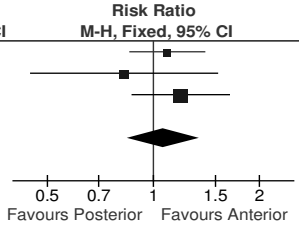


Figure 12 Long-term ability to relieve bloating

Study or Subgroup	Anterior Events	Total	Posterior Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Baigrie	11	11	10	11	19.6%	1.10 [0.86, 1.40]
Watson 1999	12	41	17	48	29.3%	0.83 [0.45, 1.52]
Watson 2004	36	53	25	44	51.1%	1.20 [0.87, 1.64]
Total (95% CI)		**105**		**103**	**100.0%**	**1.07 [0.84, 1.35]**
Total events	59		52			

Heterogeneity: Chi² = 1.21, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)



In line with the short-term outcome, there were no differences in inability to belch, gas bloating, satisfaction with intervention and willingness to undergo surgery again (Table 5). Sensitivity analysis of outcomes with zero events in one arm (heartburn and reoperation rate) yielded similar results. Funnel plots did not demonstrated evidence of publication bias.

Subgroup analysis after exclusion of an RCT that performed 90 degree LAF[14] yielded similar results: PPI use (25% *vs* 13%; RR 1.97; 95% CI [1.03, 3.76]; *P*=0.04), Dakkak dysphagia score (4.2 *vs* 5.3; WMD -1.46; 95% CI [-4.10, 1.17]; *P*=0.28) and ability to relieve bloating (44% *vs* 46%; RR 0.93; 95% CI [0.65, 1.34]; *P*=0.71). The differences in heartburn (28% *vs* 10%; RR 2.41; 95% CI [0.95, 6.11]; *P*=0.06) and reoperation rate (12% *vs* 6%; RR 2.01; 95% CI [1.00, 4.07]; *P*=0.05) were similar as well and the only discrepancy compared with the main analysis was that the differences of the subgroup were at the limit of statistical significance.

Figure 13 Funnel plot short-term heartburn

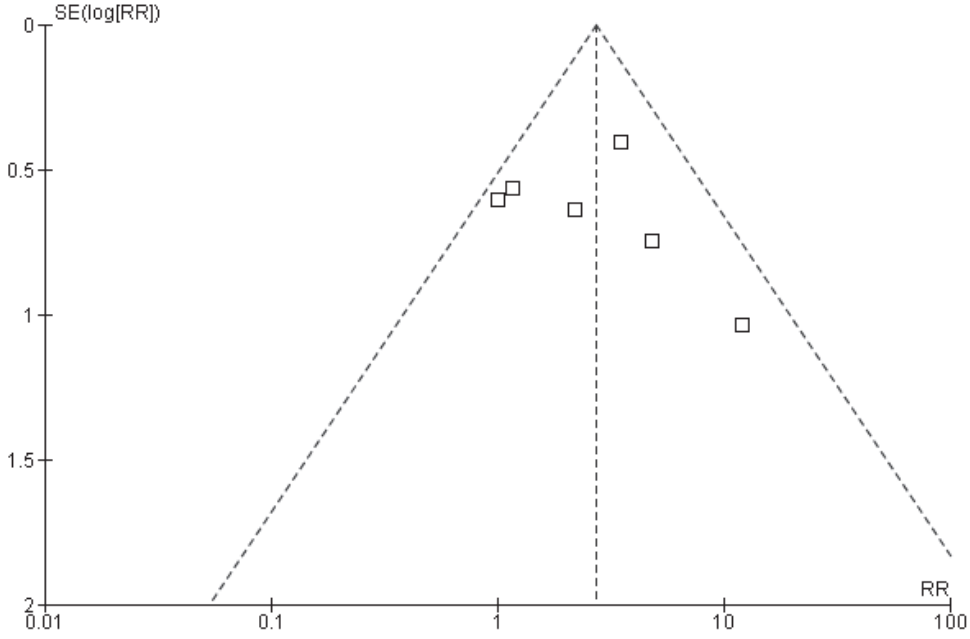


Table 4 Short-term outcome

Short-term outcom	RCTs (*n*)	LAF	LPF	RR	WMD	CI	*P*-value
Esophagitis	3	8/67 [12%]	4/72 [6%]	2.17		0.67, 7.02	0.19
Regurgitation	5	36/225 [16%]	25/214 [12%]	1.09		0.28, 4.24	0.90
Inability to belch	5	21/201 [10%]	44/188 [23%]	0.52		0.21, 1.25	0.14
Gas boating	6	50/245 [20%]	63/245 [26%]	0.76		0.56, 1.03	0.07
Satisfaction with intervention	5	213/258 [83%]	214/253 [85%]	0.98		0.91, 1.05	0.55
Willing to repeat surgery	5	257/276 [93%]	241/270 [89%]	1.04		0.96, 1.14	0.35
LES pressure (mm Hg)	6	17.7 (*n*=135)	16.6 (*n*=133)		-3.87	-10.56, 2.82	0.26
Conversion rate	6	7/298 [2%]	4/290 [1%]	1.57		0.50, 4.91	0.44
Operating time (min)	5	67 (*n*=280)	68 (*n*=272)		-1.60	-8.79, 5.58	0.66
In-hospital complications	5	17/286 [6%]	15/278 [5%]	1.06		0.54, 2.08	0.86
Length of hospital stay (days)	4	2.5 (*n*=208)	2.4 (*n*=199)		0.09	-0.05, 0.24	0.21

Table 5 Long-term outcome

Long-term outcome	RCTs (*n*)	LAF	LPF	RR	CI	*P*-value
Inability to belch	4	24/155 [15%]	49/158 [31%]	0.53	0.25, 1.11	0.09
Gas bloating	3	53/131 [40%]	46/140 [33%]	1.12	0.84, 1.49	0.45
Satisfaction with intervention	4	167/204 [82%]	195/214 [91%]	0.89	0.74, 1.08	0.23
Willing to repeat surgery	3	121/132 [92%]	126/135 [93%]	0.99	0.90, 1.09	0.84

RCT, Randomized clinical trial; LAF, Laparoscopic anterior fundoplication; LPF, Laparoscopic posterior fundoplication; RR, Risk ratio; WMD, Weighted mean difference; CI, Confidence interval

Discussion

Between 2004 and 2010, seven RCTs were published comparing LAF and LPF for GERD[8,11,12,14,16,17,41]. These individual trials are inconclusive and are too small to identify significant differences regarding the most important determinants of successful antireflux surgery: objective reflux control and the need for surgical reintervention. Previous meta-analysis on antireflux surgery[7,20,38,43] have not reviewed nine recent publications on six out of seven original RCTs comparing LAF to LPF[8,13-17,41,42,44]. More importantly, four recent papers[13,14,16,17] on five and ten-year outcome have not yet been pooled in meta-analysis. Long-term follow-up is critical to evaluate differences in reflux control and reoperation rate. Previous systematic reviews on antireflux surgery lack meta-analysis of long-term outcome and definite conclusions regarding the surgical procedure of choice[7,20,38,43]. The current meta-analysis aims to provide this evidence by pooling short and long-term outcomes separately.

The methodological quality of the seven RCTs included in the current meta-analysis was good, with a mean Jadad score of 4. Surgical techniques of the included trials were standardized and similar: in all patients a 90-180° anterior or 180-360° posterior fundoplication was created after crural repair. Two trials divided the short gastric vessels in the LPF group[10,14-16,42]. This is not likely to introduce any bias since it has previously been demonstrated that division of the short gastric vessels does not influence outcome[20]. One trial enrolled a small number of patients with esophageal dysmotility[9]. The current study analyzed patients with and without esophageal dysmotility together as four RCTs have shown that outcome of fundoplication is similar in patients with normal and abnormal esophageal motility[45-48]. There were no other potential sources of bias.

The current short-term results demonstrate that esophageal acid exposure time, as measured with 24-hr pH monitoring, is higher after LAF. The clinical impact of this higher acid exposure is illustrated by a two-fold higher rate of recurrent heartburn compared with LPF. The short-term reoperation rate is twice as high after LAF with the notable fact that 80% of these reinterventions are performed for recurrent GERD. In the short-term this is counterbalanced by a lower LES relaxation nadir pressure, resulting in a lower Dakkak dysphagia score and less difficulty to relieve bloating in the LAF group. Physiological studies have previously demonstrated that LES relaxation nadir pressure is the only standard manometry parameter correlated with postfundoplication dysphagia[49,50].

The present long-term results demonstrate that Dakkak dysphagia scores and ability to relieve bloating become similar with extension of follow-up. The individual results of the 4 RCTs underline that dysphagia decreases during long-term follow-

up[12,14,16,17]. The current results demonstrate that differences in these postfundoplication symptoms between LAF and LPF are most prominent in the early postoperative period and gradually fade with time. In contrast, the higher rate of heartburn after LAF persists during long-term follow-up. Twice as many patients have recurrent GERD after LAF, with more PPI use compared with LPF. The long-term reoperation rate is twice as high after LAF as well and recurrent GERD is the indication for surgical reintervention in more than 80% of the patients. There are no differences in the ability to belch and gas bloating in both the short and the long-term. The high PPI use after LAF probably explains why patient satisfaction was similar in both groups, despite the higher rate of recurrent GERD compared with LPF. The short and long-term results of subgroup analysis after exclusion of two RCTs[10,11] that performed 90 degree LAF were similar.

Based on the current results LPF should be regarded as the fundoplication of choice for GERD. LPF comprises both posterior total (Nissen) and posterior partial fundoplication. A modified Toupet fundoplication, including crural repair and division of the short gastric vessels, is by far the most commonly performed posterior partial fundoplication[7]. The current study does not include separate analysis of posterior total and posterior partial fundoplication, since the individual results of 10 RCTs and two meta-analyses of these studies have demonstrated that reflux control is similar[7,20]. A subgroup analysis of the first meta-analysis demonstrated no differences in reflux recurrence detected by either endoscopy and/or pH-metry or symptoms between posterior partial (Toupet) fundoplication and posterior total fundoplication (Nissen) at 30 [6-60] months[20]. The second meta-analysis showed that Toupet fundoplication has a similar rate of recurrent pathological acid exposure, esophagitis and reflux symptoms compared with Nissen fundoplication at 23 months [12-60], with homogeneity of one, two and five-year outcome[7]. A recent systematic review that included 10-year follow-up studies confirmed that there are no differences in esophagitis, heartburn and reflux recurrence[43]. The second meta-analysis also found that posterior partial fundoplication reduces dysphagia, gas-related symptoms and reoperation rate compared with posterior total fundoplication[7]. Based on the level 1a evidence provided by our previous meta-analysis[7] and the present study, it could be argued that laparoscopic posterior partial fundoplication offers effective reflux control with minimal postfundoplication symptoms, and can be considered the surgical procedure of choice for GERD.

In conclusion, LAF is associated with higher esophageal acid exposure time and prevalence of heartburn compared with LPF. In the short-term this is counterbalanced by less severe dysphagia compared with LPF. However, dysphagia scores become similar in the long-term, with a persistent higher rate of

recurrent heartburn and PPI use after LAF. The reoperation rate is twice as high after LAF as well, mainly due to reinterventions for recurrent GERD. Perioperative outcomes, patient satisfaction and the prevalence of gas-related symptoms are similar. These results lend level 1a support for the use of LPF as the surgical treatment of choice for GERD.

References

(1) Draaisma WA, Rijnhart-de Jong HG, Broeders IA et al. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. Ann Surg 2006; 244:34-41.

(2) Broeders JA, Rijnhart-de Jong HG, Draaisma WA et al. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. Ann Surg 2009; 250:698-706.

(3) Salminen PT, Hiekkanen HI, Rantala AP et al. Comparison of long-term outcome of laparoscopic and conventional nissen fundoplication: a prospective randomized study with an 11-year follow-up. Ann Surg 2007; 246:201-206.

(4) Horvath KD, Jobe BA, Herron DM et al. Laparoscopic Toupet fundoplication is an inadequate procedure for patients with severe reflux disease. J Gastrointest Surg 1999; 3:583-591.

(5) Patti MG, Robinson T, Galvani C et al. Total fundoplication is superior to partial fundoplication even when esophageal peristalsis is weak. J Am Coll Surg 2004; 198:863-869.

(6. Eubanks TR, Omelanczuk P, Richards C et al. Outcomes of laparoscopic antireflux procedures. Am J Surg 2000; 179:391-395.

(7) Broeders JA, Mauritz FA, Ahmed AU et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. Br J Surg 2010; 97:1318-1330.

(8) Khan M, Smythe A, Globe J et al. Randomized controlled trial of laparoscopic anterior versus posterior fundoplication for gastro-oesophageal reflux disease. in press Aust NZ J Surg 2010.

(9) Watson DI, Jamieson GG, Pike GK et al. Prospective randomized double-blind trial between laparoscopic Nissen fundoplication and anterior partial fundoplication. Br J Surg 1999; 86:123-130.

(10) Watson DI, Jamieson GG, Lally C et al. Multicenter, prospective, double-blind, randomized trial of laparoscopic nissen vs anterior 90 degrees partial fundoplication. Arch Surg 2004; 139:1160-1167.

(11) Spence GM, Watson DI, Jamiesion GG et al. Single center prospective randomized trial of laparoscopic Nissen versus anterior 90 degrees fundoplication. J Gastrointest Surg 2006; 10:698-705.

(12) Baigrie RJ, Cullis SN, Ndhluni AJ et al. Randomized double-blind trial of laparoscopic Nissen fundoplication versus anterior partial fundoplication. Br J Surg 2005; 92:819-823.

(13) Ludemann R, Watson DI, Jamieson GG et al. Five-year follow-up of a randomized clinical trial of laparoscopic total versus anterior 180 degrees fundoplication. Br J Surg 2005; 92:240-243.

(14) Nijjar R, Watson D, Jamieson G et al. Five-year follow-up of a multicenter, double-blind randomized clinical trial of laparoscopic Nissen vs anterior 90 degrees partial fundoplication. Arch Surg 2010; 145:552-557.

(15) Hagedorn C, Jonson C, Lonroth H et al. Efficacy of an anterior as compared with a posterior laparoscopic partial fundoplication: results of a randomized, controlled clinical trial. Ann Surg 2003; 238:189-196.

(16) Engström C, Lönroth H, Mardani J et al. An anterior or posterior approach to partial fundoplication? Long-term results of a randomized trial. World J Surg 2007; 31:1221-1225.

(17) Cai W, Watson DI, Lally CJ et al. Ten-year clinical outcome of a prospective randomized clinical trial of laparoscopic Nissen versus anterior 180(degrees) partial fundoplication. Br J Surg 2008; 95:1501-1505.

(18) Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Chichester: John Wiley & Sons; 2008.

(19) BMJ Clinical Evidence website. Search Filters. http://clinicalevidence.bmj.com/ceweb/about/search_filters.jsp [accessed 1 June 2010].

(20) Catarci M, Gentileschi P, Papi C et al. Evidence-based appraisal of antireflux fundoplication. Ann Surg 2004; 239:325-337.

(21) Dakkak M, Bennett JR. A new dysphagia score with objective validation. J Clin Gastroenterol 1992; 14:99-100.

(22. Moher D, Cook DJ, Eastwood S et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999; 354:1896-1900.

(23) Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283:2008-2012.

(24) Clarke M, Horton R. Bringing it all together: Lancet-Cochrane collaborate on systematic reviews. Lancet 2001; 357:1728.

(25) Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5:13.

(26. Jadad AR, Moore RA, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17:1-12.

(27) Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21:1539-1558.

(28) Higgins JP, Thompson SG, Deeks JJ et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327:557-560.

(29) DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7:177-188.

(30) Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50:1088-1101.

(31) Egger M, Davey SG, Schneider M et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315:629-634.

(32) Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. Stat Med 2001; 20:641-654.

(33) Fein M, Bueter M, Thalheimer A et al. Ten-year outcome of laparoscopic antireflux surgery. J Gastrointest Surg 2008; 12:1893-1899.

(34) Polfo N, Borgonovo G, Puglisi M et al. Partial fundoplication (DOR) versus fundoplication (Nissen-Rossetti) in the therapy of the reflux gastric esophageal disease. Ann Gastroenterol Hepatol (Paris) 1983; 19:191.

(35) Stewart GD, Watson AJ, Lamb PJ et al. Comparison of three different procedures for antireflux surgery. Br J Surg 2004; 91:724-729.

(36) Watson A. Update: total versus partial laparoscopic fundoplication. Dig Surg 1998; 15:172-180.

(37) Wong AS, Myers JC, Jamieson GG. Esophageal pH profile following laparoscopic total fundoplication compared to anterior fundoplication. J Gastrointest Surg 2008; 12:1341-1345.

(38) Varin O, Velstra B, De SS et al. Total vs partial fundoplication in the treatment of gastroesophageal reflux disease: a meta-analysis. Arch Surg 2009; 144:273-278.

(39) Fein M, Seyfried F. Is there a role for anything other than a Nissen's operation? J Gastrointest Surg 2010; 14 Suppl 1:S67-74.

(40) Terzic A, Muller M, Hermeneit S et al. The laparoscopic therapy of GERD - semifundoplication according to Dor or Toupet? A prospective, randomised study. Z Gastroenterol 2007; 45:803.

(41) Chrysos E, Athanasakis E, Pechlivanides G et al. The effect of total and anterior partial fundoplication on antireflux mechanisms of the gastroesophageal junction. Am J Surg 2004; 188:39-44.

(42) Engström C, Ruth M, Lönroth H et al. Manometric characteristics of the gastroesophageal junction after anterior versus posterior partial fundoplication. Dis Esophagus 2005; 18:31-36.

(43) Shan CX, Zhang W, Zheng XM et al. Evidence-based appraisal in laparoscopic Nissen and Toupet fundoplications for gastroesophageal reflux disease. World J Gastroenterol 2010; 16:3063-3071.

(44). Woodcock SA, Watson DI, Lally C et al. Quality of life following laparoscopic anterior 90 degrees versus Nissen fundoplication: results from a multicenter randomized trial. World J Surg 2006; 30:1856-1863.

(45. Rydberg L, Ruth M, Lundell L. Mechanism of action of antireflux procedures. Br J Surg 1999; 86:405-410.

(46) Fibbe C, Layer P, Keller J et al. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized, clinical, and manometric study. Gastroenterology 2001; 121:5-14.

(47) Chrysos E, Tsiaoussis J, Zoras OJ et al. Laparoscopic surgery for gastroesophageal reflux disease patients with impaired esophageal peristalsis: total or partial fundoplication? J Am Coll Surg 2003; 197:8-15.

(48) Booth MI, Stratford J, Jones L et al. Randomized clinical trial of laparoscopic total (Nissen) versus posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. Br J Surg 2008; 95:57-63.

(49) Scheffer RC, Samsom M, Frakking TG et al. Long-term effect of fundoplication on motility of the oesophagus and oesophagogastric junction. Br J Surg 2004; 91:1466-1472.

(50) Mathew G, Watson DI, Myers JC et al. Oesophageal motility before and after laparoscopic Nissen fundoplication. Br J Surg 1997; 84:1465-1469.

(51) Anderson JA, Myers JC, Watson DI et al. Concurrent fluoroscopy and manometry reveal differences in laparoscopic Nissen and anterior fundoplication. Dig Dis Sci 1998; 43:847-853.

12

Five-year outcome of laparoscopic anterior partial *versus* Nissen fundoplication: 4 randomized trials

J.A.J.L. Broeders[1]
D.J.G.H. Roks[1]
G. G. Jamieson[1]
P.G. Devitt[1]
R.J. Baigrie[2]
D.I. Watson[3]

[1]Discipline of Surgery, Royal Adelaide Hospital, University of Adelaide, Australia
[2]Gastrointestinal Unit, Kingsbury Hospital, University of Cape Town, South Africa
[3]Dep. of Surgery, Flinders University and Medical Centre, Bedford Park, Australia

International Society for Diseases of the Esophagus Australasian Section
Hobart, Australia, February 2011

Submitted

Abstract

Objective: To compare longer term (5-year) outcomes for reflux control and post-surgery side effects following laparoscopic anterior (90° and 180°) partial vs. Nissen fundoplication for gastroesophageal reflux.

Summary Background Data: Laparoscopic Nissen fundoplication is the most frequently performed surgical procedure for gastroesophageal reflux. It achieves excellent control of reflux, but in some patients is followed by troublesome side effects. To reduce the risk of side effects laparoscopic anterior partial fundoplication variants have been advocated, although some studies suggest poorer reflux control.

Methods: From 1995 to 2003, 461 patients with gastroesophageal reflux were enrolled in 4 randomized controlled trials comparing anterior partial vs. Nissen fundoplication. Two trials evaluated anterior 180°, and 2 anterior 90° partial fundoplication. The original trial data were combined and a re-analysis from original data was undertaken to determine outcomes at 5-years follow-up. Reflux symptom control and side effects were evaluated in a blinded fashion using standardized questionnaires, including 0-10 analog scores (0=no symptoms, 10=severe symptoms).

Results: At 5 years, patients who underwent an anterior 90° or 180° partial fundoplication had less side effects compared with Nissen fundoplication and were equally satisfied with the overall outcome. Reflux control, measured by heartburn scores and antisecretory medication use, was similar for anterior 180° partial vs. Nissen fundoplication, but inferior after anterior 90° partial vs. Nissen fundoplication.

Conclusions*:* Anterior 180° partial fundoplication achieves durable control of reflux symptoms and less side effects compared with Nissen fundoplication. Although reflux control following anterior 90° partial fundoplication appears less effective than after Nissen fundoplication. This data supports the use of anterior 180° partial fundoplication for the surgical treatment of gastroesophageal reflux.

Introduction

Laparoscopic fundoplication is the surgical approach of choice for the treatment of gastroesophageal reflux disease. It achieves similar long-term reflux control, with less short and long-term problems, compared to open fundoplication.[1] Laparoscopic Nissen fundoplication is the most frequently performed antireflux operation and alters the anatomy of the gastroesophageal junction. The gastroesophageal junction serves three functions. The first is to allow swallowed solids and liquids to pass from esophagus to the stomach. The second is to allow venting of gas from the stomach to the mouth (i.e. belching), and the third function is to prevent the backward flow of gastric contents into the esophagus (i.e. gastroesophageal reflux). Nissen fundoplication restores the third function and provides excellent reflux control.[1-3] However, it delivers a supracompetent valve which can impair the first two functions. Three meta-analyses have demonstrated that Nissen fundoplication is followed by a significant incidence of troublesome postfundoplication side effects, including troublesome postoperative dysphagia and gas related problems.[4-6]

Laparoscopic partial fundoplication procedures have been proposed as alternatives and aim to reduce the incidence of post-fundoplication side effects. Recently published American guidelines for antireflux surgery state that partial fundoplication provides similar 5-year reflux control, but with less postoperative dysphagia and fewer reoperations compared with Nissen fundoplication.[7] The guidelines suggested that laparoscopic anterior partial fundoplication may be less effective in the long-term. However, there may be important differences between different anterior partial fundoplication variants (e.g. 90° vs. 120° vs. 180°), and therefore generalizing all anterior partial fundoplication procedures into a single category might not be appropriate. Further, specific differences between different anterior partial fundoplication variants are not well understood. A recent meta-analysis also pooled anterior 90°, 120° and 180° partial fundoplications, and compared this group to pooled results of posterior 180°, 200° and Nissen fundoplication.[8] This analysis also suggested that reflux control for the pooled anterior fundoplication types was inferior to the pooled results of the posterior and Nissen fundoplication procedures.[8] However, this analysis failed to recognize and consider important differences between the fundoplication subtypes, and that technical differences might be important for achieving good clinical outcomes. Further, this meta-analysis did not access raw data from the original trials. Hence, it is not appropriate to extrapolate its conclusions to specific fundoplication procedures.

To overcome the problems inherent in previous studies, we combined raw data sets from 4 randomized controlled trials of laparoscopic anterior partial vs. laparoscopic Nissen fundoplication, and used the original data to determine the clinical outcomes at 5-years follow-up. Two of the trials compared anterior 90° partial with Nissen fundoplication,[9;10] and 2 compared anterior 180° with Nissen fundoplication.[11;12] These combined data sets allowed randomized comparisons of both anterior partial fundoplication variants with Nissen fundoplication.

Methods

Study design and participants

Data sets from 4 previously reported randomized controlled trials of anterior 180° [11;12] or anterior 90° [9;10] partial fundoplication vs. Nissen fundoplication were combined and reanalyzed (Figure 1). Patients presenting for primary antireflux surgery from 1995 to 2003 were recruited into these trials. Two trials compared anterior 90° partial vs. Nissen fundoplication[9;10] and 2 compared anterior 180° partial vs. Nissen fundoplication.[11;12] Five-year outcome data for 2 of the trials has been reported previously.[13;14]

All trials used a common methodology. Procedures were standardized across all centers, follow-up was undertaken in a blinded fashion, and common standardized symptom and outcome scores were used in all studies. All enrolled patients had objective evidence of gastroesophageal reflux disease at either 24-hour pH monitoring (pH <4 for more than 7% of time) or upper endoscopy (ulcerative esophagitis).[9-12] 393 patients underwent laparoscopic fundoplication in either Adelaide, South Australia[9-11] or in Cape Town, South Africa.[12] Sixty eight patients underwent surgery elsewhere in Australia or New Zealand within a multicentre trial of anterior 90° vs. Nissen fundoplication which was coordinated from Adelaide.[9] The lead clinician in the South African study worked in Adelaide in 1995, and participated in the development of the first anterior 180° partial vs. Nissen fundoplication trial undertaken in Adelaide.[11] He applied the same surgical techniques, clinical outcome scores and follow-up methodology in the South African trial.

Exclusion criteria were: age under 18 yrs or over 75 yrs, esophageal motility disorders which precluded Nissen fundoplication, contemporaneous abdominal procedures, and previous gastric or esophago-gastric junction surgery. Data for preoperative work-up, perioperative care and follow-up was collected prospectively and entered into computerized databases. Follow-up was undertaken yearly by "blinded" research nurses. The human research ethics committees of the hospitals in which surgery was undertaken approved the protocols of all trials.

Surgical procedures

In each trial, patients were randomized 1:1 to undergo either anterior (90° or 180°) partial or Nissen fundoplication. All procedures were commenced laparoscopically. The surgical techniques have been described in detail elsewhere.[9-12] The initial steps for all three types of fundoplication were identical: hiatal dissection with minimal use of diathermy, preservation of the hepatic branch of the vagus nerve, mobilization of the distal esophagus and routine posterior hiatal repair. Short gastric blood vessels were not routinely divided, except in patients undergoing Nissen fundoplication in one of the 4 trials.[9]

Laparoscopic anterior 90° partial fundoplication was fashioned by first stabilizing the intra-abdominal esophagus with a posterior esophagopexy suture. The angle of His was then accentuated by placing two sutures between the left side of the esophagus and the adjacent gastric fundus – the upper suture also incorporating the hiatal rim. Next, the gastric fundus was sutured loosely over the left side and the front of the esophagus using an apical suture that anchored the fundus to the anterior esophagus and the apex of the hiatal rim in the midline. The inferior edge of the fundal fold was also sutured to the anterior esophagus in the midline.[9;10]

Laparoscopic anterior 180° partial fundoplication was constructed by suturing the anterior fundal wall to the right and left hiatal pillars and the apex of the hiatal rim using five to six sutures.[11;12] The key difference between the 2 anterior partial fundoplication techniques was that the fundus was anchored to the right hiatal pillar during anterior 180° fundoplication, but not during anterior 90° fundoplication.

Laparoscopic Nissen fundoplication entailed construction of a loose 1 and 2 cm long 360° fundoplication with a 52 to 60 Fr intra-esophageal bougie present to help ensure a tension-free wrap .[9-12;15] Three sutures were used to secure the wrap.[9-12;15]

Clinical outcomes

Preoperative, perioperative and follow-up data were collected prospectively. Follow-up entailed the application of a standardized set of questions, administered each year by either postal questionnaire or telephone interview, 5-year follow-up data was analyzed. Other events during the follow-up period, such as endoscopic dilatation for dysphagia or surgical reoperation, were also identified prospectively and recorded. Visual analog scores were used to assess symptoms. Heartburn was evaluated using an analog score (0=no heartburn; 10=severe heartburn) and by determining the use of antisecretory medications. The presence of dysphagia (yes/no question) and analog scores for solids and liquids (0=no dysphagia; 10=severe dysphagia) were recorded. A validated 0-45 dysphagia score[16] was used to quantify the ability to swallow nine types of liquids and solids (0=no

dysphagia; 45=severe dysphagia).[17] Patients were also asked if they were able to eat a normal diet. Gas-related symptoms were assessed by yes/no questions which determined the ability to belch, presence of abdominal bloating symptoms, ability to relieve bloating by belching, and increased flatulence. Patient satisfaction was scored using a analog score (0=dissatisfied; 10=satisfied), and a Visick score (1= no symptoms; 2= mild symptoms; 3= moderate symptoms; 4= moderate symptoms interfering with life; 5= symptoms as bad or worse after surgery).[17] Patients were also asked whether they still regarded their initial decision to undergo surgery to be correct.

Statistical Analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS inc., Chicago, IL). Data were analyzed according to the intention-to-treat principle. Continuous variables were expressed as mean ± standard deviation [SD] and groups were compared using the Mann-Whitney U test. Ordinal variables were expressed as percentages and differences between groups were analyzed using the χ^2 test. Differences in the number of patients undergoing endoscopic dilatation for dysphagia or reoperation were determined using Kaplan-Meier survival curves with log-rank tests.

Results

461 patients were enrolled in the 4 randomized controlled trials and underwent either laparoscopic anterior partial fundoplication (n=233) or laparoscopic Nissen fundoplication (n=228) for gastroesophageal reflux. A 5-year outcome was available for 434 (94.1%). Nine (2.0%) patients died during follow-up, and clinical outcome scores were available for 425 (92.2%) patients 5 years after surgery; anterior partial (n=211), Nissen fundoplication (n=214). Full details of patient follow-up are summarized in Figure 1. Data was available from a subset of 172 patients for comparison of anterior 90° partial (n=90) vs. Nissen fundoplication (n=82), and from 253 patients for comparison of anterior 180° partial (n=121) vs. Nissen fundoplication (n=132). Baseline patient characteristics were similar for the anterior partial and Nissen groups (Table 1).

Figure 1 Study profile: CONSORT analysis 5-year follow-up for the anterior 90° partial (90°LAF), anterior 180° partial (180°LAF) and Nissen fundoplication (LNF) groups

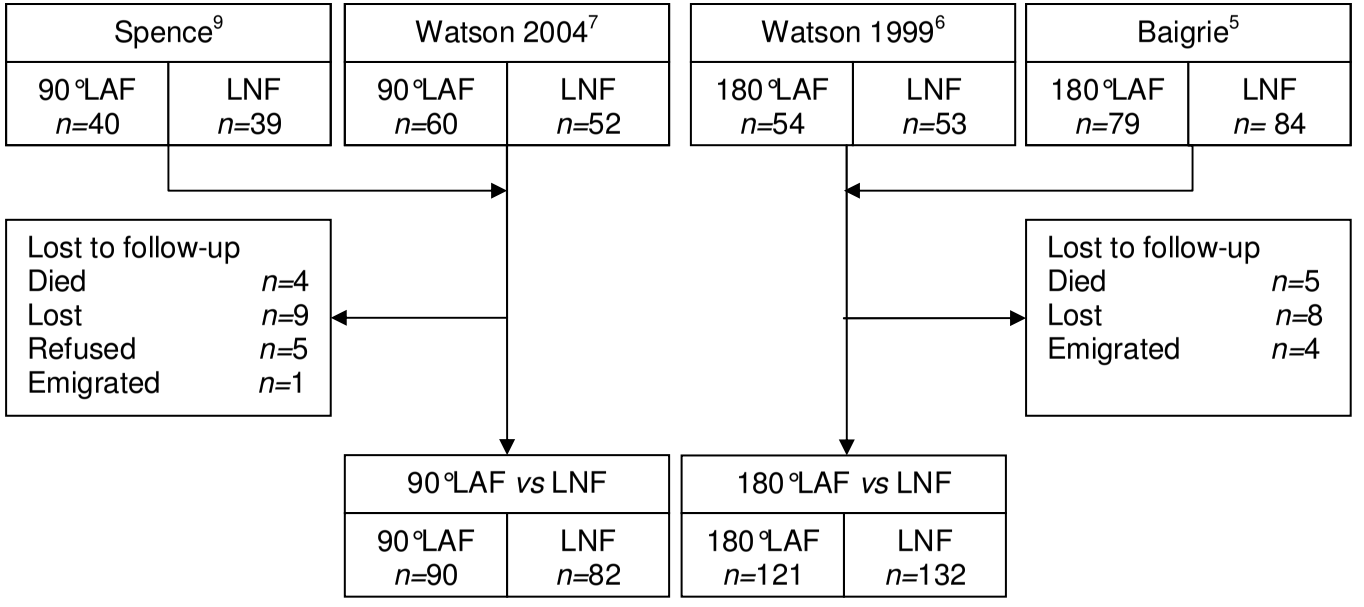


Table 1 Baseline characteristics of patients according to treatment group

	Anterior 90° *vs.* Nissen fundoplication		**Anterior 180° *vs* Nissen fundoplication**	
	Anterior 90°	Nissen	Anterior 180°	Nissen
Patients (*n*)	90	82	121	132
Age (yr)	46.5 (22-76)	47.7 (22-72)	44.9 (20-74)	44.7 (16-71)
Male / female sex	52 / 38	48 / 34	72 / 49	82 / 50
Body mass index (kg/m^2)*	29.5 [5.1]	30.0 [5.7]	27.7 [4.3]	30.0 [6.6]
Follow-up interval (months)*	64.7 [9.6]	63.2 [8.2]	67.7 [10.1]	67.4 [9.6]

* values are gives as mean [SD]

Anterior 90° partial vs. Nissen fundoplication

Outcomes at 5 years for anterior 90° partial vs. Nissen fundoplication are summarized in Table 2. Heartburn scores were higher following anterior 90° partial fundoplication and the use of antisecretory medication was more common. However, dysphagia was less common, more patients were able to eat a normal diet, the mean analog score for dysphagia for solid food was lower, and the mean 0-45 dysphagia score was lower following anterior 90° partial fundoplication. Gas-related symptoms were less common after anterior 90° partial fundoplication, with better preserved ability to belch, and less flatulence. All measures of overall satisfaction with the outcome of surgery were similar for the 2 procedures.

There were no significant differences in the number of endoscopic dilatations performed for dysphagia (2.0% *vs.* 6.0%; *P*=0.202) or the overall number of reoperations (10.0% *vs.* 4.9%; *P*=0.212) undertaken within the 5 yr follow-up period (Figure 2). In the group which underwent anterior 90° partial fundoplication most reoperations were performed for recurrent reflux (6.7%), whereas in the Nissen fundoplication group most reoperations were for dysphagia (3.7%).

Anterior 180° partial vs. Nissen fundoplication

The outcomes at 5 years for anterior 180° partial vs. Nissen fundoplication are summarized in Table 3. Heartburn scores and the use of antisecretory medication were similar for the 2 procedures. Dysphagia was less common following anterior 180° partial fundoplication, the mean analog scores for dysphagia for solids and liquids was lower, and the mean 0-45 dysphagia score was lower following anterior 180° partial fundoplication. Gas-related symptoms were also less common after anterior 180° partial fundoplication, belching ability and the ability to relieve bloating were better preserved, and flatulence was less troublesome. All measures of overall satisfaction with the outcome of surgery were similar.

There were no significant differences in the number of endoscopic dilatations performed for dysphagia (2.0% *vs.* 5.0%; *P*=0.191) or the overall number of reoperations (9.9% *vs.* 6.1%; *P*=0.256) undertaken (Figure 2). In the group which underwent anterior 180° partial fundoplication most reoperations were performed for recurrent reflux (7.4%), whereas in the Nissen fundoplication group most reoperations were for dysphagia (6.1%).

Table 2 Symptomatic outcome at 5 years after anterior 90° and Nissen fundoplication

	Anterior 90°	**Nissen**	***P*-value**
Reflux symptoms			
Analog heartburn score*	2.2 [2.5] (*n*=78)	1.6 [2.5] (*n*=73)	0.043
Use of antisecretory drugs	29/84 [34.5%]	9/76 [11.8%]	0.001
Dysphagia			
Dysphagia	26/84 [30.9%]	38/76 [50.0%]	0.014
Analog score for dysphagia for liquids*	0.7 [1.6] (*n*=90)	1.2 [2.5] (*n*=82)	0.399
Analog score for dysphagia for solids*	1.6 [2.4] (*n*=89)	2.9 [3.0] (*n*=81)	0.001
0-45 Dysphagia score*	6.4 [8.3] (*n*=90)	10.8 [11.0] (*n*=82)	0.007
Normal diet	83/87 [95.4%]	68/82 [82.9%]	0.009
Dilatation for dysphagia	2/90 [2.2%]	5/82 [6.1%]	0.202
Gas-related symptoms			
Inability to belch	3/87 [3.4%]	29/82 [35.4%]	<0.001
Gas bloating	48/89 [53.9%]	47/82 [57.3%]	0.656
Inability to relieve bloating	32/64 [50.0%]	26/61 [42.6%]	0.408
Increased flatulence	36/88 [40.9%]	55/82 [67.1%]	0.001
Patient satisfaction			
Analog score for satisfaction*	7.3 [3.3] (*n*=90)	7.5 [3.0] (*n*=82)	0.975
Correct decision for surgery?	72/87 [82.8%]	68/81 [84.0%]	0.836
Visick score			0.404
1 (no symptoms)	24 [27.6%]	17 [20.7%]	
2 (mild symptoms)	36 [41.4%]	37 [45.1%]	
3 (moderate symptoms)	7 [8.0%]	7 [8.5%]	
4 (symptoms interfering with life)	8 [9.2%]	14 [17.1%]	
5 (symptoms not improved)	12 [13.8%]	7 [8.5%]	
Visick 1 and 2 (no or mild symptoms)	60/87 [69.0%]	54/82 [65.9%]	0.666

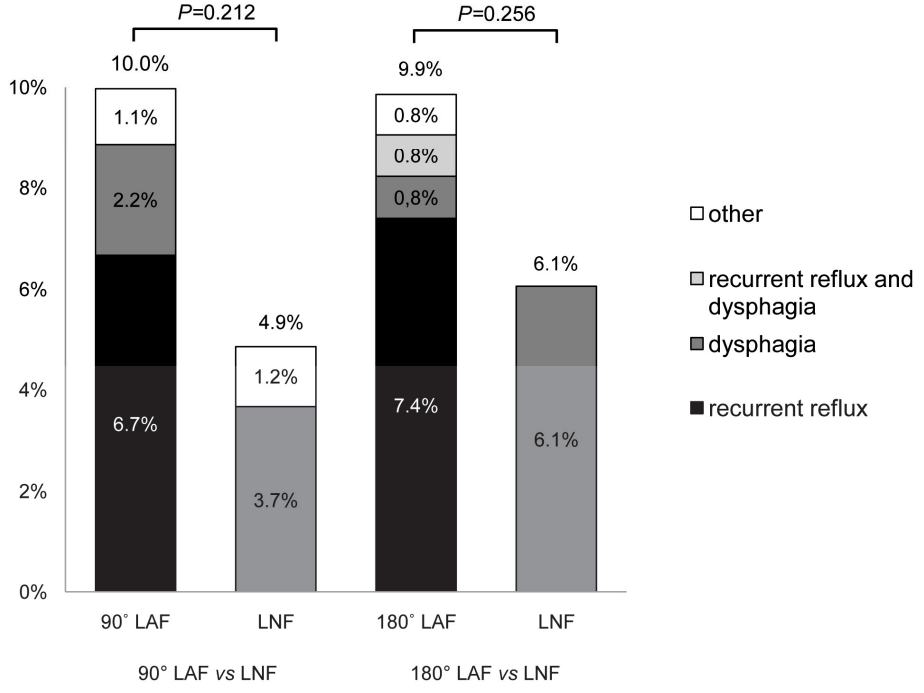
* values are gives as mean [SD]

Table 3 Symptomatic outcome at 5 years after anterior 180° and Nissen fundoplication

	Anterior 180°	Nissen	*P*-value
Reflux symptoms			
Analog heartburn score*	1.8 [2.7] (*n*=120)	1.6 [2.7] (*n*=132)	0.316
Use of antisecretory drugs	2/51 [3.9%]	4/52 [7.7%]	0.414
Dysphagia			
Dysphagia	8/38 [21.1%]	19/33 [57.6%]	0.002
Analog score for dysphagia for liquids*	0.5 [1.4] (*n*=121)	1.2 [1.8] (*n*=132)	<0.001
Analog score for dysphagia for solids*	1.3 [2.1] (*n*=121)	2.5 [2.8] (*n*=131)	<0.001
0-45 Dysphagia score*	5.3 [7.3] (*n*=120)	8.8 [9.5] (*n*=132)	0.003
Normal diet	106/119 [89.1%]	114/131 [87.0%]	0.618
Dilatation for dysphagia	2/121 [1.7%]	6/132 [4.5%]	0.191
Gas-related symptoms			
Inability to belch	19/120 [15.8%]	46/132 [34.8%]	0.001
Gas bloating	63/120 [52.5%]	77/132 [58.3%]	0.352
Inability to relieve bloating	30/100 [30.0%]	55/123 [44.7%]	0.024
Increased flatulence	57/110 [51.8%]	79/119 [66.4%]	0.025
Patient satisfaction			
Analog score for satisfaction*	8.5 [2.2] (*n*=119)	8.2 [2.8] (*n*=130)	0.643
Correct decision for surgery?	107/116 [92.2%]	111/124 [89.5%]	0.465
Visick score			0.254
1 (no symptoms)	55 [47.4%]	51 [39.5%]	
2 (mild symptoms)	41 [35.3%]	54 [41.9%]	
3 (moderate symptoms)	13 [11.2%]	10 [7.8%]	
4 (symptoms interfering with life)	5 [4.3%]	6 [4.7%]	
5 (symptoms not improved)	2 [1.7%]	8 [6.2%]	
Visick 1 and 2 (no or mild symptoms)	96/116 [82.8%]	105/129 [81.4%]	0.781

* values are gives as mean [SD]

Figure 2 Reoperation rate and indications for reoperation at 5 years after anterior 90° partial (90°LAF) *versus* Nissen fundoplication (LNF), and anterior 180° partial (180°LAF) *versus* Nissen fundoplication (LNF)



Discussion

Antireflux surgery aims to provide durable reflux control with minimal postfundoplication side effects. In general, for most patients this is achieved, although some are troubled by side effects. To minimize the risk of side effects, routine use of a partial fundoplication has been proposed. However, the perception that there is a paucity of long-term follow-up data for antireflux surgery, has recently led to published American guidelines for the surgical treatment of reflux recommending "controlled studies with long-term follow-up" to determine the surgical therapy of choice.[7] Long-term follow-up data is available in many relevant randomized trials,[13;14;18;19] and excellent outcomes have been demonstrated for anterior partial fundoplication variants in randomized trials at 5 and 10 years follow-up.[13;14;18] In contrast, the 5-year outcomes of another trial has suggested inferior reflux control after anterior partial fundoplication.[19] In our current study we provide further analysis of long-term outcome data from 4 randomized trials, and by combining the 5-year outcome data sets for further analysis of the original data we have accessed the largest randomized data set which evaluates anterior partial vs. Nissen fundoplication. The American guidelines for antireflux surgery correctly conclude that differences in outcome between anterior 90° and 180° partial fundoplication have not been investigated.[7] To identify potential differences in outcome between the anterior fundoplication sub-types we have stratified and compared these subtypes separately with Nissen fundoplication in a randomized fashion.

At five-years follow-up, control of heartburn symptoms were similar for anterior 180° partial vs. Nissen fundoplication, but inferior for anterior 90° fundoplication vs. Nissen fundoplication. The use of antisecretory medication after anterior 180° partial fundoplication was similar to Nissen fundoplication, but more common after anterior 90° partial fundoplication vs. Nissen fundoplication. This supports the contention that anterior 90° partial fundoplication creates a less effective antireflux barrier than the Nissen fundoplication. It should be noted, however, that use of antisecretory medication does not imply that all patients using these medications have recurrent reflux. Earlier studies have demonstrated that only a small proportion of these patients have abnormal esophageal acid exposure on pH monitoring[1;2;20] or endoscopic evidence of fundoplication disruption.[3] Others have demonstrated that approximately 2/3's of patients who take these medications after fundoplication, use them for atypical abdominal symptoms, unrelated to the original symptoms, or use medication in combination with non-steroidal anti-inflammatory agents for gastric mucosal protection.[1;20] The use of antisecretory medications should therefore only be interpreted as an "relative" indicator of recurrent reflux.[1;20]

Both anterior 90° and 180° partial fundoplications were associated with less dysphagia and gas-related symptoms compared with Nissen fundoplication, and the extent of the reduction in this problem was similar for both anterior partial fundoplication procedures. Consistent with these outcomes was a higher incidence of reoperation for recurrent reflux after anterior partial fundoplication, a higher incidence of reoperation for dysphagia after Nissen fundoplication, even though the overall number of operative revision procedures were not significantly different for all procedures. Measures of overall patient satisfaction were not significantly different for both types of anterior partial fundoplication and Nissen fundoplication. Overall, this suggests that the best clinical outcome at 5-years follow-up was achieved following anterior 180° partial fundoplication.

The long-term differences in postfundoplication symptoms between anterior and Nissen fundoplication are supported by studies that have evaluated physiological effects of fundoplication. Impaired lower esophageal sphincter relaxation correlates with post-fundoplication dysphagia.[21;22] A recent meta-analysis suggested that lower esophageal sphincter relaxation is more likely to be incomplete after Nissen than anterior partial fundoplication.[8] This is probably a consequence of placement of the stomach behind the intra-abdominal esophagus, and this mechanism probably contributes to the higher incidence of dysphagia after Nissen fundoplication. Furthermore, it is commonly assumed that impairment of the ventilation of swallowed air from the stomach (i.e. inability to belch) causes gas bloating and flatulence after fundoplication.[23] A yet unpublished study by our group suggests that air venting from the stomach is easier after partial than Nissen fundoplication, and this could explain a reduced risk of gas bloat and flatulence.

A previously reported randomized trial reported by Hagedorn et al demonstrated poorer reflux control 5 years after an anterior 120° partial fundoplication, compared with posterior partial fundoplication.[19;24] Might different types of anterior partial fundoplication have different outcomes? The key difference between the anterior 180° and the 90° and 120° variants is extent of anchorage of the fundoplication to the hiatal rim on the right side of the esophagus. In the anterior 180° partial fundoplication the gastric fundus is sutured securely to the right hiatal pillar and to the esophageal wall with 3 to 4 sutures, whereas the stomach is not sutured to the right hiatal pillar in the 90° and 120° variants. When undertaking revision surgery for recurrent reflux, we have noted that an anterior 180° fundoplication always remains securely attached to the right hiatal pillar, whereas with the lesser anterior 90° and 120° partial fundoplications lack of anchorage on the right side can allow the fundoplication to unravel to some extent in some patients. This might account for differences in the rates of recurrent reflux. In general posterior partial fundoplications are also anchored to the hiatal rim, and the Nissen fundoplication is

constructed in a manner which does not allow it to “unwind”. Variation in construction probably accounts for different clinical outcomes between different wrap types at late follow-up, and we now believe that secure anchorage of a partial fundoplication to a rigid structure such as the hiatal rim during construction is a key step for achieving effective long-term control of reflux.

Strengths of our current study are the randomized design, common protocols across all trials, and the large sample size (n=461). Surgical techniques for construction of the fundoplication were identical, except that in one trial short gastric vessels were routinely divided in the Nissen fundoplication arm.[9] However, multiple randomized trials have shown that division of the short gastric blood vessels during Nissen fundoplication provides no advantage.[5] Bias associated with incomplete follow-up[25] was limited by the high level of complete follow-up at 5 years across our combined data set.

A potential limitation of our study is that 3 of the 4 trials were performed in Australia,[9-11] and one in South Africa.[12] However, the principal investigator of the South African trial worked with the Australian research group during the first trial, and then applied identical surgical techniques and questionnaires in the South African patient population.[12] The only difference in data collection was that the use of antisecretory medication was not assessed in the South African trial.[12] Another limitation is that we relied on clinical follow-up using validated questionnaires and we did not repeat pH monitoring or esophageal manometry at 5 years. Objective studies were undertaken at early follow-up in each trial, and the results have been reported previously.[9-11] Our previous experience with trying to obtain compliance with objective follow-up in otherwise well patients has shown that a high rate of compliance with studies such as manometry and pH monitoring at multiple points during clinical trails is not feasible in our communities.[11;25]

Recently published meta-analyses comparing posterior partial (Toupet) with Nissen fundoplication, have also concluded that posterior partial fundoplication offers similar reflux control, but with fewer troublesome postfundoplication side effects compared with the Nissen procedure.[4;26] Our study demonstrates that anterior 180° partial fundoplication has the same advantages over Nissen fundoplication. Two randomized controlled trials of an anterior vs. posterior partial fundoplication have been reported and both suggest better reflux control following posterior fundoplication, less side effects after anterior partial fundoplication, and equivalent overall satisfaction with the outcome of surgery.[19;27] However, as discussed above, Hagedorn et al evaluated an anterior 120° not a 180° partial fundoplication.[19;24] The trial reported by Khan et al did evaluate an anterior 180° partial fundoplication, but only reported 12 months follow-up, and this follow-up was incomplete, being available for only 57% of the enrolled patients at this early time point.[27] Hence,

more trials are needed to address the relative advantages, if any, of anterior 180° vs. posterior partial fundoplication for the surgical treatment for gastroesophageal reflux.

In conclusion, in this comparison of anterior 90° and anterior 180° vs. Nissen fundoplication at 5-years follow-up, anterior 180° partial fundoplication achieved the best overall outcome, with equivalent reflux symptom control but less side effects compared with Nissen fundoplication. Reflux control following anterior 90° partial fundoplication appears less effective than after Nissen fundoplication, and overall this suggests that an anterior 180° partial fundoplication is an appropriate operation for the treatment of uncomplicated gastroesophageal reflux disease, and in our centers this is now the most commonly performed antireflux procedure.

Acknowledgements

The authors acknowledge the support of Dr Stephen Archer, Dr Justin Bessell, Dr Michael Booth, Dr Richard Cade, Dr Graham Cullingford, Professor David Fletcher, Dr James Hurley, Dr George Kiroff, Professor Christopher Martin, Dr Ian Martin, Professor Lesley Nathanson and Professor John Windsor who contributed patients to a multicenter trial of anterior 90° partial vs. Nissen fundoplication.[10] Dr Philip Game and Dr Robert Britten-Jones contributed patients to the trial of anterior 180° partial vs. Nissen fundoplication undertaken in Adelaide, South Australia.[11] The randomized trials conducted in Australia were supported by research project grants from the National Health and Medical Research Council (NHMRC) of Australia (grant Nos 157986 & 480401). These trials were registered with the Australasian Clinical Trials Register (ACTRN12607000298415, ACTRN12607000303448 & ACTRN12607000304437).

References

(1) Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. Ann Surg 2009; 250(5):698-706.

(2) Draaisma WA, Rijnhart-de Jong HG, Broeders IA, Smout AJ, Furnee EJ, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. Ann Surg 2006; 244(1):34-41.

(3) Salminen PT, Hiekkanen HI, Rantala AP, Ovaska JT. Comparison of long-term outcome of laparoscopic and conventional nissen fundoplication: a prospective randomized study with an 11-year follow-up. Ann Surg 2007; 246(2):201-206.

(4) Broeders JA, Mauritz FA, Ahmed AU, Draaisma WA, Ruurda JP, Gooszen HG et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. Br J Surg 2010; 97(9):1318-1330.

(5) Catarci M, Gentileschi P, Papi C, Carrara A, Marrese R, Gaspari AL et al. Evidence-based appraisal of antireflux fundoplication. Ann Surg 2004; 239(3):325-337.

(6) Varin O, Velstra B, De SS, Ceelen W. Total vs partial fundoplication in the treatment of gastroesophageal reflux disease: a meta-analysis. Arch Surg 2009; 144(3):273-278.

(7) Stefanidis D, Hope WW, Kohn GP, Reardon PR, Richardson WS, Fanelli RD. Guidelines for surgical treatment of gastroesophageal reflux disease. Surg Endosc 2010; 24(11):2647-2669.

(8) Broeders JA, Roks DJ, Ali U.A., Draaisma WA. Laparoscopic anterior versus posterior fundoplication for gastroesphageal reflux disease; systematic review and meta-analysis of randomized clinical trials. In press Ann Surg 2011.

(9) Watson DI, Jamieson GG, Lally C, Archer S, Bessell JR, Booth M et al. Multicenter, prospective, double-blind, randomized trial of laparoscopic nissen vs anterior 90 degrees partial fundoplication. Arch Surg 2004; 139(11):1160-1167.

(10) Spence GM, Watson DI, Jamiesion GG, Lally CJ, Devitt PG. Single center prospective randomized trial of laparoscopic Nissen versus anterior 90 degrees fundoplication. J Gastrointest Surg 2006; 10(5):698-705.

(11) Watson DI, Jamieson GG, Pike GK, Davies N, Richardson M, Devitt PG. Prospective randomized double-blind trial between laparoscopic Nissen fundoplication and anterior partial fundoplication. Br J Surg 1999; 86(1):123-130.

(12) Baigrie RJ, Cullis SN, Ndhluni AJ, Cariem A. Randomized double-blind trial of laparoscopic Nissen fundoplication versus anterior partial fundoplication. Br J Surg 2005; 92(7):819-823.

(13) Ludemann R, Watson DI, Jamieson GG, Game PA, Devitt PG. Five-year follow-up of a randomized clinical trial of laparoscopic total versus anterior 180 degrees fundoplication. Br J Surg 2005; 92(2):240-243.

(14) Nijjar R, Watson D, Jamieson G, Archer S. Five-year follow-up of a multicenter, double-blind randomized clinical trial of laparoscopic Nissen vs anterior 90 degrees partial fundoplication. Arch Surg 2010; 145(6):552-557.

(15) Jamieson GG, Watson DI, Britten-Jones R, Mitchell PC, Anvari M. Laparoscopic Nissen fundoplication. Ann Surg 1994; 220(2):137-145.

(16) Dakkak M, Bennett JR. A new dysphagia score with objective validation. J Clin Gastroenterol 1992; 14(2):99-100.

(17) Watson DI, Pike GK, Baigrie RJ, Mathew G, Devitt PG, Britten-Jones R et al. Prospective double-blind randomized trial of laparoscopic Nissen fundoplication with division and without division of short gastric vessels. Ann Surg 1997; 226(5):642-652.

(18) Cai W, Watson DI, Lally CJ, Devitt PG, Game PA, Jamieson GG. Ten-year clinical outcome of a prospective randomized clinical trial of laparoscopic Nissen versus anterior 180(degrees) partial fundoplication. Br J Surg 2008; 95(12):1501-1505.

(19) Engström C, Lönroth H, Mardani J, Lundell L. An anterior or posterior approach to partial fundoplication? Long-term results of a randomized trial. World J Surg 2007; 31(6):1221-1225.

(20) Wijnhoven BP, Lally CJ, Kelly JJ, Myers JC, Watson DI. Use of antireflux medication after antireflux surgery. J Gastrointest Surg 2008; 12(3):510-517.

(21) Scheffer RC, Samsom M, Frakking TG, Smout AJ, Gooszen HG. Long-term effect of fundoplication on motility of the oesophagus and oesophagogastric junction. Br J Surg 2004; 91(11):1466-1472.

(22) Mathew G, Watson DI, Myers JC, Holloway RH, Jamieson GG. Oesophageal motility before and after laparoscopic Nissen fundoplication. Br J Surg 1997; 84(10):1465-1469.

(23) Woodward ER, Thomas HF, McAlhany JC. Comparison of crural repair and Nissen fundoplication in the treatment of esophageal hiatus hernia with peptic esophagitis. Ann Surg 1971; 173(5):782-792.

(24) Hagedorn C, Jonson C, Lonroth H, Ruth M, Thune A, Lundell L. Efficacy of an anterior as compared with a posterior laparoscopic partial fundoplication: results of a randomized, controlled clinical trial. Ann Surg 2003; 238(2):189-196.

(25) Ludemann R, Watson DI, Jamieson GG. Influence of follow-up methodology and completeness on apparent clinical outcome of fundoplication. Am J Surg 2003; 186(2):143-147.

(26) Shan CX, Zhang W, Zheng XM, Jiang DZ, Liu S, Qiu M. Evidence-based appraisal in laparoscopic Nissen and Toupet fundoplications for gastroesophageal reflux disease. World J Gastroenterol 2010; 16(24):3063-3071.

(27) Khan M, Smythe A, Globe J, Stoddard CJ, Ackroyd R. Randomized controlled trial of laparoscopic anterior versus posterior fundoplication for gastro-oesophageal reflux disease. ANZ J Surg 2010; 80(7-8):500-505.

13

Laparoscopic Nissen fundoplication after failed EsophyX® fundoplication

E.J.B. Furnée[1]
J.A.J.L. Broeders[1]
W.A. Draaisma[1]
M.P. Schwartz[2]
E.J. Hazebroek[1]
A.J.P.M. Smout[3]
P.J.J. van Rijn[4]
I.A.M.J. Broeders[5]

[1]Dep. of Surgery, University Medical Center Utrecht
[2]Dep.of Gastroenterology, Meander Medical Center, Amersfoort
[3]Dep.of Gastroenterology,University Medical Center Utrecht
[4]Dep. of Surgery, Lange Land Hospital, Zoetermeer
[5]Dep. of Surgery, Meander Medical Center, Amersfoort

British Journal of Surgery 2010; 97:1051-5.

Abstract

***Background*:** Reflux control may be ineffective in a substantial number of patients after endoluminal EsophyX fundoplication for gastro-oesophageal reflux disease. Subsequent laparoscopic Nissen fundoplication (LNF) might be required to relieve symptoms. The aim of this study was to evaluate the outcome of LNF after previous EsophyX fundoplication.

***Methods*:** EsophyX failure was defined as recurrence or persistence of typical symptoms, with or without anatomical failure of the wrap or persisting pathological oesophageal acid exposure. Consecutive patients who underwent LNF after failed EsophyX were identified. Symptomatic outcome was obtained by standardised questionnaire and objective outcome by endoscopy, oesophageal manometry and pH monitoring.

***Results*:** Eleven patients were included. During LNF, intraoperative gastric perforation occurred in two patients, and one patient developed a subphrenic abscess postoperatively. Daily heartburn was present in one patient after LNF, and three had troublesome daily dysphagia. Compared to before EsophyX, general quality of life did not increase significantly after LNF. Oesophageal acid exposure was normalised in all patients after surgery. Oesophagitis was absent after LNF in all, except one patient who had persisting grade A oesophagitis.

***Conclusion*:** Symptomatic and objective reflux control are satisfactory after LNF for failed EsophyX fundoplication. Previous EsophyX, however, is associated with a risk of gastric injury during LNF and a relatively high rate of post-fundoplication dysphagia.

Introduction

Endoscopic treatments for gastro-oesophageal reflux disease (GORD) have been introduced as alternatives to long-term acid-suppressing drugs and to avoid prolonged recuperation after antireflux surgery[1,2]. Treatment on an outpatient basis has been claimed as an advantage[3,4]. The techniques have been developed with the aim of providing reflux control comparable to fundoplication without side effects, such as dysphagia and gas bloating[5,6]. The EsophyX plication system is an endoscopic suturing technique that has been promoted on this basis.

A large prospective study using the EsophyX device reported a significant reduction in reflux symptoms with cessation of PPI usage in approximately 70% of patients[7]. Oesophageal acid exposure, however, was normalised in only 37% at 12 months follow-up. Patients with recurrent or persistent GORD after endoluminal EsophyX fundoplication may be candidates for subsequent surgery.

The aim of this study was to evaluate the influence of previous endoluminal EsophyX fundoplication on symptomatic and objective outcomes of subsequent LNF.

Methods

Patients who had LNF for persistent or recurrent GORD symptoms who had previously undergone EsophyX fundoplication (EsophyX, EndoGastric Solutions, Redmond, WA, USA) between 2006 and 2008 were identified from a prospectively created database. Preoperative workup and intra- and postoperative course of the initial endoscopic procedure, and subsequent LNF were recorded for all patients. The EsophyX procedure was performed as described previously[7]. Patients with sliding hiatal hernia larger than 3cm, oesophageal stricture, Barrett's oesophagus, reflux oesophagitis grade C or D, and previous oesophageal or gastric surgery were not considered candidates for the EsophyX procedure.

Laparoscopic Nissen fundoplication was performed in one of the three participating hospitals by three experienced surgeons. All visible polypropylene fasteners of the EsophyX fundoplication were cut by sharp dissection, and the EsophyX wrap fully mobilised. Subsequently, a Nissen fundoplication was created in all patients, as previously described[8]. This involved oesophageal mobilisation until at least 3 cm of the distal part was positioned intra-abdominally, posterior crural repair and a floppy 360° Nissen fundoplication after division of the short gastric vessels.

Standardised questionnaires were used to obtain symptomatic information before treatment, and after LNF. Reflux-related symptoms were evaluated by the validated Gastro-Esophageal Reflux Disease Health Related Quality of Life (GERD-HRQoL) score[9,10]. Patients rated preoperative symptoms as resolved, improved, unchanged

or worsened according to the Visick grading system[11]. They were also asked to score their general quality of life using a visual analogue scale (VAS)[12].
Upper endoscopy, stationary oesophageal manometry, and ambulatory oesophageal 24-hour pH monitoring were performed in all patients before EsophyX and upper endoscopy repeated in all patients afterwards. All patients were asked to undergo these investigations plus barium oesophagogram after LNF. Written informed consent was obtained from all participating patients.
During upper endoscopy, the presence of reflux oesophagitis (graded according to the Los Angeles classification[13]), oesophageal stricture, Barrett's oesophagus and sliding hiatal hernia (ie, the distance between the squamocolumnar junction and diaphragmatic impression) were obtained. Evidence of (partial) disruption of the wrap was evaluated during endoscopy after EsophyX and LNF.
Oesophageal manometry and pH monitoring were performed as previously described[14,15] Barium oesophagogram was performed after LNF to assess the presence of wrap disruption, cephalad slippage of the gastro-oesophageal junction through the wrap (telescoping), intrathoracic wrap migration and hiatal herniation.

Statistical analysis

Values were expressed as mean ± SD. Data were analysed using SPSS version 15.0 for Windows (SPSS, Chicago, Illinois, USA). The paired samples *t* test was used for statistical analysis of differences between continuous values before and after the endoluminal EsophyX fundoplication, and after LNF.

Results

Of 88 patients who underwent EsophyX fundoplication, seven had persistent symptoms and four developed recurrent symptoms during follow-up. These eleven patients underwent LNF after the EsophyX fundoplication. Basic demographics of these eleven patients are presented in *Table 1*. Before EsophyX, all eleven patients experienced symptoms of heartburn (before the primary EsophyX procedure.), two (patients) had regurgitation, (and) one (had) dysphagia and all 11 had been treated with antisecretory drugs with refractory symptoms in seven. After EsophyX, endoscopy showed disruption of all fasteners in three patients, and partial disruption in five. Three of these eight patients had oesophagitis. The other five had no oesophagitis, but oesophageal pH monitoring was not performed because anatomical failure of the repair combined with the recurrence of primary symptoms was the indication for LNF. In the remaining three patients, the EsophyX wrap was intact, but pH monitoring showed abnormal oesophageal acid exposure in two

Table 1 Baseline characteristics

	Total (n = 11)
Male/ female	6 / 5
Age (years)	45.8 ± 14.5
Body mass index (kg/m^2)	24.9 ± 2.8
Time to follow-up (months)	11.2 ± 8.7
Patients available at follow-up	
- symptomatic follow-up	11
- 24-hour pH monitoring	7
- upper endoscopy	11
- barium oesophagogram	9

values are given as mean ± SD, unless otherwise stated

patients and typical symptomatic recurrence in the third. LNF was performed after a mean period of 8.1 ± 5.2 months post-EsophyX fundoplication.

Gastric perforation occurred in two patients during LNF. Conversion to laparotomy was necessary in one patient. Mean duration of operation was 95.8 ± 25.6 minutes. One patient developed a left-sided subphrenic abscess requiring surgical exploration. Oesophageal or gastric perforation as a cause for this complication was not, however, apparent during this laparotomy. There were no other postoperative complications. Mean hospital stay was 3.4 ± 1.1 days.

In seven patients, preoperative symptoms were resolved or improved (*Table 2*). Three patients who rated their symptoms as worsened, had new-onset daily dysphagia, and underwent endoscopic dilatation without satisfactory outcome. The fourth patient with worsened symptomatic outcome had daily heartburn after Nissen fundoplication, but pathological oesophageal acid exposure was not demonstrated by postoperative pH monitoring. General quality of life and the GERD-HRQoL score were improved, although this was only statistically significant for GERD-HRQoL(*Table 2*).

Four patients refused pH monitoring and two refused barium oesophagogram after LNF (*Table 1*). Three of these four patients rated their preoperative symptoms as resolved or improved, and one had worsened symptoms due to troublesome dysphagia.

Table 2 Symptomatic variables

	Total (n = 11)
Self-rated change in symptoms as compared to preoperative status (Visick grading system)	
resolved	5
improved	2
unchanged	0
worsened	4
GERD-HRQoL score	
before EsophyX fundoplication	20.7 ± 6.0
follow-up	6.6 ± 7.5*
General quality of life (VAS)	
before EsophyX fundoplication	44.1 ± 22.8
follow-up	54.5 ± 30.2†
increase (%)	23.6

GERD-HRQoL, Gastro-Esophageal Reflux Disease Health Related Quality of Life; VAS, visual analogue scale, values are given as mean ± SD unless otherwise stated, * P=0.001 (preoperative vs. follow-up), † P=0.179 (preoperative vs. follow-up)

Of five patients with oesophagitis before the EsophyX, this resolved in three after LNF and progressed from grade A to grade B in two. Two other patients developed oesophagitis after the EsophyX. After LNF, one patient had oesophagitis grade A (table 3).

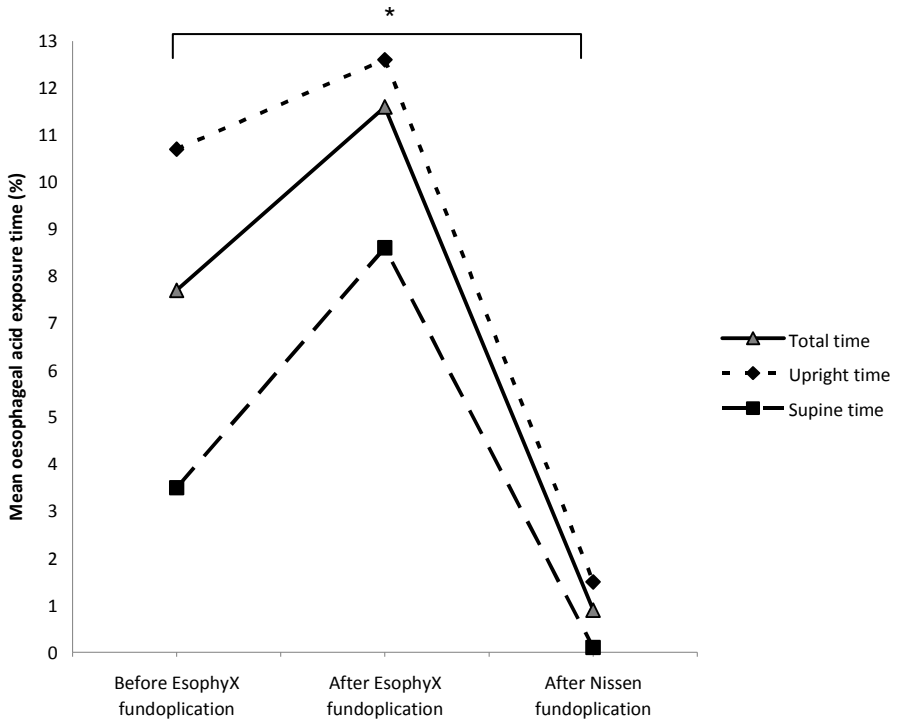
Oesophageal manometry showed a decrease in mean LOS pressure after EsophyX from 1.3 ± 0.8 kPa to 1.0 ± 0.9 kPa, and a rise to 1.8 ± 0.8 kPa after LNF. Mean oesophageal acid exposure times during pH monitoring were increased after the EsophyX procedure, but reduced after Nissen fundoplication (*Figure 1*). Oesophageal acid exposure was normalised in all patients after LNF.

Barium oesophagogram series showed normal anatomy in ten patients. One had intrathoracic wrap migration. This patient had no post-operative symptoms.

Table 3 Grade of oesophagitis according to the Los Angeles classification

	Before EsophyX fundoplication (n = 11)	After EsophyX fundoplication (n = 11)	After Nissen fundoplication (n = 11)
None	6	7	10
grade A	4	1	1
grade B	1	3	0

Figure 1 Mean oesophageal acid exposure times



* *P*-value with < 0.050 for mean total and upright oesophageal acid exposure times (paired-samples *t* test)

Discussion

LNF after previous endoluminal EsophyX fundoplication was associated with a risk of gastric injury. Objective reflux control and reduction of reflux symptoms after LNF was satisfactory. Daily complaints of dysphagia after Nissen fundoplication, however, were encountered in 27% of patients. General quality of life did not significantly improve after surgery. Postoperative scores according to the Visick grading system[11] were lower compared to studies on patients with Nissen fundoplication as a primary treatment[15].

The high incidence of dysphagia after LNF was the main contributor to the poor Visick scores and the overall lack of impact on quality of life. All three patients with troublesome dysphagia after surgery had an endoscopic dilatation, but dysphagia persisted in all of them. As a result, recurrent heartburn after EsophyX may be easier to control by medical therapy than troublesome dysphagia after LNF. Patients should be warned against this possible poor symptomatic outcome before EsophyX is undertaken. The presence of refractory dysphagia after LNF in a large proportion of patients who had undergone EsophyX, supports the view that an EsophyX procedure is far from ideal as a treatment modality for GORD. This seems particularly evident bearing in mind the moderate objective reflux control achieved by the primary EsophyX procedures [7].

After EsophyX fundoplication, the (remnants of the) wrap had to be freed by cutting the polypropylene fasteners before a Nissen fundoplication could be performed . The fasteners tend to remain fixed to crura with firm adhesions between the stomach, oesophagus, and diaphragm. Mobilisation and dissection of the stomach from the oesophagus and diaphragm in the presence of the fasteners and adhesion was associated with an increased risk of injury to the gastric wall. A relatively high incidence of stomach perforations (27%) occurred in the current study compared to 0-2% during primary antireflux surgery[16,17] and 13% during redo antireflux surgery[18]. This is understandable in the perspective of the procedure. The fasteners perforate both the distal oesophagus and gastric fundus, but the line of fasteners is covered by the EsophyX fundoplication. During release, all fasteners are cut, and fastener channels that are not present as visible perforations are not covered by definition during subsequent Nissen fundoplication. This probably explains the development of the intra-abdominal abscess in one patient, as no oesophageal or gastric perforation could be detected during reoperation. The macro- and micro-injuries of the gastric wall had major consequences in the current study. In one of the obvious intraoperative perforations, conversion to laparotomy was required and the patient who developed a subphrenic abscess during the postoperative period, also required a laparotomy. Surgeons dealing with this kind

of surgery should therefore be aware of the increased risk of gastric injury during LNF after EsophyX. Patients should be informed about this prior to EsophyX fundoplication.
Although the number of patients in the current study was small, LNF after previous failed EsophyX fundoplication, seems not to be as straightforward as previously thought.

References

(1) Chen D, Barber C, McLoughlin P, Thasvaneswaran P, Jamieson GG, Maddern GJ. Systematic review of endoscopic treatments for gastro-oesophageal reflux disease. *Br J Surg* 2009; **96**: 128–136.

(2) Goldsmith H, Herman L. Endoluminal gastroplication. A new therapeutic endoscopic procedure for gastroesophageal reflux disease. *Gastroenterol Nurs* 2002; **25**: 15–19.

(3) Oleynikov D, Oelschlager B. New alternatives in the management of gastroesophageal reflux disease. *Am J Surg* 2003; **186**: 106–111.

(4) Rothstein RI. Endoscopic therapy of gastroesophageal reflux disease: outcomes of the randomized-controlled trials done to date. *J Clin Gastroenterol* 2008; **42**: 594–602.

(5) Schwartz MP, Wellink H, Gooszen HG, Conchillo JM, Samsom M, Smout AJ. Endoscopic gastroplication for the treatment of gastro-oesophageal reflux disease: a randomised, sham-controlled trial. *Gut* 2007; **56**: 20–28.

(6) Schiefke I, Soeder H, Zabel-Langhennig A, Teich N, Neumann S, Barte G *et al*. Endoluminal gastroplication: what are the predictors of outcome? *Scand J Gastroenterol* 2004; **39**: 1296–1303.

(7) Cadière GB, Buset M, Muls V, Rajan A, Rösch T, Eckardt AJ *et al*. Antireflux transoral incisionless fundoplication using EsophyX: 12-month results of a prospective multicenter study. *World J Surg* 2008; **32**: 1676–1688.

(8) Draaisma WA, Ruurda JP, Scheffer RC, Simmermacher RK, Gooszen HG, Rijnhart-de Jong HG *et al*. Randomized clinical trial of standard laparoscopic versus robot-assisted laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease. *Br J Surg* 2006; **93**: 1351–1359.

(9) Velanovich V, Karmy-Jones R. Measuring gastroesophageal reflux disease: relationship between the Health-Related Quality of Life score and physiologic parameters. *Am Surg* 1998; **64**: 649–653.

(10) Velanovich V, Vallance SR, Gusz JR, Tapia FV, Harkabus MA. Quality of life scale for gastroesophageal reflux disease. *J Am Coll Surg* 1996; **183**: 217–224.

(11) Rijnhart-de Jong HG, Draaisma WA, Smout AJ, Broeders IA, Gooszen HG. The Visick score: a good measure for the overall effect of antireflux surgery? *Scand J Gastroenterol* 2008; **43**: 787–793.

(12) de Boer AG, van Lanschot JJ, Stalmeier PF, van Sandick JW, Hulscher JB, de Haes JC *et al*. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? *Qual Life Res* 2004; **13**: 311–320.

(13) Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP *et al*. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999; **45**: 172–180.

(14) Furnee EJ, Draaisma WA, Broeders IA, Smout AJ, Gooszen HG. Surgical reintervention after antireflux surgery for gastroesophageal reflux disease: a prospective cohort study in 130 patients. *Arch Surg* 2008; **143**: 267–274.

(15) Draaisma WA, Rijnhart-de Jong HG, Broeders IA, Smout AJ, Furnee EJ, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. *Ann Surg* 2006; **244**: 34–41.

(16) Chrysos E, Tsiaoussis J, Athanasakis E, Zoras O, Vassilakis JS, Xynos E. Laparoscopic vs open approach for Nissen fundoplication. A comparative study. *Surg Endosc* 2002; **16**: 1679–1684.

(17) Bais JE, Bartelsman JF, Bonjer HJ, Cuesta MA, Go PM, Klinkenberg-Knol EC *et al.* Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. *Lancet* 2000; **355**: 170–174.

(18) Furnee EJ, Draaisma WA, Broeders IA, Gooszen HG. Surgical Reintervention After Failed Antireflux Surgery: A Systematic Review of the Literature. *J Gastrointest Surg* 2009; **13**: 1539–1549.

Part III

Physiological effects

14

Effects of anti-reflux surgery on weakly acidic reflux and belching

J.A.J.L. Broeders[1]
A.J. Bredenoord[2]
E.J. Hazebroek[1]
I.A.M.J. Broeders[3]
H.G. Gooszen[1]
A.J.P.M. Smout[2]

[1]Dep. of Surgery, University Medical Center Utrecht
[2]Dep. of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam
[3]Dep. of Surgery, Meander Medical Center, Amersfoort

Gut 2011; in press.

Abstract

Background: Laparoscopic Nissen fundoplication (LNF) is the most frequently performed operation for gastro-oesophageal reflux disease (GORD). However, 12% of the patients have persistent reflux symptoms and 19% develop gas-related symptoms after LNF. Weakly acidic reflux and inability to belch have been alleged to cause these symptoms, respectively. The effect of LNF on weakly acidic reflux and (supra)gastric belching was evaluated.

Methods: In 31 patients upper GI endoscopy, stationary oesophageal manometry and 24-h impedance-pH monitoring off acid secretion inhibiting drugs was performed before and 6 months after primary LNF for PPI-refractory GORD. Patients filled out validated questionnaires on GERD-HRQoL before and 3, 6 and 12 months after surgery.

Results: LNF reduced reflux symptoms (18.6→1.6;*P*=0.015). The procedure drastically reduced the incidence (number per 24 hour) of acid (76.0→1.6;*P*<0.001) and weakly acidic (13.6→5.7;*P*=0.001) as well as liquid (53.4→5.4;*P*<0.001) and mixed reflux episodes (36.3→1.9;*P*<0.001). In contrast, gas reflux was reduced to lesser extent (35.6→25.7;*P*=0.022). Proximal, mid-oesophageal and distal reflux were reduced to a similar extent. Persistent GORD symptoms were neither preceded by acid nor by weakly acidic reflux. The number of air swallows did not change, but the number of gastric belches (GBs) was greatly reduced (68.5→23.9;*P*<0.001). Twenty-three patients had supragastric belches (SGBs), both before and after surgery, whereas 8 patients had no SGBs at all. The majority of SGBs were not reflux-associated and the frequency was greatly increased after LNF (20.8→46.0;*P*=0.036). Reflux-associated SGBs were abolished after surgery (14.0→0.4;*P*<0.001).

Conclusions: LNF similarly controls acid and weakly acidic reflux, but gas reflux is reduced to lesser extent. Persistent reflux symptoms are neither caused by acid nor by weakly acidic reflux. LNF alters the belching pattern by reducing GBs (air venting from stomach) and increasing SGBs (no air venting from stomach). This explains the increase in belching experienced by some patients after LNF, despite the reduction in gastric belching. It can be hypothesised that the reduction in GBs after LNF incites patients to increase SGBs in a futile attempt to vent air from the stomach.

Introduction

Laparoscopic Nissen fundoplication (LNF) is the most frequently performed operation for gastro-oesophageal reflux disease (GORD).[1] LNF has been recommended as the surgical therapy of choice by both the European Study Group for Antireflux Surgery[2] and the Society of American Gastrointestinal Endoscopic Surgeons.[3] However, a recent meta-analysis has demonstrated that 12 percent of the patients report refractory reflux symptoms after LNF.[4] Weakly acidic reflux has been alleged to be the main cause of persistent reflux complaints. In the last three years, four studies have been conducted that evaluated acid and weakly acidic reflux after fundoplication using twenty-four hour combined intraluminal impedance-pH monitoring. However, results of the four previous studies are contradictory with regard the effect of fundoplication on weakly acidic reflux and its role as the main cause of refractory reflux symptoms.[5-8]

Three meta-analyses demonstrated that gas-related symptoms are the most common complaint after LNF.[4,9,10] Fifteen per cent of the patients develop inability to belch[4], 19 per cent develop gas bloating[9] and 59 per cent report flatulence after LNF.[10] Gastric belching is a physiological mechanism that serves to vent ingested air from the stomach. Accumulation of swallowed air[11] causes distention of the proximal stomach which results in a transient relaxation of the lower oesophageal sphincter (TLOSR) by a vagally mediated reflex.[12-15] During a TLOSR air can be vented from the stomach. It is commonly assumed that an inability to vent air from the stomach by gastric belching is the cause of the gas-related symptoms that frequently occur after LNF.[11,16-21] Others, however, have suggested that gas-related symptoms are due to excessive air swallowing after fundoplication.[22] Until now, belching after fundoplication has only been studied indirectly using measurement of belched gas volumes[20] or manometric evaluation of the so-called common cavity phenomenon.[17,23-25] Two papers from Adelaide, Australia, have described that patients who have undergone fundoplication often report that they are still able to belch, in the absence of TLOSRs and common cavities.[17,23] Therefore, it was hypothesised that the mechanism of belching is different after fundoplication and that belches consisted of swallowed air that has been retained in the oesophagus due to failed peristalsis.[23]

Intraluminal impedance monitoring has made it possible to detect the passage of air through the oesophagus, either in aboral or oral direction.[26,27] This technique enables one to identify all individual air swallows and belches during a prolonged period of time and to discriminate gastric belches (GBs) from supragastric belches (SGBs). GBs are accompanied by TLOSRs and result in venting of air from the stomach. Our group has demonstrated that SGBs originate from oesophageal air

ingestion, usually brought about by creating a negative intrathoracic pressure while closing the glottis, followed by immediate expulsion of this air in oral direction.[28] In contrast to GBs, SGBs are not accompanied by TLOSRs and air venting from the stomach.[28] Excessive supragastric belching is a behavioural disorder which benefits from speech therapy.[29] We have subsequently shown that SGBs occur more frequently in GORD patients than in healthy subjects and these belches often occur in close association with acid and weakly acidic reflux episodes. In fact, supragastric belching elicits reflux in some cases and is the patient's response to an unpleasant oesophageal sensation in others.[30] The four previous studies that addressed effect of LNF on weakly acidic reflux using impedance monitoring have yielded opposing results and have not evaluated the impact of LNF on belching.[5-8] Therefore, the current study aimed to evaluated the effect of LNF on weakly acidic reflux and gastric and supragastric belching.

Methods

Study design and data collection

From January 2008 till December 2009, all patients that underwent impedance-pH monitoring and were on the waiting list for primary LNF have been prospectively included. Preoperative data, clinical outcome and the results of objective investigations were prospectively entered into a computerised database by an independent data manager (HGR).

Surgical procedures

All LNFs were performed between January 2008 and December 2009. In all patients a standardised, floppy 360° LNF of 2.5 to 3.0 cm was constructed after ligation and division of the short gastric vessels, full mobilisation of the oesophagus and posterior crural repair.[31-33] LNF was performed by two surgeons beyond the learning curve for LNF,[34] either at the University Medical Center Utrecht (EJH and IAMJB) or the tertiary teaching hospital; Meander Medical Center (IAMJB).

Clinical assessment

Before surgery and at 3 months, 6 months and 12 months after surgery, patients were asked by telephone to complete validated questionnaires by mail. Reflux symptoms were assessed using the GERD Health-Related Quality of Life score (GERD-HRQoL) that has been validated[35] and compared to physiologic parameters.[36] The European Organisation for Research and Treatment of Cancer QLQ-OES 18 questionnaire was used, as it has been validated for the detection of changes in dysphagia.[37] The validated Short-Form 36 (SF-36)[38] and a visual

analogue scale (VAS) validated for Quality of Life (QoL) assessment after oesophageal surgery[39] were used to measure the impact on QoL.

Upper GI endoscopy

Before surgery and 6 months after surgery, patients underwent upper GI endoscopy at the department of Gastroenterology of the University Medical Center Utrecht. Hiatal hernia size and the Los Angeles classification oesophagitis grade[40] were determined endoscopically.

Stationary oesophageal manometry

All manometric recordings were conducted after suspending medication that potentially affects gastrointestinal motility 7 days in advance and were performed by two senior clinicians of the Gastrointestinal Research Unit of the University Medical Center Utrecht (JO and JS). A water-perfused system with a multiple-lumen catheter with an incorporated sleeve sensor was used (Dentsleeve International Ltd, Mississauga, Canada). After transnasal introduction, the catheter was retracted to determine the proximal border of the lower oesophageal sphincter (LOS). The sleeve sensor was positioned at the level of the LOS and intraluminal oesophageal pressures were recorded at 5, 10, 15, 20 and 25 cm above the proximal margin. Thereafter, the manometric response to ten standardised wet swallows was studied (5-ml water bolus). The gastric baseline pressure was registered 2 cm below the distal margin of the sleeve sensor and served as the zero reference point.

Ambulatory 24-h combined oesophageal impedance-pH monitoring

Ambulatory 24-h oesophageal impedance-pH testing was performed in the University Medical Center Utrecht. A combined impedance-pH catheter (VersaFlex, Alpine Biomed, Fountain Valley, CA, USA) was introduced transnasally, after cessation of at least 7 days of all medication that affects gastrointestinal motility and secretion. This catheter has a single antimony pH electrode and eight ring electrodes for recording of impedance signals. The catheter was positioned with the pH electrode at 5 cm and the impedance recording segments at 2–4, 4–6, 6–8, 8–10, 14–16 and 16–18 cm above the manometrically determined upper margin of the LOS. The tracings were recorded in a digital data logger (Medical Measurements Systems, Enschede, The Netherlands), using a sampling frequency of 50 Hz.[50] Patients were instructed to register body position, GORD symptoms, meals and beverages in a diary. In addition, they were asked to press a button on the digital data logger at the beginning of each symptom episode. If the patients experienced symptoms during the measurement, the symptom index (SI) was

calculated separately for all reflux events, GBs and SGBs. A SI of at least 50 per cent was considered to be positive.[41]

Data analysis

The analysis of the 24-h impedance-pH recordings was performed manually by a single observer (JAJLB) using a dedicated software program (MMS, Enschede, The Netherlands). In case of uncertainty another expert observer was consulted (AJB). To minimize observer bias, both observers were blinded for patient characteristics and pre- or postoperative status. The criteria used for classification of air-containing swallows (air swallows), gas, liquid, mixed, acid and weakly acidic reflux have been published before.[5] Normal values for total, acid and weakly acidic reflux episodes were 75, 50 and 33 per 24-h respectively.[42] In addition, the proximal extent of the refluxate in centimeters above the LOS was determined for each individual reflux episode. Liquid-containing reflux episodes (pure liquid and mixed reflux) were classified as proximal (≥15cm above LOS), mid-oesophageal (5-15cm above LOS) or distal (≤5 cm above LOS), based on the extent of the liquid component. The mean proximal extent and the total oesophageal reflux distance (TORD) were calculated for liquid-containing reflux episodes. The latter is the sum of the proximal extent of all individual reflux episodes in centimetres above the LOS.

Gas-containing reflux episodes (pure gas and mixed liquid-gas reflux episodes) were regarded as GBs if the gas component reached the most proximal channel.[43] SGBs were identified using the criteria described by Bredenoord et al.[28] A SGB was defined as a rapid rise in impedance (≥1000Ω) moving in an aboral direction, followed by a return to baseline moving from distally to proximally. This pattern reflects expulsion of air after rapid oesophageal air ingestion. SGBs were considered to be related to reflux when a SGB occurred immediately prior (<1s) to the onset of the reflux episode or during a reflux episode, with the onset of the SGB within 10 seconds after the start of the reflux episode.[30] The number of air swallows, reflux episodes and belches were normalized to a 24-h period. Periods of meal consumption were disregarded. Reference values for the number of air swallows, GBs and SGBs were those of healthy volunteers: 176, 33 and 2 per 24-h respectively.[30,43]

Statistical analysis

The statistical analysis was performed using SPSS version 15.0 (SPSS Inc. Chicago, IL). Continuous variables were expressed as mean ± standard error of the mean (SEM) unless stated otherwise. The Wilcoxon signed rank test was used to determine significant effects of surgery.

Comparisons between the SGB– and SBG+ group for either pre- or postoperative data were performed using the Mann-Whitney *U*-test. Differences with a $P < 0.050$ were considered statistically significant.

Results

Subjects

Thirty-one patients with PPI-refractory GORD with pathological acid exposure on pH monitoring were studied (11 men: mean age 48 years, range 26-67 years). Mean body mass index was 28.0 (1.1) and mean hiatal hernia size was 2.1 (0.4) cm at baseline.

Upper GI endoscopy and stationary oesophageal manometry

Before surgery, 15 patients had oesophagitis and 16 patients had non-erosive GORD. After LNF, oesophagitis was found to be healed in all but five patients, one patient refused post-operative upper GI endoscopy (table 1). These six patients all had a total oesophageal acid exposure time smaller < 1.5% and less than 11 reflux episodes on postoperative impedance-pH monitoring.

All patients underwent pre- and postoperative manometry. LNF increased LOS resting pressure (1.2 (0.1) to 2.0 (0.2) kPa; P=0.002) and LOS relaxation nadir pressure (0.2 (0.0) to 0.9 (0.1) kPa; P<0.001), but distal contraction amplitude did not increase significantly (9.2 (0.5) to 10.5 (1.0) kPa; NS).

Table 1 Grade of oesophagitis

	Pre-op (*n*=31)	**Post-op (*n*=30)**
Grade of oesophagitis		
- None	16	25
- Grade A	8	3
- Grade B	4	2
- Grade C	2	0
- Grade D	1	0

Control of acid and weakly acidic reflux

All patients completed pre- and postoperative oesophageal impedance-pH testing. LNF reduced upright (15.5 (1.3) to 1.5 (0.4); *P*<0.001), supine (11.3 (2.3) to 0.8 (0.6); *P*<0.001) and total (13.8 (1.3) to 1.1 (0.4); *P*<0.001) acid exposure time. Impedance-pH monitoring demonstrated that LNF led to an impressive decrease in total number of reflux episodes below normal values (–92%; 89.6 (6.7) to 7.3 (0.9); *P*<0.001), with a similar reduction of acid (76.0 (5.5) to 1.6 (0.7); *P*<0.001) and weakly acidic reflux (13.6 (2.8) to 5.7 (0.7); *P*=0.001). LNF greatly decreased liquid (**–**90%; 53.4 (5.1) to 5.4 (0.8); *P*<0.001) and mixed reflux (**–**95%; 36.3 (3.8) to 1.9 (0.5); *P*<0.001), with no differences in control of acid and weakly acidic reflux. The decrease in gas reflux was far less pronounced, albeit statistically significant (**–**28%; 35.6 (3.9) to 25.7 (5.7); *P*=0.022) (for details see table 2).

Table 2 Total number of liquid-containing reflux episodes and number of liquid, mixed and gas reflux events per 24 hour

	Pre-op (*n*=31)	**Post-op (*n*=31)**	**Change (%)**	***P*-value**
Total reflux episodes	**89.6 (6.7)**	**7.3 (0.9)**	**–92**	**< 0.001**
- Acid reflux	76.0 (5.5)	1.6 (0.7)		< 0.001
- Weakly acidic reflux	13.6 (2.8)	5.7 (0.7)		0.001
Liquid reflux	**53.4 (5.1)**	**5.4 (0.8)**	**–90**	**< 0.001**
- Acid reflux	44.6 (4.4)	1.3 (0.6)		< 0.001
- Weakly acidic reflux	8.7 (1.9)	4.2 (0.6)		0.017
Mixed reflux	**36.3 (3.8)**	**1.9 (0.5)**	**–95**	**< 0.001**
- Acid reflux	31.3 (2.9)	0.4 (0.2)		< 0.001
- Weakly acidic reflux	4.9 (1.5)	1.5 (0.4)		0.002
Gas reflux	**35.6 (3.9)**	**25.7 (5.7)**	**–28**	**0.022**

The reduction in proximal (**–**93%; 34.0 (4.8) to 2.4 (0.4); *P*<0.001), mid-oesophageal (**–**91%; 49.9 (4.5) to 4.4 (0.7); *P*<0.001) and distal reflux was similar (**–**91%; 5.6 (0.9) to 0.5 (0.3); *P*<0.001), with no differences between acid and weakly acidic reflux. LNF greatly reduced the TORD (–92%; 1025 (88.8) cm to 78.9 (9.5) cm; *P*<0.001) and the proportional reduction was the same as the reduction in total reflux episodes (–92%). Surgery did not change mean proximal reflux extent (-4.4%; 11.3 (0.3) cm to 10.8 (0.6) cm; NS) (for details see table 3).

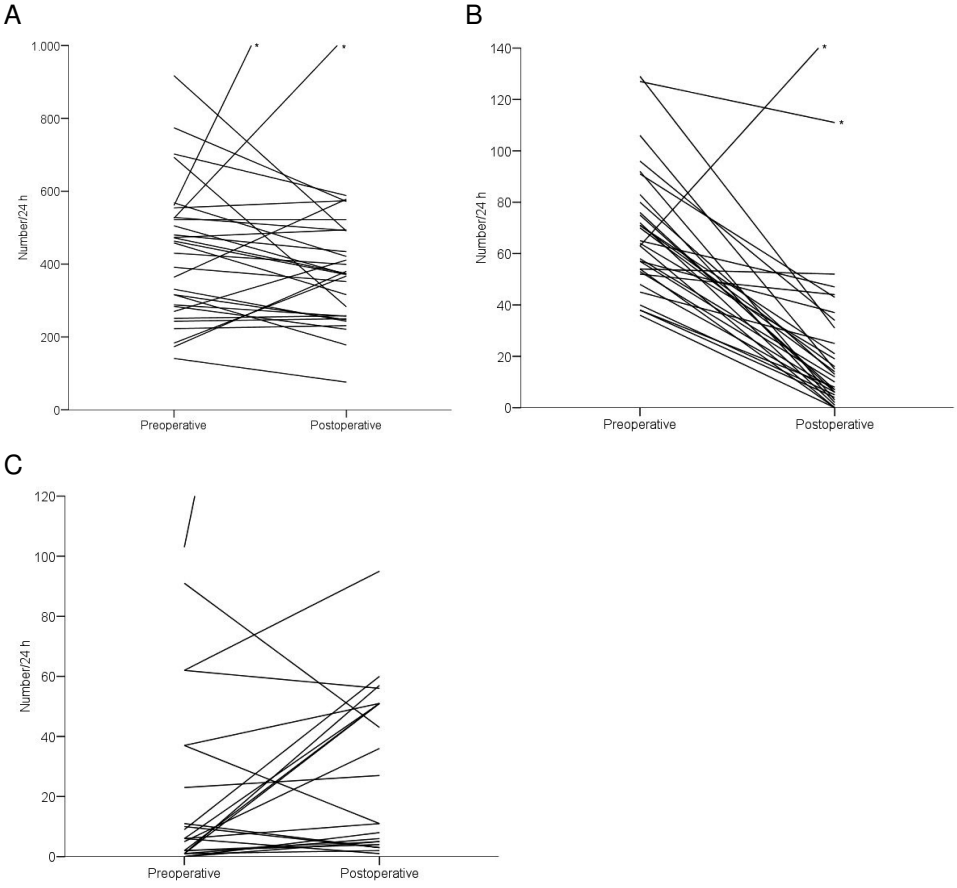
Table 3 Extent of liquid-containing reflux events per 24 hour, total oesophageal reflux distance (TORD) and mean proximal reflux extent

	Pre-op (*n*=31)	Post-op (*n*=31)	Change (%)	*P*-value
Proximal reflux	**34.0 (4.8)**	**2.4 (0.4)**	**–93**	**< 0.001**
- Acid reflux	29.2 (3.6)	0.4 (0.2)		< 0.001
- Weakly acidic reflux	4.8 (2.0)	2.0 (0.4)		0.034
Mid-oesophageal reflux	**49.9 (4.5)**	**4.4 (0.7)**	**–91**	**< 0.001**
- Acid reflux	42.5 (4.0)	0.9 (0.4)		< 0.001
- Weakly acidic reflux	7.5 (1.3)	3.5 (0.5)		0.004
Distal reflux	**5.6 (0.9)**	**0.5 (0.3)**	**–91**	**< 0.001**
- Acid reflux	4.3 (0.7)	0.3 (0.2)		< 0.001
- Weakly acidic reflux	1.3 (0.4)	0.2 (0.1)		0.003
TORD (cm)	**1025 (89)**	**78.9 (9.5)**	**–92**	**< 0.001**
Mean proximal reflux extent (cm)	**11.3 (0.3)**	**10.8 (0.6)**	**–4.4**	**0.281**

Belching

There were two patients who developed excessive air swallowing and gastric belching after surgery, these patients have been marked in figures 1a and 1b. The number of air swallows was higher than the reference value and was not affected by the operation (figure 1a: 432 (33) to 430 (48); NS). GBs were present in all patients before surgery and were completely abolished in three patients after surgery. Before surgery the number of GBs was higher than the normal value and decreased markedly below the reference value after surgery (figure 1b: –65%; 68.5 (4.3) to 23.9 (5.8); $P<0.001$). Supragastric belching was patient-dependent: 23 patients had SGBs both before and after LNF (SGB+), whereas 8 patients did not exhibit any SGBs, neither before nor after LNF (SGB–). Posthoc analysis of the patients with and without SGBs did not reveal any differences in demographics, hiatal hernia size, oesophagitis grade, manometry parameters, air swallows and reflux episodes. The only difference between patients with SGBs and without SGBs was a lower number of GBs (63.5 (4.5) *versus* 82.9 (8.9); $P=0.043$) and gas reflux (29.6 (3.9) *versus* (52.9 (7.3); $P=0.010$) before LNF in SGB+ patients, compared to SGB– patients. In SGB+ patients, SGBs were well above normal values before and after surgery. Preoperatively, the majority of the SGBs was not reflux-associated.

Figure 1 Number of air swallows (A; *n*=31), gastric belches (B; *n*=31) and supragastric belches not associated with reflux (C; *n*=24)



* The two patients who developed excessive air swallowing and gastric belching after surgery

The number of SGBs not associated with reflux doubled after fundoplication (figure 1c: +121%; 20.8 (6.3) to 46.0 (18); *P*=0.036). Reflux-associated SGBs were virtually abolished by LNF: both SGBs immediately preceding reflux episodes (–96%; 5.0 (1.4) to 0.2 (0.1); *P*=0.001) and SGBs during reflux episodes (–98%; 9.0 (2.3) to 0.2 (0.2); *P*<0.001) were eliminated almost completely by LNF. Details on belching are given in table 4.

Table 4 Air swallows, gastric belches and supragastric belches (SGBs) per 24 hour

	Pre-op	Post-op	Change (%)	*P*-value
Air swallows (*n*=31)	**432 (33)**	**430 (48)**	**–0.6**	**0.185**
Gastric belches (*n*=31)	**68.5 (4.3)**	**23.9 (5.8)**	**–65**	**< 0.001**
SGBs not associated with reflux (*n*=24)	**20.8 (6.3)**	**46.0 (18)**	**+121**	**0.036**
SGBs associated with reflux (*n*=24)				
- SGBs preceding reflux episode	5.0 (1.4)	0.2 (0.1)	–96	0.001
- SGBs during reflux episode	9.0 (2.3)	0.2 (0.2)	–98	< 0.001

Symptomatic outcome

LNF reduced reflux symptoms (GERD-QoL: 18.6 (2.7) to 1.6 (0.7); *P*=0.015) and dysphagia (34.4 (2.1) to 22.4 (1.2); *P*=0.018). QoL increased after LNF according to the VAS-score (50.2 (5.2) to 71.5 (4.0); *P*=0.051) and SF-36 score (54.4 (5.6) to 72.1 (4.8); *P*=0.021). Details on symptomatic outcome are given in table 5. There were 15 patients who reported persisting GORD symptoms during postoperative impedance-pH monitoring, whereas 16 patients were asymptomatic. The 15 patients reported 86 symptoms of which only two were related to acid reflux and one was related to weakly acidic reflux. None of the patients had a positive SI for acid and weakly acidic reflux after LNF. Of the 83 symptoms that were not reflux-related, 13 belch symptoms and 2 heartburn symptoms were related to GBs. Of the 83 symptoms, another 20 belching symptoms and 4 heartburn symptoms were related to SGBs. As a result, 3 out of 15 patients had a positive SI for belch symptoms and GBs and another 2 out of 15 patients had a positive SI for belch symptoms and SGBs after LNF. Only one of those five patients reported belching symptoms before surgery. The two patients who developed excessive air swallowing and gastric belching after surgery (marked in figure 1a and 1b), both had a positive symptom index for belching symptoms and GBs. Both patients developed belching symptoms and hyperflatulence and one of the two also had gas bloating symptoms after surgery.

Table 5 Reflux symptoms (GERD-HRQoL), dysphagia (QLQ-OES 18) and quality of life (Short-Form 36 and VAS score)

	Pre-op	3 months	6 months	12 months
Reflux symptoms				
- GERD-HRQoL	18.6 (2.7)	4.3 (1.6) *	2.4 (1.0) *	1.6 (0.7) *
Dysphagia				
- QLQ-OES18	34.4 (2.1)	29.2 (1.7) *	27.3 (1.7) *	24.4 (1.2) *
Quality of life				
- VAS score	50.2 (5.2)	52.2 (4.3)	54.6 (5.1)	71.5 (4.0) †
- Short-Form 36	54.4 (5.6)	64.3 (4.3)	70.1 (5.2) *	72.1 (4.8) *

* $P < 0.050$ versus pre-op, † $P = 0.051$ versus pre-op

Discussion

Laparoscopic Nissen Fundoplication (LNF) is the most frequently performed operation for GORD.[1] However, recent meta-analyses have demonstrated that a substantial number of patients report gas-related symptoms and persistent refractory reflux symptoms after this procedure.[4,9,10] Inability to belch has been postulated to cause the gas-related symptoms, but the impact of fundoplication on belching has only been evaluated indirectly.[17,20,23-25] Weakly acidic reflux has been alleged to be the main cause of persistent reflux complaints. Until now, four studies have evaluated the effect of fundoplication on acid and weakly acidic reflux. The results of these studies are contradictory, as two studies[7,8] report that the operation mainly reduces acid reflux and that the persistence of weakly acidic reflux causes postoperative reflux symptoms, whereas the other two studies[5,6] demonstrate a similar reduction in acid and weakly acidic reflux episodes.

The four previous studies have distinct limitations. The first study did not evaluate the effect of fundoplication on acid and weakly acidic reflux, as preoperative impedance-pH monitoring was not performed (n=36).[8] The two subsequent studies had limited sample sizes (n=14 and n=15)[5,6] and the fourth study did not analyse reflux events manually (n=38).[7] Since automated analysis of impedance signals is not yet sufficiently reliable, manual evaluation of oesophageal impedance tracings is the gold standard to diagnose GORD.[44] To resolve the controversy regarding control of acid and weakly acidic reflux, the current study combined pre- and postoperative impedance recordings, manual analysis and an adequate sample size.

The current study demonstrates that fundoplication similarly reduces acid and weakly acidic reflux and therefore rejects the hypothesis that persisting reflux symptoms are mainly caused by weakly acidic reflux. In addition, the current results show that refractory GORD symptoms are neither caused by acid nor by weakly acidic reflux. Belching seems to be a more important cause of persistent complaints, as one-third of the symptomatic patients have a positive relationship between postfundoplication symptoms and GBs or SGBs.

The previous studies are also contradictory regarding the effect of fundoplication on gas- and liquid-containing reflux. One study found that fundoplication selectively reduces reflux episodes as the reduction in liquid-containing reflux episodes was larger than the reduction in gas episodes.[5] However, the two other studies that evaluated gas reflux did not support this observation.[6,8] Our findings support the results of the first study as the reduction of liquid-containing reflux was three times larger than the reduction of pure gas reflux. This finding is in line with a study that demonstrated that gas passes the oesophagogastric junction more easily than liquids.[45]

Not every reflux episode is perceived as a symptom by the patient and the reduction of the number of reflux episodes is not the only factor that determines the effectiveness of antireflux surgery: the proximal extent of a reflux is important as well.[46] Only one study has evaluated the effect of fundoplication on proximal and distal reflux.[5] The current report combined the quantity and extent of the reflux episodes by calculating the TORD. The reduction in TORD and the reduction in total reflux episodes was similar, indicating that the effect of surgery was not selective for proximal or distal reflux. This was confirmed by the fact that the reductions in proximal, mid-oesophageal and distal reflux were comparable as well, with a similar mean proximal reflux extent before and after surgery. The reduction in reflux episodes lead to the elimination SGBs associated with reflux after surgery. Both SGBs that elicit reflux (SGBs immediately preceding reflux episodes) and SGBs in response to unpleasant oesophageal sensations (SGBs during reflux episodes) were abolished.

The four studies that evaluated the effect of fundoplication using impedance monitoring did not evaluate the effect of fundoplication on belching.[5-8] Previous studies that evaluated belching after fundoplication were methodologically limited by the fact that belches were recorded indirectly, using an experimental method to quantify belched volumes[20] or manometric common cavities.[17,23-25] Four of these studies[20,23-25] evaluated post-fundoplication patients and only one study[17] compared belching before and after surgery. As a result, the current report is the first study to directly evaluate the impact of fundoplication on belching. In addition, previous studies provoked belching by gas insufflation and recorded belches for

less than an hour.[17,20,23-25] Rapid infusion of a large volume of air (750-1200 ml) into the stomach does not resemble normal physiology in which swallows transport small volumes of air to the stomach. In contrast, the current study evaluated the effect on belching for 24 hours in a physiological setting, without gastric distention. It has long remained unclear why patients who had undergone fundoplication reported the ability to belch, while TLOSRs and common cavities were found to be absent in these patients.[17,23] The absent correlation between subjective and objective belching was not understood either.[17,20,23,25] The first part of the hypothesis that has been formulated to explain this discrepancy, has been confirmed by the current results, by demonstrating that fundoplication alters the belching pattern from GBs to SGBs.[23] Our results demonstrate that patients with SGBs have fewer GBs before surgery, compared to patients without SGBs. On the intra-patient level, the reduction in GBs by LNF is accompanied by an increase in SGBs after surgery. Since GBs allow air to be vented from the stomach whereas SGBs do not and fundoplication reduces gastric belching and does not alter the number of air swallows, gas bloating and flatulence are increased after fundoplication. It can be hypothesised that the gas bloating induced by a decrease in GBs elicits postfundoplication patients to actively increase the number of SGBs in a futile attempt to vent gas. This behaviour can be explained by the fact that patients associate all belches with relief of gas bloating, as they cannot discriminate GBs (air venting from stomach) from SGBs (no air venting from stomach). This hypothesis needs to be confirmed by a large study that focuses on impedance patterns and gastric air volumes postoperatively and compares symptomatic and asymptomatic patients.

TLOSRs are the major mechanism permitting the venting of air from the stomach and fundoplication reduces of the number of TLOSRs triggered by the proximal stomach.[5] It has previously been demonstrated that the TLOSR rate is higher after partial fundoplication compared to total fundoplication.[47] A study on manometric common cavities demonstrated that the reduction of GBs is less after Toupet (posterior partial) fundoplication, compared to Nissen (posterior total) fundoplication.[24] A recent meta-analysis has demonstrated that reflux control is similar after Toupet and Nissen fundoplication.[4] Toupet fundoplication is likely to be associated with a smaller decrease in GBs and less severe gas-related symptoms after surgery. An impedance study that directly compares the effect of Toupet and Nissen fundoplication on GBs has yet to confirm this potential benefit of partial fundoplication.

The inter-observer agreement between experienced reviewers for the evaluation of total reflux episodes, weakly acidic reflux and proximal reflux extent are k 0.80, k 0.70 and k 0.76 respectively.[48,49] In the present study and a similar study[5] it was

sometimes difficult to interpret impedance tracings, in particular postoperatively. In 70% of the patients the second reviewer was consulted, in the majority of the cases (50%) more than once in the same patient. It was sometimes particularly difficult to distinguish weakly acidic reflux from small elevation of the sphincter complex without reflux, which may have contributed to the high rate of weakly acidic reflux in some of the previous impedances studies post-fundoplication. The inter-observer agreement for impedance-pH monitoring post-surgery and for differentiating gastric and supragastric belching has not been reported this far. The identification of GBs and SGBs was not particularly difficult, due to the marked rise in impedance (≥1000Ω) we used as cut off point and the high sample frequency.[28] The sample frequency is of particular importance to distinguish events with high propagation velocity, such as GBs and SGBs. A minimum sample frequency of 50 Hz enables to distinguish aboral movement of gas from oral movement in 100% of the belches.[50]

In conclusion, LNF similarly controls acid and weakly acidic reflux, but gas reflux is reduced to lesser extent. Persistent reflux symptoms are neither caused by acid nor by weakly acidic reflux. However, one-third of the symptomatic patients have a positive relationship between postfundoplication symptoms and GBs or SGBs. LNF alters the belching pattern by reducing GBs (air venting from stomach) and increasing SGBs (no air venting from stomach). This explains the increase in belching experienced by some patients after LNF, despite the reduction in gastric belching. It can be hypothesised that the reduction in GBs after LNF incites patients to increase SGBs in a futile attempt to vent air from the stomach to reduce postoperative bloating.

Acknowledgements

The authors thank J. Oors and J. van der Scheur for performing the stationary oesophageal manometries and 24-h impedance-pH monitoring studies and H.G. Rijnhart-de Jong for maintaining the prospective database. A.J. Bredenoord is supported by a grant from the Netherlands Organisation for Scientific Research (NWO).

References

(1) Broeders JA, Rijnhart-de Jong HG, Draaisma WA et al. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. Ann Surg 2009; 250:698-706.

(2) Fuchs KH, Feussner H, Bonavina L et al. Current status and trends in laparoscopic antireflux surgery: results of a consensus meeting. The European Study Group for Antireflux Surgery (ESGARS). Endoscopy 1997; 29:298-308.

(3) Guidelines for surgical treatment of gastroesophageal reflux disease (GERD). Society of American Gastrointestinal Endoscopic Surgeons (SAGES). Surg Endosc 1998; 12:186-188.

(4) Broeders JA, Mauritz FA, Ahmed Ali U et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. Br J Surg 2010; 97:1318-1330.

(5) Bredenoord AJ, Draaisma WA, Weusten BL et al. Mechanisms of acid, weakly acidic and gas reflux after anti-reflux surgery. Gut 2008; 57:161-166.

(6) del Genio G, Tolone S, del Genio F et al. Total fundoplication controls acid and nonacid reflux: evaluation by pre- and postoperative 24-h pH-multichannel intraluminal impedance. Surg Endosc 2008; 22:2518-2523.

(7) Frazzoni M, Conigliaro R, Melotti G. Reflux parameters as modified by laparoscopic fundoplication in 40 patients with heartburn/regurgitation persisting despite PPI therapy. A study using impedance-pH monitoring. Dig Dis Sci in press 2010.

(8) Roman S, Poncet G, Serraj I et al. Characterization of reflux events after fundoplication using combined impedance-pH recording. Br J Surg 2007; 94:48-52.

(9) Catarci M, Gentileschi P, Papi C et al. Evidence-based appraisal of antireflux fundoplication. Ann Surg 2004; 239:325-337.

(10) Varin O, Velstra B, De SS et al. Total vs partial fundoplication in the treatment of gastroesophageal reflux disease: a meta-analysis. Arch Surg 2009; 144:273-278.

(11) Pouderoux P, Ergun GA, Lin S et al. Esophageal bolus transit imaged by ultrafast computerized tomography. Gastroenterology 1996; 110:1422-1428.

(12) Penagini R, Carmagnola S, Cantu P et al. Mechanoreceptors of the proximal stomach: Role in triggering transient lower esophageal sphincter relaxation. Gastroenterology 2004; 126:49-56.

(13) Scheffer RC, Akkermans LM, Bais JE et al. Elicitation of transient lower oesophageal sphincter relaxations in response to gastric distension and meal ingestion. Neurogastroenterol Motil 2002; 14:647-655.

(14) Kahrilas PJ, Shi G, Manka M et al. Increased frequency of transient lower esophageal sphincter relaxation induced by gastric distention in reflux patients with hiatal hernia. Gastroenterology 2000; 118:688-695.

(15) Martin CJ, Patrikios J, Dent J. Abolition of gas reflux and transient lower esophageal sphincter relaxation by vagal blockade in the dog. Gastroenterology 1986; 91:890-896.

(16) Camilleri M, Dubois D, Coulie B et al. Prevalence and socioeconomic impact of upper gastrointestinal disorders in the United States: results of the US Upper Gastrointestinal Study. Clin Gastroenterol Hepatol 2005; 3:543-552.

(17) Johnsson F, Holloway RH, Ireland AC et al. Effect of fundoplication on transient lower oesophageal sphincter relaxation and gas reflux. Br J Surg 1997; 84:686-689.

(18) Low DE, Mercer CD, James EC et al. Post Nissen syndrome. Surg Gynecol Obstet 1988; 167:1-5.

(19) McNally EF, Kelly JE, Ingelfinger FJ. Mechanism of belching: effects of gastric distension with air. Gastroenterology 1964; 46:254-259.

(20) Smith D, King NA, Waldron B et al. Study of belching ability in antireflux surgery patients and normal volunteers. Br J Surg 1991; 78:32-35.

(21) Woodward ER, Thomas HF, McAlhany JC. Comparison of crural repair and Nissen fundoplication in the treatment of esophageal hiatus hernia with peptic esophagitis. Ann Surg 1971; 173:782-792.

(22) Kamolz T, Bammer T, Granderath FA et al. Comorbidity of aerophagia in GERD patients: outcome of laparoscopic antireflux surgery. Scand J Gastroenterol 2002; 37:138-143.

(23) Tew S, Ackroyd R, Jamieson GG et al. Belching and bloating: facts and fantasy after antireflux surgery. Br J Surg 2000; 87:477-481.

(24) Rydberg L, Ruth M, Lundell L. Mechanism of action of antireflux procedures. Br J Surg 1999; 86:405-410.

(25) Straathof JW, Ringers J, Lamers CB et al. Provocation of transient lower esophageal sphincter relaxations by gastric distension with air. Am J Gastroenterol 2001; 96:2317-2323.

(26) Sifrim D, Silny J, Holloway RH et al. Patterns of gas and liquid reflux during transient lower oesophageal sphincter relaxation: a study using intraluminal electrical impedance. Gut 1999; 44:47-54.

(27) Fass J, Silny J, Braun J et al. Measuring esophageal motility with a new intraluminal impedance device. First clinical results in reflux patients. Scand J Gastroenterol 1994; 29:693-702.

(28) Bredenoord AJ, Weusten BL, Sifrim D et al. Aerophagia, gastric, and supragastric belching: a study using intraluminal electrical impedance monitoring. Gut 2004; 53:1561-1565.

(29) Hemmink GJ, Ten CL, Bredenoord AJ et al. Speech therapy in patients with excessive supragastric belching--a pilot study. Neurogastroenterol Motil 2010; 22:24-3.

(30) Hemmink GJ, Bredenoord AJ, Weusten BL et al. Supragastric belching in patients with reflux symptoms. Am J Gastroenterol 2009; 104:1992-1997.

(31) Bais JE, Bartelsman JF, Bonjer HJ et al. Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. Lancet 2000; 355:170-174.

(32) Draaisma WA, Ruurda JP, Scheffer RC et al. Randomized clinical trial of standard laparoscopic versus robot-assisted laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease. Br J Surg 2006; 93:1351-1359.

(33) Draaisma WA, Buskens E, Bais JE et al. Randomized clinical trial and follow-up study of cost-effectiveness of laparoscopic versus conventional Nissen fundoplication. Br J Surg 2006; 93:690-697.

(34) Broeders JA, Draaisma WA, Rijnhart-de Jong HG et al. The impact of surgeon experience on five-year outcome of laparoscopic Nissen fundoplication. Arch Surg in press 2010.

(35. Velanovich V, Vallance SR, Gusz JR et al. Quality of life scale for gastroesophageal reflux disease. J Am Coll Surg 1996; 183:217-224.

(36) Velanovich V, Karmy-Jones R. Measuring gastroesophageal reflux disease: relationship between the Health-Related Quality of Life score and physiologic parameters. Am Surg 1998; 64:649-653.

(37) Blazeby JM, Conroy T, Hammerlid E et al. Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with oesophageal cancer. Eur J Cancer 2003; 39:1384-1394.

(38) Aaronson NK, Muller M, Cohen PD et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998; 51:1055-1068.

(39) de Boer AG, van Lanschot JJ, Stalmeier PF et al. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? Qual Life Res 2004; 13:311-320.

(40) Lundell LR, Dent J, Bennett JR et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999; 45:172-180.

(41) Wiener GJ, Richter JE, Copper JB et al. The symptom index: a clinically important parameter of ambulatory 24-hour esophageal pH monitoring. Am J Gastroenterol 1988; 83:358-361.

(42) Zerbib F, des Varannes SB, Roman S et al. Normal values and day-to-day variability of 24-h ambulatory oesophageal impedance-pH monitoring in a Belgian-French cohort of healthy subjects. Aliment Pharmacol Ther 2005; 22:1011-1021.

(43) Bredenoord AJ, Weusten BL, Timmer R et al. Air swallowing, belching, and reflux in patients with gastroesophageal reflux disease. Am J Gastroenterol 2006; 101:1721-1726.

(44. Roman S, Bruley d, V, Pouderoux P et al. Ambulatory 24-h oesophageal impedance-pH recordings: reliability of automatic analysis for gastro-oesophageal reflux assessment. Neurogastroenterol Motil 2006; 18:978-986.

(45) Pandolfino JE, Shi G, Trueworthy B et al. Esophagogastric junction opening during relaxation distinguishes nonhernia reflux patients, hernia patients, and normal subjects. Gastroenterology 2003; 125:1018-1024.

(46) Bredenoord AJ, Weusten BL, Curvers WL et al. Determinants of perception of heartburn and regurgitation. Gut 2006; 55:313-318.

(47) Scheffer RC, Samsom M, Hebbard GS et al. Effects of partial (Belsey Mark IV) and complete (Nissen) fundoplication on proximal gastric function and esophagogastric junction dynamics. Am J Gastroenterol 2006; 101:479-487.

(48) Hemmink GJ, Aanen MC, Bredenoord AJ et al. Automatic analysis of 24-h oesophageal impedance signals for detection of gastro-oesophageal reflux: how far are we? Scand J Gastroenterol 2010; in press.

(49) Ravi K, DeVault KR, Murray JA et al. Inter-observer agreement for multichannel intraluminal impedance-pH testing. Dis Esophagus 2010.

(50) Bredenoord AJ, Weusten BL, Timmer R et al. Minimum sample frequency for multichannel intraluminal impedance measurement of the oesophagus. Neurogastroenterol Motil 2004; 16:713-719.

15

Reflux and belching after laparoscopic Toupet *versus* Nissen fundoplication

J.A.J.L. Broeders[1]
A.J. Bredenoord[2]
E.J. Hazebroek[1]
I.A.M.J. Broeders[3]
H.G. Gooszen[1]
A.J.P.M. Smout[2]

[1]Dep. of Surgery, University Medical Center Utrecht
[2]Dep. of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam
[3]Dep. of Surgery, Meander Medical Center, Amersfoort

Annals of Surgery; revision.

Abstract

Objective: To investigate differences in effects of laparoscopic Toupet fundoplication (LTF) and laparoscopic Nissen fundoplication (LNF) on reflux characteristics and belching.

Summary of background data: LNF greatly reduces the ability of the stomach to vent ingested air by gastric belching. This frequently leads to postoperative symptoms including inability to belch, gas bloating and flatulence. LTF allegedly provides less effective reflux control compared with LNF, but theoretically may allow for gastric belches (GBs) with a limitation of gas-related symptoms.

Methods: Endoscopy, stationary esophageal manometry and 24-hr impedance-pH monitoring off PPIs was performed before and 6 months after fundoplication for PPI-refractory GERD (n=14 LTF *vs* n=28 LNF). GBs were defined as gas components of pure gas and mixed reflux episodes reaching the proximal esophagus. Absolute reductions (Δ) were compared.

Results: Reflux symptoms and the 24-hour incidence of acid (Δ–77.6*vs*–76.7), weakly acidic (Δ–9.4*vs*–6.6), liquid (Δ–59.0*vs*–49.8) and mixed reflux episodes (Δ–28.0*vs*–33.5) were reduced to a similar extent after LTF and LNF, respectively. The reduction in proximal, mid-esophageal and distal reflux episodes were similar in both groups as well. Persistent symptoms were not related to acid or weakly acidic reflux. LTF had no significant impact on the number of gas reflux episodes (Δ–3.6;P=0.363), whereas LNF significantly reduced gas reflux episodes (Δ–17.0;P=0.002). After LTF, GBs (Δ–29.3*vs*–50.6;P=0.026) were significantly less reduced and the prevalence of gas bloating (7.1*vs*21.4%;P=0.242) and flatulence (7.1*vs*42.9%;P=0.018) was lower compared to LNF. Twenty-eight patients (67%) showed supragastric belches (SGBs) before and after surgery. The increase in SGBs without reflux (Δ+32.4*vs*+25.5) and the decrease in reflux-associated SGBs (Δ–12.1*vs*–14.0) were similar after LTF and LNF.

Conclusions: LTF and LNF alter the belching pattern by reducing GBs (air venting from stomach) and increasing SGBs (no air venting from stomach). However, gas reflux and GBs are reduced less after LTF than after LNF, resulting in more air venting from the stomach and less gas bloating and flatulence, while a similar degree of short-term reflux inhibition is obtained. These results support the use of LTF in the surgical treatment of gastroesophageal reflux disease.

Introduction

Laparoscopic fundoplication is the standard surgical treatment of gastroesophageal reflux disease (GERD).[1-3] A fundoplication is created by wrapping the fundus of the stomach anteriorly or posteriorly around the esophagus. A recent meta-analysis has demonstrated that laparoscopic posterior fundoplication has superior reflux control compared with laparoscopic anterior fundoplication and should be considered the surgical therapy of choice.[4] Recently published American guidelines for antireflux surgery recommend laparoscopic total posterior (Nissen) fundoplication and partial posterior (Toupet) fundoplication as surgical procedures for GERD.[5] Laparoscopic Nissen fundoplication (LNF) provides excellent 10-year reflux control,[1] but three meta-analyses have recently demonstrated that LNF is associated with a high rate of gas-related symptoms.[6-8] Fifteen percent of the patients develop inability to belch[6], 19 per cent suffer from gas bloating[7] and 59 per cent report increased flatulence after LNF.[8]

Gastric belching is a physiological mechanism that serves to vent ingested air from the stomach. It is commonly assumed that an inability to vent air from the stomach by gastric belching causes gas-related symptoms.[9-15] A previous study indeed demonstrated that patients with an objective reduction of gastric belches (GBs) after fundoplication, have higher symptom scores for inability to belch and gas bloating, compared with patients who not have an objective reduction of GBs.[16] Our group has recently demonstrated that after LNF the number of GBs is significantly reduced.[17] Laparoscopic Toupet fundoplication (LTF) has been hypothesized to reduce GBs to a lesser extent and may theoretically reduce gas-related symptoms compared with LNF. Until now, two studies have compared the effects of LTF and LNF on belching. The results of these studies are contradictory and belches in these studies were measured with manometry by evaluating the so-called common cavity phenomenon.[16,18] However, common cavities have been shown to be not very reliable for the detection of gastric belching.[16,19] Esophageal impedance monitoring has made it possible to detect the passage of air through the esophagus directly and is much more reliable for detection of GBs during a prolonged period of time.[20,21]

Several uncontrolled studies have reported less effective long-term reflux control after LTF, compared with LNF.[22-25] However, the effect of LTF on weakly acidic reflux and proximal reflux extent has not yet been studied. These two factors are important in the evaluation of the effectiveness of antireflux surgery, since weakly acidic reflux can elicit reflux symptoms that do not respond to treatment with acid-suppressing drugs.[26,27] In addition, weakly acidic reflux has been alleged to be the main cause of reflux complaints that persist after fundoplication.[28,29] The proximal

extent of the refluxate determines whether a reflux episode is perceived as a symptom by the patient.[26] Intraluminal impedance monitoring enables one to evaluate both acid and weakly acidic reflux, as well as proximal reflux extent.[30] Therefore, the current study used this technique to investigate differences in effects of LTF and LNF on reflux characteristics and belching.

Methods

Study design and data collection

From January 2008 till April 2010 we prospectively included consecutive patients that underwent impedance-pH monitoring and were on the waiting list for primary laparoscopic fundoplication for proton pump inhibitor-refractory GERD with pathological acid exposure. Preoperative data, clinical outcome and the results of objective investigations were prospectively entered into a computerized database by an independent data manager (HGR). Patients who underwent LTF were matched to a LNF control group[17] according to total esophageal acid exposure time on 24-h impedance-pH monitoring before surgery (ratio 1: 2).

Surgical procedures

All laparoscopic fundoplications were performed between January 2008 and April 2010 either at the University Medical Center Utrecht (EJH and IAMJB) or another large teaching hospital; Meander Medical Center (IAMJB). The first series of patients all underwent LNF and the surgical therapy of choice for GERD in our centers was changed after a meta-analysis demonstrated that LTF reduces dysphagia.[6] The two participating surgeons both contributed to both LTFs and LNFs and were well beyond the learning curve for both procedures at the start of the study, with 150 LTFs plus 100 LNFs (EJH) and 40 LTFs plus 300 LNFs (IAMJB), respectively.[31] In all patients a standardized fundoplication was performed that aimed to create a loose valve to minimize postfundoplication symptoms. After full mobilization of the distal esophagus, surgeons verified that the gastroesophageal junction was placed in the abdomen without tension. The short gastric vessels were ligated and divided and it was made sure that the fundoplication was tension-free as well. A floppy fundoplication of 2.5-3.0 cm was constructed after posterior crural repair. LTF was defined as a posterior fundoplication with a 270 degree circumference[32] and LNF was defined as a posterior fundoplication with a circumference of 360 degrees.[33-35] The margins of the LTF wrap were fixed to the esophagus and to the crural arch anterosuperiorly and the wrap was fixed to the crural repair with one or two posterior sutures. One of the sutures of the LNF wrap incorporated the esophageal wall and the posterior

aspect of the wrap was fixed to the crural repair in an identical fashion to the LTF wrap.

Clinical assessment

Patients were asked by telephone to complete validated questionnaires by mail, preoperatively and 6 months postoperatively. The GERD Health-Related Quality of Life score (GERD-HRQoL) that has been validated[36] and compared with physiologic parameters,[37] was used to evaluate reflux symptoms. Changes in dysphagia were detected with the validated European Organisation for Research and Treatment of Cancer QLQ-OES 18 questionnaire.[38] Health-related Quality of Life (QoL) was assessed using the validated Short-Form 36 (SF-36)[39]. In addition, patients were asked to indicate the presence of inability to belch, gas bloating and increased flatulence in comparison with their preoperative state on a binary scale (absent/present).

Upper GI endoscopy

Hiatal hernia size and esophagitis according to the Los Angeles classification[40] were determined endoscopically at the department of Gastroenterology of the University Medical Center Utrecht.

Stationary esophageal manometry

Manometry was performed at the Gastrointestinal Research Unit of the University Medical Center Utrecht, after suspending medication that potentially affects gastrointestinal motility 7 days in advance. A multiple-lumen water-perfused catheter with an incorporated sleeve sensor (Dentsleeve International Ltd, Mississauga, Canada) and a low-compliance perfusion system was used. The catheter was slowly withdrawn to determine the proximal border of the lower esophageal sphincter (LES) after transnasal introduction. Next, the sleeve sensor was positioned at the level of the LES and intraluminal esophageal pressures were recorded at 5, 10, 15, 20 and 25 cm above the proximal margin. Subsequently, the manometric response to ten standardized wet swallows (5-ml water bolus) was studied. The gastric baseline pressure (registered 2 cm below the distal margin of the sleeve sensor) served as the zero reference point.

Ambulatory 24-h combined esophageal impedance-pH monitoring

Ambulatory 24-h esophageal impedance-pH testing was performed at the Gastrointestinal Research Unit of the University Medical Center Utrecht. After cessation of at least 7 days of all medication that could affect gastrointestinal motility and secretion, a combined impedance-pH catheter (VersaFlex, Alpine

Biomed, Fountain Valley, CA, USA) was introduced transnasally. The catheter had eight ring electrodes for recording of impedance signals and a single antimony pH electrode. The catheter was positioned with the impedance recording segments at 2–4, 4–6, 6–8, 8–10, 14–16 and 16–18 cm and the pH electrode at 5 cm and above the manometrically determined upper margin of the LES. A digital data logger (Medical Measurements Systems, Enschede, The Netherlands), with a sampling frequency of 50 Hz recorded the tracings.[41] Patients were asked to press a button on the digital data logger at the beginning of each symptom episode and to register body position, GERD symptoms, meals and beverages in a diary. The symptom index (SI) was calculated separately for all reflux events, GBs and supra gastric belches (SGBs), if symptoms were recorded during the measurement. A SI of at least 50 per cent was regarded to be positive.[42]

Data analysis

The classification of reflux characteristics, gastric and supragastric belches used was identical to the classification described in two of our studies that compared these parameters before and after LNF.[17,43] The 24-h impedance-pH tracings were manually analyzed by a single observer (JAJLB) but facilitated by a dedicated software program (MMS, Enschede, The Netherlands). Another expert observer was consulted in case of uncertainty (AJB). In order to minimize observer bias, both observers were blinded for patient characteristics and pre- or postoperative status. Criteria for the classification of air-containing swallows (air swallows), gas, liquid, mixed, acid and weakly acidic reflux episodes have been published earlier.[43] Normal values for the number of total, acid and weakly acidic reflux episodes were 75, 50 and 33 per 24-h respectively.[44] For each individual reflux episode the proximal extent of the refluxate in centimeters above the LES was determined. The extent of the liquid component of liquid-containing reflux episodes (pure liquid and mixed reflux) determined classification as proximal (≥15cm above LES), mid-esophageal (5-15cm above LES) or distal reflux (≤5 cm above LES).[17] The total esophageal reflux distance (TERD) and mean proximal extent were calculated for liquid-containing reflux episodes. The TERD was defined as the sum of the proximal extent above the LES of all individual reflux episodes in centimetres.[17]

Gas components of pure gas and mixed liquid-gas reflux episodes that reached the most proximal channel were regarded as GBs.[45] The criteria described by Bredenoord et al were used to identify SGBs.[46] SGBs were defined as rapid increases in impedance (≥1000Ω) moving in an aboral direction, followed by a return to baseline moving from distal to proximal. This indicated a pattern that reflects expulsion of air after rapid esophageal air ingestion. A SGB was considered to be related to reflux when it occurred immediately prior (<1s) to the

onset of the reflux episode or when occurring during a reflux episode, with onset within 10 seconds after the start of the reflux episode.[47] Periods of meal consumption were disregarded and the total number of reflux episodes, air swallows and belches were normalized to a 24-h period.

Statistical analysis

Continuous variables were expressed as mean ± standard error of the mean (SEM) unless stated otherwise. Effects of surgery on continuous variables were expressed as absolute differences between pre- and postoperative values (Δ). Comparison of absolute differences and preoperative values between the LTF and the LNF group were performed using the Mann-Whitney *U*-test. The Wilcoxon signed rank test was used to determine significant effects of surgery in either the LTF or the LNF group. The χ^2 test was used to compare groups for nominal variables. $P < 0.05$ was considered statistically significant. The statistical analysis was performed using SPSS version 15.0 (SPSS Inc. Chicago, IL).

Results

Subjects

Fourteen patients that underwent LTF were compared to 28 LNF controls who were matched based on total esophageal acid exposure (16.0 (2.3) vs. 14.3 (1.3)%; $P = 0.626$). There were no patients with prominent laryngopharyngeal reflux. Baseline characteristics were comparable for both groups (table 1).

Table 1 Baseline characteristics of patients according to treatment group after LTF and LNF

	LTF	**LNF**
Patients (*n*)	14	28
Age [range]	47.4 [23-64]	48.5 [26-67]
Male / female sex	7 / 7	11 / 17
Body mass index (kg/m^2) *	29.8 (1.2)	28.3 (1.2)
Hiatal hernia (cm) *	2.1 (0.7)	2.3 (0.4)
Total esophageal acid exposure (%) *	16.0 (2.3)	14.3 (1.3)

* values are given as mean (SEM)

Upper GI endoscopy and stationary esophageal manometry

In both groups, half of the patients had esophagitis and the other half had non-erosive GERD before surgery. The prevalence of esophagitis was 2/12 [17%] after LTF and 5/27 [19%] after LNF. All patients completed pre- and postoperative manometry. LTF and LNF increased both LES resting pressure and distal contraction amplitude to a similar extent, but did not alter distal contraction amplitude (table 2).

Control of acid and weakly acidic reflux

All patients completed pre- and postoperative esophageal impedance-pH testing. Total acid exposure time was reduced after LTF and LNF to a similar extent (table 2: Δ−13.5 (2.0) vs. −13.0 (1.3)). The reduction in total number of reflux episodes was similar after LTF and LNF (Δ−87.0 (8.5) vs. −83.4 (6.3)), with a similar reduction in acid (Δ−77.6 (6.5) vs. −76.7 (5.7)) and weakly acidic reflux episodes (Δ−9.4 (4.7) vs. −6.6 (1.9)). LTF and LNF greatly decreased liquid (Δ−59.0 (9.2) vs. −49.8 (5.3)) and mixed reflux episodes (Δ−28.0 (5.9) vs. −33.5 (2.9)), with no differences in control of acid and weakly acidic reflux episodes (table 3). LTF had no significant impact on number of gas reflux episodes (Δ−3.6; P = 0.363), whereas LNF significantly reduced the number of gas reflux episodes (Δ−17.0; P = 0.002). Details on gas reflux events are given in figure 1.

The reduction in proximal reflux was significantly higher after LTF (Δ−44.1 (6.5) vs. −29.9; P = 0.038). This was probably due to the significantly higher number of proximal reflux episodes before LTF, compared with the LNF group (49.4 (6.5) vs. 32.3 (3.7); P = 0.017). The reduction in mid-esophageal (Δ−38.2 (5.1) vs. −48.0 (4.6)) and distal reflux (Δ−4.6 (1.9) vs. −5.4 (1.0)) were similar after LTF and LNF. LTF and LNF reduced the TERD to a similar extent (Δ−1094 (118) cm vs. −940 (73) cm) and did not change mean proximal reflux extent (Δ−2.1 (0.7) cm vs. −0.1 (0.6) cm). Details on reflux extent are given in table 4.

Belching

Fundoplication did not affect the numbers of air swallows, with no differences between LTF and LNF (Δ−4.8 (33) vs. −51.7 (28)). The number of GBs before surgery was similar in the LTF group and the LNF group (57.8 (9.5) vs. 67.8 (4.0); P = 0.140). GBs were present in all patients before surgery and were completely abolished in two patients in the LNF group. Both LTF and LNF reduced the number of GBs.

Table 2 Mean LES pressure, LES relaxation pressure, distal contraction amplitude and total esophageal acid exposure time after LTF and LNF

	LTF			LNF		
	Pre-op (*n*=14)	Post-op (*n*=14)	Δ	Pre-op (*n*=28)	Post-op (*n*=28)	Δ
Manometry						
- LES resting pressure (kPa)	1.5 (0.4)	2.0 (0.2)	+0.5 (0.3)	1.2 (0.2)	2.0 (0.2)	+0.8 (0.2)
- LES relaxation nadir pressure (kPa)	0.1 (0.1)	0.6 (0.2)	+0.4 (0.2)	0.2 (0.1)	0.9 (0.1)	+0.7 (0.1)
- Mean distal contraction amplitude (kPa)	7.7 (0.8)	8.4 (0.6)	+0.8 (0.6)	9.1 (0.5)	10.5 (1.0)	+1.4 (0.8)
24-hr pH monitoring						
- Total acid exposure (%)	16.0 (2.3)	2.5 (1.0)	–13.5 (2.0)	14.3 (1.3)	1.2 (0.5)	–13.0 (1.3)

Table 3 Total number of liquid-containing reflux episodes and number of liquid and mixed reflux events per 24 hour after LTF and LNF

	LTF			LNF		
	Pre-op (*n*=14)	Post-op (*n*=14)	Δ	Pre-op (*n*=28)	Post-op (*n*=28)	Δ
Total reflux episodes	**105.5 (8.7)**	**18.5 (6.1)**	**–87.0 (8.5)**	**90.7 (6.3)**	**7.4 (1.0)**	**–83.4 (6.3)**
- Acid reflux	89.6 (7.4)	12.1 (5.7)	–77.6 (6.5)	78.5 (5.6)	1.8 (0.8)	–76.7 (5.7)
- Weakly acidic reflux	15.9 (4.7)	6.4 (1.4)	–9.4 (4.7)	12.3 (2.2)	5.6 (0.7)	–6.6 (1.9)
Liquid reflux	**72.9 (10)**	**13.9 (3.6)**	**–59.0 (9.2)**	**55.4 (5.4)**	**5.6 (0.8)**	**–49.8 (5.3)**
- Acid reflux	61.4 (8.4)	8.7 (3.4)		47.0 (4.7)	1.4 (0.7)	
- Weakly acidic reflux	11.6 (3.3)	5.2 (1.2)		8.4 (1.9)	4.3 (0.6)	
Mixed reflux	**32.6 (4.5)**	**4.6 (2.9)**	**–28.0 (5.9)**	**35.3 (2.9)**	**1.8 (0.5)**	**–33.5 (2.9)**
- Acid reflux	28.3 (4.3)	3.4 (2.5)		31.5 (2.6)	0.4 (0.2)	
- Weakly acidic reflux	4.3 (2.0)	1.2 (0.5)		3.8 (0.6)	1.4 (0.4)	

However, the number of GBs was significantly less reduced after LTF, compared with LNF (Δ−29.3 vs. −50.6; *P* = 0.026). Details on GBs are given in figure 2. Supragastric belching only occurred in specific patients; it was observed in 7 patients in the LTF group and in 21 patients in the LNF group both before and after surgery (SGB+), whereas 7 patients in each group did not exhibit any SGBs, neither before nor after fundoplication (SGB−). The number of SGBs not associated with reflux increased to a similar extent after LTF and LNF (Δ+32.4 (7.1) vs. +25.5 (16)). The reduction in reflux-associated SGBs, both SGBs immediately preceding reflux episodes and SGBs during reflux episodes, was similar after LTF and LNF (Δ−12.1 (7.8) vs. −14.0 (3.6)). Details on air swallows and SGBs are given in table 5.

Symptomatic outcome

The prevalence of inability to belch (0/14 [0%] vs. 2/28 [7.1%]; *P* = 0.306), gas bloating (1/14 [7.1%] vs. 6/28 [21.4%]; *P* = 0.242) and increased flatulence (1/14 [7.1%] vs. 12/28 [42.9%]; *P* = 0.018) was lower after LTF than after LNF. The reduction in reflux symptoms (GERD-QoL: from 20.6 (2.3) to 4.2 (1.7) vs. from 17.6 (2.4) to 3.6 (0.9)) and dysphagia (QLQ-OES 18: from 35.0 (3.9) to 26.0 (2.3) vs. from 33.8 (1.4) to 27.6 (1.4)) and the increase in QoL (SF-36: from 58.1 (7.3) to 69.7 (6.6) vs. from 54.6 (5.1) to 67.3 (4.8)) were similar after LTF and LNF.

None of the 23 patients with symptoms during postoperative impedance-pH monitoring had a positive SI for acid and/or weakly acidic reflux after surgery. Only 5 out of 127 symptoms were preceded by acid reflux or weakly acidic reflux. One patient in the LNF group had a positive SI for belching symptoms and GBs and two patients in each group had a positive SI for belching symptoms and SGBs.

Table 4 Extent of liquid-containing reflux events per 24 hour, total esophageal **r**eflux distance (TERD) and mean proximal reflux extent after LTF and LNF

	LTF			LNF		
	Pre-op (*n*=14)	Post-op (*n*=14)	Δ	Pre-op (*n*=28)	Post-op (*n*=28)	Δ
Proximal reflux	49.4 (6.5) *	5.2 (2.0)	–44.1 (6.5) ‡	32.3 (3.7)	2.3 (0.4)	–29.9 (3.6)
Mid-esophageal reflux	48.9 (4.4)	10.6 (3.7)	–38.2 (5.1)	52.5 (4.7)	4.5 (0.7)	–48.0 (4.6)
Distal reflux	7.3 (2.1)	2.6 (0.7)	–4.6 (1.9)	6.0 (1.0)	0.5 (0.3)	–5.4 (1.0)
TERD (cm)	1283 (119)	190 (66)	–1094 (118)	1019 (74)	78.8 (9.7)	–940 (73)
Mean proximal reflux extent (cm)	12.1 (0.4)	10.0 (0.6)	–2.1 (0.7)	11.3 (0.3)	11.2 (0.6)	–0.1 (0.6)

* $P = 0.017$ versus LNF group, ‡ $P = 0.038$ versus LNF group

Table 5 Air swallows and supragastric belches (SGBs) per 24 hour after LTF and LNF

	LTF			LNF		
	Pre-op	Post-op	Δ	Pre-op	Post-op	Δ
Air swallows (LTF *n*=14, LNF *n*=28)	**418 (80)**	**414 (84)**	**−4.8 (33)**	**415 (35)**	**363 (24)**	**−51.7 (28)**
SGBs without reflux (LTF *n*=7, LNF *n*=21)	**11.3 (4.1)**	**43.7 (9.2)**	**+32.4 (7.1)**	**19.8 (6.6)**	**45.3 (20)**	**+25.5 (16)**
SGBs with reflux	**21.9 (6.3)**	**9.7 (4.2)**	**−12.1 (7.8)**	**14.4 (3.6)**	**0.5 (0.2)**	**−14.0 (3.6)**
- SGBs before reflux	7.6 (3.6)	7.3 (3.8)		4.9 (1.5)	0.2 (0.1)	
- SGBs during reflux (LTF *n*=7, LNF *n*=21)	14.3 (3.9)	2.4 (1.5)		9.6 (2.4)	0.2 (0.2)	

Figure 1 Mean number of gas reflux events per 24 hour after LTF and LNF

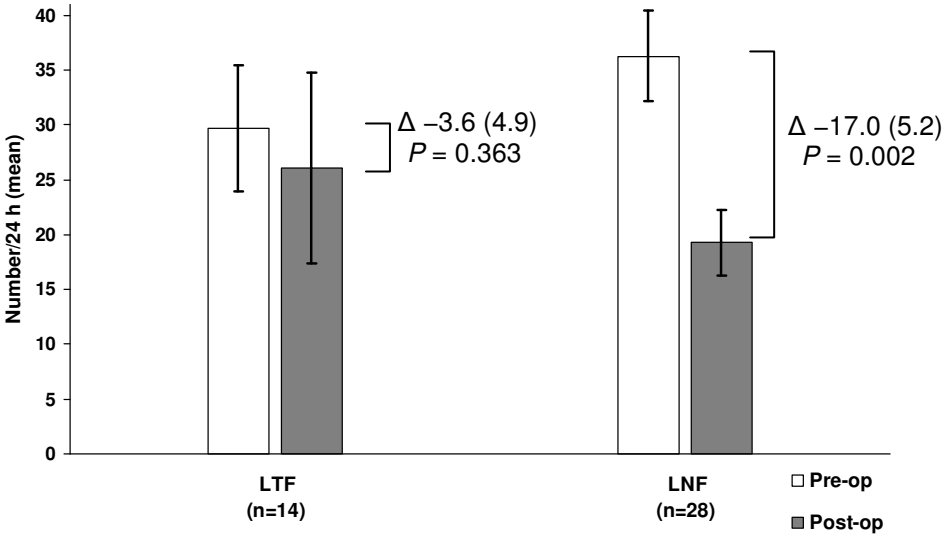
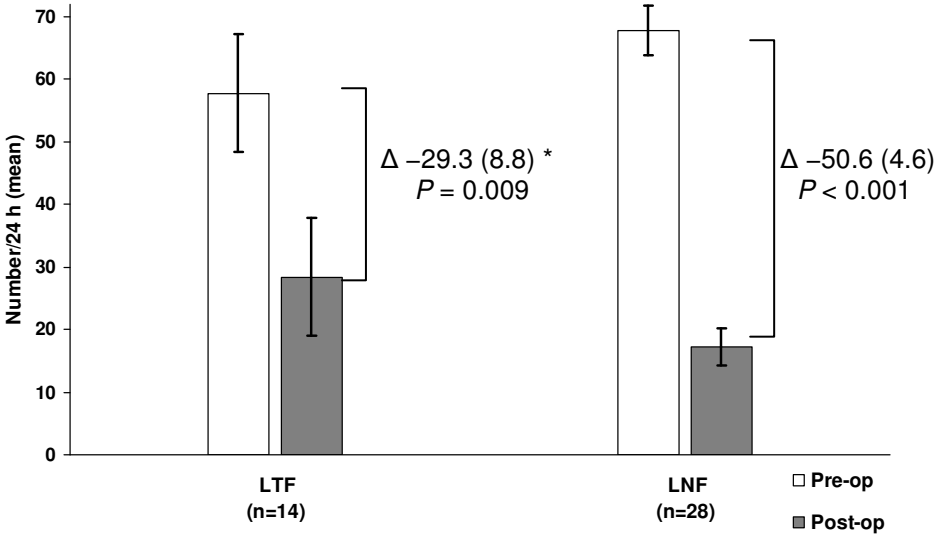


Figure 2 Mean number of gastric belches per 24 hour after LTF and LNF



* $P = 0.026$ versus Δ LNF group

Discussion

This study demonstrates that LTF and LNF reduce reflux to a similar extent in the short-term, but that there are distinct differences in gastric belching after both procedures. In line with previous studies in LNF patients,[17,43] the current results show that fundoplication has no impact on the number of air swallows. The present study demonstrates that both LTF and LNF alter the belching pattern by reducing GBs and increasing SGBs. The first serve to vent ingested air from the stomach, whereas the latter are esophageal belches that do not allow air ventilation from the stomach.[46] Consequently, fundoplication reduces air venting, which causes gas-related symptoms. However, gas reflux and GBs are reduced less after LTF, resulting in more air venting and less gas bloating and flatulence compared with LNF.

The results of the two studies that have previously evaluated differences in GBs between LTF and LNF are contradictory.[16,18] One study reported a lower incidence of GBs after LNF than after LTF,[18] whereas the other study found similar numbers of GBs after both procedures.[16] Both studies did not evaluate the reduction in belches after fundoplication, provoked belching by gas insufflation and recorded belches for less than 30 minutes.[16,18] Rapid infusion of a large volume of air (750 ml) into the stomach does not resemble normal physiology in which swallows transport small volumes of air to the stomach. In contrast, the current study evaluated the effect on belching for 24 hours in a physiological setting, without gastric distention. In addition, the studies are methodologically limited by the fact that belches were recorded indirectly, using manometric common cavities.[16,18] This is a distinct limitation since common cavities are absent in more than half of the gas reflux episodes detected by impedance.[19] The low number of common cavities observed in manometric studies (0.4 [18] and 2.3 [16] per 30 minutes) are in contrast with the numbers observed with direct evaluation of GBs using 24-h impedance monitoring (20.4).[17] The rates of gas-related symptoms of the current study are similar to the rates of inability to belch (7.8% vs. 15.7%) and gas bloating (22.5% vs. 35.9%) reported by a recent meta-analysis comparing LTF and LNF and the prevalence of increased flatulence was also similar to the results of the only randomized trial that compared increased flatulence after LTF and LNF (67.2% vs. 74.6%).[48]

Previous studies have evaluated reflux after LNF using impedance monitoring.[17,28,29,43,49] These studies have demonstrated that LNF selectively reduces reflux episodes as the reduction in liquid-containing reflux episodes is larger than the reduction in gas episodes. The current study is the first study that evaluated the effect of LTF on weakly acidic reflux and proximal extent of the reflux

episodes. Our study demonstrates that LTF reduces acid and weakly acidic reflux to a similar extent as LNF. LTF reduced liquid-containing reflux, but had no impact on pure gas reflux and the reduction in liquid-containing reflux after LNF was five times larger than the reduction in pure gas reflux. This does not imply that the gastroesophageal junction is an intelligent sphincter. Flow trough the esophagus is highly dependent on both the cross-sectional area of its lumen and the viscosity of the fluid flowing trough it.[50] The low viscosity of gaseous substances allows passage of a highly compliant esophagogastric junction more easily than liquids.[51] This observation potentially explains the ability of LTF to provide similar reduction of liquid-containing reflux compared with LNF, without reducing gas reflux. A difference in distensibility of the cross-sectional area of the lumen after LTF and LNF is another potential explanation for the difference in handling of gas and liquids.[50,51] The effectiveness of antireflux surgery is not only determined by reduction in the number of reflux episodes, the proximal reflux extent is important as well.[26] The current report combined the quantity and extent of the reflux episodes by calculating the TERD.[17] The reduction in TERD, proximal, mid-esophageal and distal reflux were similar after LTF and LNF. The improvement of reflux symptoms was similar after LTF and LNF as well. In addition, the current results show that refractory GERD symptoms are neither caused by acid nor by weakly acidic reflux. Belching seems to be a more important cause of persistent complaints, as one-fifth of the symptomatic patients had a positive relationship between postfundoplication symptoms and belches. The reduction of reflux lead to a great decrease in the number of SGBs associated with reflux after surgery.

The present physiological study was too small to provide evidence that LTF significantly reduces inability to belch and gas bloating compared with LNF, but the meta-analyses have previously shown that LTF reduces these gas-related symptoms.[6,7] Another limitation of the study was the lack of randomization, though a randomized design is less critical in physiological studies than in studies that focus on clinical endpoints. The first patients that participated in this consecutive study underwent LNF and the surgical therapy of choice for GERD was changed after a meta-analysis demonstrated that LTF reduces dysphagia.[6] Therefore, preoperative characteristics did not determine whether LTF or LNF was performed. The absence of selection bias is illustrated by the fact that the groups were similar at baseline. Surgeon experience has probably not biased the results since both surgeons completed the learning curve for both procedures[31] and one surgeon had more experience in LTF (EJH) whereas the other was more experienced in LNF (IAMJ).

The current results demonstrate no differences in the short-term reduction of acid and weakly acidic reflux after LTF and LNF. Limited amounts of reflux are part of

the normal physiology of the gastroesophageal junction. LTF and LNF did not eliminate reflux but reduced the total number of reflux episodes to a similar extent and well below the normal value. Consequently, both procedures rendered patients asymptomatic in the short-term. Time is the enemy of both procedures and consequently a difference in reflux control between LTF and LNF could potentially develop with extension of follow-up. Based on the results of 7 randomized trials, two recent meta-analyses[6,52] and the American guidelines for antireflux surgery[5] concluded that reflux control is similar up to five years after LTF and LNF. However, comparative studies with follow-up beyond five years have demonstrated that reflux symptoms are more frequent after LTF than after LNF.[22-25] It is likely that these uncontrolled studies advocated LTF in patients with poor esophageal peristalsis in an attempt to reduce postoperative dysphagia. This is a potential source of bias, since poor esophageal peristalsis has recently been identified as an independent predictor of recurrent reflux disease after fundoplication.[53] Therefore, the long-term results of the 7 randomized trials will have to confirm that the reduction of reflux remains similar after LTF and LNF with extension of follow-up beyond five years. Until this evidence is available, both procedures are appropriate for the surgical treatment of GERD. Patients should be informed about the higher rate of gas-related symptoms after LNF and the potentially higher rate of reflux after five years associated with LTF. The decision to perform LTF or LNF must be made after a conversation between surgeon and patient that explores these cons and pros.

In conclusion, the reduction in acid reflux and weakly acidic reflux and proximal reflux extent are similar after LTF and LNF. Persistent reflux symptoms are neither caused by acid nor by weakly acidic reflux. Both procedures alter the belching pattern by reducing GBs (air venting from stomach) and increasing SGBs (no air venting from stomach). However, gas reflux and GBs are reduced less after LTF than after LNF, resulting in more air venting from the stomach and less gas bloating and flatulence, while reflux is reduced to a similar extent in the short-term.

Acknowledgements

The authors thank J. Oors and J. van der Scheur for performing the stationary esophageal manometries and 24-h impedance-pH monitoring studies and H.G. Rijnhart-de Jong for maintaining the prospective database. A.J. Bredenoord is supported by a grant from the Netherlands Organisation for Scientific Research.

References

(1) Broeders JA, Rijnhart-de Jong HG, Draaisma WA et al. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. Ann Surg 2009; 250:698-706.

(2) Draaisma WA, Rijnhart-de Jong HG, Broeders IA et al. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. Ann Surg 2006; 244:34-41.

(3) Salminen PT, Hiekkanen HI, Rantala AP et al. Comparison of long-term outcome of laparoscopic and conventional nissen fundoplication: a prospective randomized study with an 11-year follow-up. Ann Surg 2007; 246:201-206.

(4) Broeders JA, Roks DJ, Ahmed Ali U et al. Laparoscopic Anterior versus Posterior Fundoplication for Gastroesophageal Reflux Disease: Systematic Review and Meta-analysis of Randomized Clinical Trials. Ann Surg 2011; in press.

(5) Stefanidis D, Hope WW, Kohn GP et al. Guidelines for surgical treatment of gastroesophageal reflux disease. Surg Endosc 2010; 24:2647-2669.

(6) Broeders JA, Mauritz FA, Ahmed AU et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. Br J Surg 2010; 97:1318-1330.

(7) Catarci M, Gentileschi P, Papi C et al. Evidence-based appraisal of antireflux fundoplication. Ann Surg 2004; 239:325-337.

(8) Varin O, Velstra B, De SS et al. Total vs partial fundoplication in the treatment of gastroesophageal reflux disease: a meta-analysis. Arch Surg 2009; 144:273-278.

(9) Camilleri M, Dubois D, Coulie B et al. Prevalence and socioeconomic impact of upper gastrointestinal disorders in the United States: results of the US Upper Gastrointestinal Study. Clin Gastroenterol Hepatol 2005; 3:543-552.

(10) Johnsson F, Holloway RH, Ireland AC et al. Effect of fundoplication on transient lower oesophageal sphincter relaxation and gas reflux. Br J Surg 1997; 84:686-689.

(11) Low DE, Mercer CD, James EC et al. Post Nissen syndrome. Surg Gynecol Obstet 1988; 167:1-5.

(12) McNally EF, Kelly JE, Ingelfinger FJ. Mechanism of belching: effects of gastric distension with air. Gastroenterology 1964; 46:254-259.

(13) Pouderoux P, Ergun GA, Lin S et al. Esophageal bolus transit imaged by ultrafast computerized tomography. Gastroenterology 1996; 110:1422-1428.

(14) Smith D, King NA, Waldron B et al. Study of belching ability in antireflux surgery patients and normal volunteers. Br J Surg 1991; 78:32-35.

(15) Woodward ER, Thomas HF, McAlhany JC. Comparison of crural repair and Nissen fundoplication in the treatment of esophageal hiatus hernia with peptic esophagitis. Ann Surg 1971; 173:782-792.

(16) Straathof JW, Ringers J, Lamers CB et al. Provocation of transient lower esophageal sphincter relaxations by gastric distension with air. Am J Gastroenterol 2001; 96:2317-2323.

(17) Broeders JA, Bredenoord AJ, Hazebroek EJ et al. Effects of anti-reflux surgery on weakly acidic reflux and belching. Gut 2011; 60:435-441.

(18) Rydberg L, Ruth M, Lundell L. Mechanism of action of antireflux procedures. Br J Surg 1999; 86:405-410.

(19) Aanen MC, Bredenoord AJ, Samsom M et al. The gastro-oesophageal common cavity revisited. Neurogastroenterol Motil 2006; 18:1056-1061.

(20) Fass J, Silny J, Braun J et al. Measuring esophageal motility with a new intraluminal impedance device. First clinical results in reflux patients. Scand J Gastroenterol 1994; 29:693-702.

(21) Sifrim D, Silny J, Holloway RH et al. Patterns of gas and liquid reflux during transient lower oesophageal sphincter relaxation: a study using intraluminal electrical impedance. Gut 1999; 44:47-54.

(22. Dallemagne B, Weerts J, Markiewicz S et al. Clinical results of laparoscopic fundoplication at ten years after surgery. Surg Endosc 2006; 20:159-165.

(23) Fein M, Bueter M, Thalheimer A et al. Ten-year outcome of laparoscopic antireflux surgery. J Gastrointest Surg 2008; 12:1893-1899.

(24) Horvath KD, Jobe BA, Herron DM et al. Laparoscopic Toupet fundoplication is an inadequate procedure for patients with severe reflux disease. J Gastrointest Surg 1999; 3:583-591.

(25) Patti MG, Robinson T, Galvani C et al. Total fundoplication is superior to partial fundoplication even when esophageal peristalsis is weak. J Am Coll Surg 2004; 198:863-869.

(26) Bredenoord AJ, Weusten BL, Curvers WL et al. Determinants of perception of heartburn and regurgitation. Gut 2006; 55:313-318.

(27) Vela MF, Camacho-Lobato L, Srinivasan R et al. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. Gastroenterology 2001; 120:1599-1606.

(28) Frazzoni M, Conigliaro R, Melotti G. Weakly acidic refluxes have a major role in the pathogenesis of proton pump inhibitor-resistant reflux oesophagitis. Aliment Pharmacol Ther 2011; 33:601-606.

(29) Roman S, Poncet G, Serraj I et al. Characterization of reflux events after fundoplication using combined impedance-pH recording. Br J Surg 2007; 94:48-52.

(30) Sifrim D, Castell D, Dent J et al. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. Gut 2004; 53:1024-1031.

(31) Watson DI, Baigrie RJ, Jamieson GG. A learning curve for laparoscopic fundoplication. Definable, avoidable, or a waste of time? Ann Surg 1996; 224:198-203.

(32) Radajewski R, Hazebroek EJ, Berry H et al. Short-term symptom and quality-of-life comparison between laparoscopic Nissen and Toupet fundoplications. Dis Esophagus 2009; 22:84-88.

(33) Bais JE, Bartelsman JF, Bonjer HJ et al. Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. Lancet 2000; 355:170-174.

(34) Draaisma WA, Buskens E, Bais JE et al. Randomized clinical trial and follow-up study of cost-effectiveness of laparoscopic versus conventional Nissen fundoplication. Br J Surg 2006; 93:690-697.

(35) Draaisma WA, Ruurda JP, Scheffer RC et al. Randomized clinical trial of standard laparoscopic versus robot-assisted laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease. Br J Surg 2006; 93:1351-1359.

(36) Velanovich V, Vallance SR, Gusz JR et al. Quality of life scale for gastroesophageal reflux disease. J Am Coll Surg 1996; 183:217-224.

(37) Velanovich V, Karmy-Jones R. Measuring gastroesophageal reflux disease: relationship between the Health-Related Quality of Life score and physiologic parameters. Am Surg 1998; 64:649-653.

(38) Blazeby JM, Conroy T, Hammerlid E et al. Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with oesophageal cancer. Eur J Cancer 2003; 39:1384-1394.

(39) Aaronson NK, Muller M, Cohen PD et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998; 51:1055-1068.

(40) Lundell LR, Dent J, Bennett JR et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999; 45:172-180.

(41) Bredenoord AJ, Weusten BL, Timmer R et al. Minimum sample frequency for multichannel intraluminal impedance measurement of the oesophagus. Neurogastroenterol Motil 2004; 16:713-719.

(42) Wiener GJ, Richter JE, Copper JB et al. The symptom index: a clinically important parameter of ambulatory 24-hour esophageal pH monitoring. Am J Gastroenterol 1988; 83:358-361.

(43) Bredenoord AJ, Draaisma WA, Weusten BL et al. Mechanisms of acid, weakly acidic and gas reflux after anti-reflux surgery. Gut 2008; 57:161-166.

(44) Zerbib F, des Varannes SB, Roman S et al. Normal values and day-to-day variability of 24-h ambulatory oesophageal impedance-pH monitoring in a Belgian-French cohort of healthy subjects. Aliment Pharmacol Ther 2005; 22:1011-1021.

(45) Bredenoord AJ, Weusten BL, Timmer R et al. Air swallowing, belching, and reflux in patients with gastroesophageal reflux disease. Am J Gastroenterol 2006; 101:1721-1726.

(46) Bredenoord AJ, Weusten BL, Sifrim D et al. Aerophagia, gastric, and supragastric belching: a study using intraluminal electrical impedance monitoring. Gut 2004; 53:1561-1565.

(47) Hemmink GJ, Bredenoord AJ, Weusten BL et al. Supragastric belching in patients with reflux symptoms. Am J Gastroenterol 2009; 104:1992-1997.

(48) Booth MI, Stratford J, Jones L et al. Randomized clinical trial of laparoscopic total (Nissen) versus posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. Br J Surg 2008; 95:57-63.

(49) del Genio G, Tolone S, del Genio F et al. Total fundoplication controls acid and nonacid reflux: evaluation by pre- and postoperative 24-h pH-multichannel intraluminal impedance. Surg Endosc 2008; 22:2518-2523.

(50) Pandolfino JE, Shi G, Curry J et al. Esophagogastric junction distensibility: a factor contributing to sphincter incompetence. Am J Physiol Gastrointest Liver Physiol 2002; 282:G1052-G1058.

(51) Pandolfino JE, Shi G, Trueworthy B et al. Esophagogastric junction opening during relaxation distinguishes nonhernia reflux patients, hernia patients, and normal subjects. Gastroenterology 2003; 125:1018-1024.

(52) Shan CX, Zhang W, Zheng XM et al. Evidence-based appraisal in laparoscopic Nissen and Toupet fundoplications for gastroesophageal reflux disease. World J Gastroenterol 2010; 16:3063-3071.

(53) Broeders JA, Roks DJ, Draaisma WA et al. Predictors of objectively identified recurrent reflux after primary Nissen fundoplication. Br J Surg 2011; in press.

16
Summary

The studies presented in this thesis have addressed the current status of surgical treatment of gastro-oesophageal reflux disease (GORD). The thesis aimed to clarify which patients benefit from anti-reflux surgery, to determine the surgical approach and fundoplication type of choice and to evaluate the physiological effects of fundoplication. The first part studied indications for laparoscopic anti-reflux surgery, predictors or recurrent reflux disease and the impact of oesophageal peristalsis on dysphagia after fundoplication. The second part compared long-term results of the conventional and laparoscopic approach to anti-reflux surgery and the effect of surgeon experience on outcome. The effectiveness and side-effects of various fundoplication types were evaluated as well. The third part focused on the physiological effects of fundoplication.

Chapter 1 offers a general introduction to the physiology of the gastro-oesophageal junction (GOJ) and the pathophysiological background of GORD. Furthermore, the history and present role of anti-reflux surgery in the treatment of GORD is addressed, including classic and potential indications for fundoplication. Subsequently, surgical approaches and fundoplication types are introduced. Finally, the significance of intraluminal impedance monitoring to evaluate physiological effects of anti-reflux surgery is elucidated.

Part I - Indications

Patients with an incomplete response to pharmacological therapy with proton pump inhibitors,[1-3] unwillingness to take lifelong medication[1-3] or extra-oesophageal manifestations[4-7] are candidates for anti-reflux surgery. Candidates for anti-reflux surgery with erosive reflux disease on upper endoscopy and/or pathological supine or bipositional reflux with a positive symptom-reflux association during 24-h pH metry, have a classic indication for anti-reflux surgery. Upper endoscopy is performed as part of the work-up for anti-reflux surgery and classifies half of the patients as erosive reflux disease (ERD) and the other half as non-erosive reflux disease (NERD).[8] Ambulatory 24-hour pH monitoring with symptom association analysis is the gold standard objective test to diagnose GORD in absence of erosions.[9] Patients can be divided into isolated upright, isolated supine and bipositional reflux based on the body position in which pathological reflux occurs during 24-h pH monitoring.[10] Traditionally, the latter two reflux patterns are considered good candidates for anti-reflux surgery.[10;11] In contrast, isolated upright reflux disease is considered to be associated with less severe manifestations of the disease and therefore surgery tends to be withheld from these patients.[10;11] **Chapter 2** compares differences in outcome after fundoplication in patients with

isolated upright reflux (*n*=81) to patients with supine (*n*=55) and bipositional reflux (*n*=98). Patients with isolated upright reflux had similarly severe objective GORD manifestations before surgery and similar 5-year outcome when compared with patients with isolated supine reflux. In contrast, bipositional reflux was associated with more severe disease in comparison with unipositional reflux and had a higher rate of recurrent oesophagitis (3.5 *vs* 9.4 *vs* 16.0%, respectively), recurrent pathological acid exposure (10.7 *vs* 18.8 *vs* 40.9%, respectively) and reoperations (8.9 *vs* 4.1 *vs* 20.0%, respectively). Despite these differences in disease severity, all three reflux patterns responded favourably to Nissen fundoplication in the long-term. Consequently, the preoperative reflux pattern should be utilised for counselling patients with bipositional reflux on surgical outcome and should not be used to withhold surgery from patients with isolated upright reflux.

Traditional candidates for fundoplication have both a pathological acid exposure time and a positive symptom-reflux correlation during 24-h pH monitoring. However, it has been estimated that 10-15 per cent of patients with GORD have a physiological acid exposure time.[12] **Chapter 3** evaluates the 5-year outcome of patients with physiological acid exposure time, but a positive relationship between symptoms and acid reflux episodes (i.e. oesophageal acid hypersensitivity).[13] The results of anti-reflux surgery in these patients (*n*=28) were directly compared with a contemporary control group of patients with pathological acid exposure and a positive symptom-reflux association (*n*=126). There were no differences in subjective and objective outcome and reoperation rate. As a result, it was demonstrated that patients with oesophageal acid hypersensitivity benefit from Nissen fundoplication as much as those with pathological acid exposure.

Up to half of the patients with pathological acid exposure time lack a positive association between symptom occurrence and reflux episodes during 24-h pH metry.[14] In **chapter 4** the impact of symptom-reflux association analysis on long-term outcome after Nissen fundoplication is evaluated. Subjective outcome and objective reflux control in patients with pathological acid exposure were comparable among those with a positive (*n*=109) and negative symptom-reflux correlation (*n*=29). These results seem to contradict the conclusion of the study described in chapter 3, which states that patients with physiological acid exposure and a positive symptom association respond favourably to anti-reflux surgery, as opposed to patients with physiological acid exposure and a negative association. However, this apparent discrepancy can be explained by the high positive predictive value and low negative predictive value of symptom-reflux correlation scores.[15] Therefore, it was concluded that patients with pathological oesophageal

acid exposure benefit from fundoplication, irrespective of whether they have a negative of positive symptom-reflux correlation.

Until recently, NERD was regarded as a milder form of GORD and considered a relative contraindication for fundoplication. However, in the late nineties studies demonstrated that impairment of quality of life and severity of symptoms are similar in patients with NERD and ERD.[16-19] In addition, it has been shown that NERD patients have a diminished response to medical treatment,[16;20-23] which would support a greater role for anti-reflux surgery in NERD than in ERD. **Chapter 5** therefore compares preoperative reflux parameters and long-term outcome of Nissen fundoplication in NERD and ERD. Preoperative reflux parameters were similar in the two groups. The subjective and objective outcome after fundoplication and reoperation rate was also comparable. Consequently, it was concluded that the absence of erosions on endoscopy in candidates for anti-reflux surgery with pathological acid exposure is not a reason to refrain from anti-reflux surgery.

Recurrent reflux disease and dysphagia are the main indications for reintervention after fundoplication. In 2009 a systematic review evaluating predictors of outcome after fundoplication found that the quality and consistency of previous studies are mixed. Consequently, it was concluded that studies with improved methodology are needed. In **chapter 6** we describe a study that followed the methodological recommendations of the review and identified objective predictors for recurrent reflux disease after fundoplication. Multivariate binary logistic regression analysis demonstrated that patients with poor oesophageal peristalsis (odds ratio per cent 0.97 [0.95- 0.99]; $P = 0.004$) or high supine acid exposure time (odds ratio per cent 1.03 [1.00-1.07]; $P = 0.025$) are independent predictors of recurrent pathological acid exposure. High supine acid exposure was also an independent predictor of surgical reintervention for recurrent GORD (odds ratio per cent 1.05 [1.01-1.08]; $P = 0.006$). Considering patients with excessive supine acid exposure are likely to gain the most from fundoplication, this group should not be denied anti-reflux surgery. However, as about half of patients with both predictors experience recurrent pathological acid exposure after Nissen fundoplication, surgery should be restricted in this group.

It is often assumed that patients with poor oesophageal peristalsis prior to surgery are more likely to develop postoperative dysphagia.[24-27] In these cases, many centres advocate tailoring of wrap circumference, by performing a partial instead of a total wrap.[25] However, two randomised clinical trials (RCTs) failed to demonstrate that outcome after fundoplication is worse in patients with poor motility, compared

with those with normal oesophageal motility.[28;29] **Chapter 7** reports the results of the largest cohort study evaluating the impact of preoperative oesophageal peristalsis on the incidence of postfundoplication dysphagia. The study demonstrated that preoperative oesophageal motility by standard manometric parameters had no impact on postoperative dysphagia scores nor dilations and reoperations for dysphagia. Therefore, we conclude that tailoring wrap circumference according to preoperative motility is probably not necessary.

Part II - Techniques

In 1956, Rudolph Nissen performed the first fundoplication for GORD[30] after the serendipitous discovery of the anti-reflux effect of wrapping the fundus of the stomach around the distal oesophagus.[31] Laparoscopic Nissen fundoplication (LNF) rapidly replaced conventional Nissen fundoplication (CNF) after its first report in 1991, despite the fact that evidence proving equivalence of the new approach was lacking at the time.[32] Subsequent studies have reported short-term benefits of LNF such as reduction of in-hospital complications, hospital stay and sick leave compared with CNF,[33;34] with similar 5-year reflux control.[35] Confirmation of superiority of LNF in terms of effectiveness or reoperation rate by long-term level 1 evidence is still lacking. In **chapter 8** we describe the 10-year outcome of an RCT comparing CNF (*n*=69) and LNF (*n*=79). There were no differences in long-term reflux control and patient satisfaction. Twice as many patients underwent reoperation after CNF compared with LNF (24 [34.8%] *vs* 12 [15.2%]; *P* = 0.006), including a higher number of incisional hernia corrections (9 *vs* 2; *P* = 0.015). Correction of an incisional hernia of an upper midline incision requires hospitalisation and carries a substantial risk for recurrence. This study is the first RCT to demonstrate that laparoscopic surgery reduces the incidence of incisional hernias and the number of cicatrical hernia corrections compared with upper midline incision in non-obese patients. In line with the 10-year results of other large RCTs,[36-38] the percentage of patients using acid-suppressing drugs slowly increased with time in both groups. However, 65 per cent of patients who used acid-suppressing drugs at 10 years after surgery did not have recurrent acid or weakly acidic reflux on pH-impedance monitoring. This finding confirms previous studies which found that only a small portion of the patients using anti-reflux medication postoperatively, have abnormal oesophageal acid exposure on 24-hr pH monitoring[35;39;40] or endoscopic fundoplication disruption.[41] The hypothesis at the time of introduction of LNF: a lower reoperation rate for incisional hernia and similar effectiveness, is strongly supported by this study and this trial lends level 1

support to the use of laparoscopic anti-reflux surgery as the surgical approach of choice for GORD.

The short-term results of this RCT[42] raised questions about the effect of operator experience on the outcome of laparoscopic anti-reflux surgery.[43-48] In **chapter 9** we evaluate the impact of surgeon experience on long-term outcome after LNF. The 5-year results of the CNF (*n*=74) and LNF (*n*=93) arm of the trial were compared with the 5-year results of a subsequent cohort study (*n*=121) that was performed after extension of the learning curve from a minimum of 5 LNFs[49] to a minimum of 30 LNFs per surgeon in accordance with new insights.[50-53] Operating time, complications, hospitalisation, early dysphagia, dilatations for dysphagia and early reoperation rate after LNF, improved significantly with increasing surgeon experience. In contrast, short-term objective reflux control and five-year clinical outcome did not improve with experience. In experienced hands, LNF reduced in-hospital complications and hospitalisation compared with CNF, with similar five-year effectiveness and reoperation rate. Therefore, we conclude that this analysis clearly illustrates the effect of experience on early outcome of laparoscopic anti-reflux surgery and represents a plea for centralisation of expertise.

The gastro-oesophageal junction (GOJ) is a functional valve that separates the gastric and oesophageal cavities and serves three functions: to allow solids and liquids to pass from the oesophagus to the stomach, to allow ventilation of gas from the stomach to the mouth (i.e. belching) and to prevent retrograde flow of liquid gastric contents into the oesophagus (i.e. gastro-oesophageal reflux). Generally, the aim of anti-reflux surgery is to restore the third function, without impairing the first two roles. Consequently, the ideal anti-reflux operation would ensure long-term reflux control with minimal postoperative dysphagia and gas-related symptoms. LNF restores the anti-reflux barrier, with excellent 10-year reflux control. However, the procedure results in a supracompetent valve, which tends to impair the two other functions of the GOJ. Consequently, the main side-effects of LNF are difficulty in swallowing solids and liquids (i.e. dysphagia) and gas-related symptoms caused by an inability to allow ventilation of gas from the stomach (i.e. inability to belch).

In 1963, André Toupet proposed partial posterior fundoplication for GORD in an attempt to minimise postfundoplication complaints.[54] Some studies have confirmed that Toupet fundoplication reduces the prevalence of postoperative dysphagia[55;56] and gas-related symptoms.[57;58] Despite these potential benefits, laparoscopic Toupet fundoplication (LTF) is not widely used, probably because uncontrolled

studies have reported less effective reflux control compared with LNF.[59-66] **Chapter 10** describes a systematic review and meta-analysis of seven RCTs comparing LNF (*n*=404) with LTF (*n*=338). This meta-analysis demonstrated that LNF is associated with a higher prevalence postoperative dysphagia, dilatations for dysphagia and number of surgical reinterventions. The prevalence of inability to belch and gas bloating was higher after LNF as well, with similar subjective and objective reflux control. These results provide level 1a support for the use of LTF as the posterior fundoplication of choice for GORD.

In 1967, Jacques Dor introduced anterior partial fundoplication to reduce the high rate of postfundoplication symptoms after Nissen fundoplication.[67] Laparoscopic anterior fundoplication (LAF) has been proposed as an alternative operation, aiming to reduce postfundoplication symptoms. Since then, several RCTs have confirmed that LAF reduces dysphagia[68-73] and gas-related symptoms,[70;71;73] when compared with posterior fundoplication. Some RCTs suggest that this is offset by a higher reflux recurrence rate,[68;69;71;73-76] though other RCTs report similar reflux control.[38;70;72] **Chapter 11** is a systematical review and meta-analysis of seven RCTs that pooled 90°, 120° and 180° LAF (*n*=345) and compared it to the pooled results of 180°, 200° and 360° posterior fundoplication (*n*=338). Oesophageal acid exposure time and the prevalence of heartburn were higher after LAF. In the short-term this was counterbalanced by less severe dysphagia. However, dysphagia scores became similar in the long-term, with a persistent substantial increase in prevalence of heartburn and proton pump inhibitor (PPI) use after LAF. The reoperation rate was twice as high after LAF as well, mainly due to reinterventions for recurrent GORD. Consequently, we conclude that pooled outcome after posterior fundoplication provides superior reflux control compared with pooled results of anterior fundoplication types, with similar long-term dysphagia rates.

The meta-analysis described in chapter 11 pooled 90°, 120° and 180° LAF and compared this group to the pooled results of 180°, 200° and 360° posterior fundoplication. The study described in **chapter 12** aimed to stratify the two most common anterior fundoplication types and compare the results to the most frequently performed posterior fundoplication, in order to identify potential differences in outcome between the anterior fundoplication types. Therefore, the study stratified the 90° and 180° LAF group and compared it to LNF only. We evaluated the original 5-year results of two RCTs comparing 90° LAF *versus* LNF and two studies that randomised 180° LAF *versus* LNF. A randomised comparison between 90° LAF (*n*=90) *versus* LNF (*n*=82*)* and 180° LAF (*n*=121) *versus* LNF (*n*=132) was made. There were no significant differences in reoperation and

dilatation rate between 90° and 180° LAF *versus* LNF within the follow-up period. At five years, 90° and 180° LAF similarly reduced dysphagia and gas-related symptoms compared with LNF. Control of reflux symptoms was inferior after 90° LAF, but similar after 180° LAF and LNF. In summary, stratification demonstrated that 180° LAF ensures durable control of reflux symptoms with minimal postfundoplication symptoms. In contrast, reflux control after 90° LAF is inferior to LNF and LNF is associated with more side-effects compared with 180° LAF.

Recently, endoluminal fundoplication using the EsophyX® device has been introduced as a less invasive endoscopic alternative for laparoscopic fundoplication. Anatomical and physiological results of endoluminal fundoplication in dogs are promising.[77] However, short-term results of clinical studies have demonstrated that about half of the patients have recurrent pathological acid exposure[78-84] and persisting oesophagitis[78;80;85] after endoluminal fundoplication. Subsequent anti-reflux surgery is the last resort in patients with recurrent PPI-refractory GORD after endoluminal fundoplication. The outcome of laparoscopic fundoplication after previous endoluminal fundoplication is described in **chapter 13**. Subjective and objective reflux control are satisfactory after LNF for failed endoluminal fundoplication. Previous endoluminal fundoplication, however, is associated with a risk of gastric perforation during LNF (27%) and a high rate of postfundoplication dysphagia.

Part III - Physiological effects

It is necessary to evaluate the physiological effects of anti-reflux surgery to understand the working mechanism of fundoplication and the differences in reflux control and post-fundoplication symptoms between fundoplication types. Regarding reflux control, previous studies have demonstrated that weakly acidic reflux can induce reflux symptoms[86] and that proximal extent determines whether a reflux episode is perceived as a symptom by the patient.[87] 24-h combined oesophageal impedance-pH monitoring has a distinct role in the evaluation of the physiological effects of fundoplication since it quantifies both acid and weakly acidic reflux[88] and proximal reflux extent.[89] It is controversial whether fundoplication mainly reduces acid reflux and that the persistence of weakly acidic reflux causes postoperative reflux symptoms,[90;91] or whether acid and weakly acidic reflux episodes are similarly reduced.[92;93] With regard to gas-related symptoms, effect of fundoplication on gastric belching has only been studied indirectly using measurement of belched gas volumes[94] or manometric evaluation.[58;95-97] It was unknown why patients who

have undergone fundoplication often report ability to belch, in absence of gastric belches on manometry.[95;97]

The study described in **chapter 14** evaluates the effect of LNF on reflux and belching using 24-h impedance-pH metry. LNF similarly controlled acid and weakly acidic reflux at six months, but gas reflux was reduced to a lesser extent. Persistent reflux symptoms were neither caused by acid, nor by weakly acidic reflux. The results demonstrated that LNF alters the belching pattern by reducing gastric belches (air venting from stomach; 68.5 → 23.9; $P < 0.001$) and increasing oesophageal belches (no air venting from stomach; 20.8 → 46.0; $P = 0.036$). This explains the increase in belching experienced by some patients after LNF, despite the reduction in gastric belching. The reduction in gastric belching after LNF increases gas bloating and flatulence. It was therefore hypothesised that the gas bloating induced by a decrease in gastric belches after LNF incites post-fundoplication patients to actively increase the number of oesophageal belches in a futile attempt to vent air from the stomach.

The results of the meta-analysis described in chapter 10 demonstrate that LTF offers similar reflux control with less dysphagia and gas-related symptoms compared with LNF. It was therefore hypothesised in **chapter 15** that LTF and LNF similarly control acid and weakly acidic reflux and that LTF reduces gastric belches to lesser extent than LNF. The effect of LTF and LNF on gastric belching has previously been evaluated, but these studies were limited by manometric evaluation and reported contradictory results.[58;96] To test the hypotheses, impedance-pH monitoring was used to compare the effect of LTF (n=14) on reflux characteristics and belching to a matched control LNF group (n=28). At six months, both LTF and LNF altered the belching pattern by reducing gastric belches (air venting from stomach) and increasing oesophageal belches (no air venting from stomach). However, gas reflux and gastric belches were reduced to lesser extent after LTF, resulting in more air venting from the stomach and less gas bloating and flatulence, while a similar degree of short-term reflux inhibition was obtained. These results provide the physiological rationale for the clinical findings of the meta-analysis and support the conclusion that LTF is the posterior fundoplication of choice for GORD.

Conclusions

The studies presented in this thesis lead to the following conclusions:

1 Candidates for anti-reflux surgery with isolated upright reflux, oesophageal acid hypersensitivity, negative symptom-reflux correlation or non-erosive reflux disease benefit from LNF as much as those with classic indications for surgery. Indications for anti-reflux surgery should be broadened and fundoplication should not be withheld from these patients.

2 Patients with poor oesophageal peristalsis or high supine acid exposure before surgery should be counselled about their higher chance of recurrent reflux after LNF.

3 Tailoring the degree of fundoplication based on preoperative oesophageal motility is probably not necessary, since oesophageal peristalsis before surgery has no impact on postfundoplication dysphagia.

4 LNF for failed endoluminal EsophyX® fundoplication provides satisfactory reflux control, but is associated with a risk of gastric perforations during LNF and a high rate of postfundoplication dysphagia.

5 Laparoscopic anti-reflux surgery reduces the reoperation rate for incisional hernia with similar long-term effectiveness compared with conventional fundoplication and should be considered the surgical approach of choice for GORD. Surgeon experience, however, affects early outcome of laparoscopic fundoplication and this pleads for centralisation of expertise.

6 Gas-related symptoms are the most common side-effects of LNF and these are caused by a reduction in the number of gastric belches that is accompanied by an increase in oesophageal belching.

7 LNF and LTF similarly control reflux symptoms, acid and weakly acidic reflux. LTF is associated with fewer reinterventions, less dysphagia and fewer gas-related symptoms compared with LNF, with a smaller reduction of gastric belches.

8 90° LAF provides inferior long-term reflux control compared with LNF. In contrast, 180° LAF reduces dysphagia and gas-related symptoms compared with LNF, with similar long-term control of reflux symptoms.

Future perspectives

Laparoscopic anti-reflux surgery reduces the reoperation rate for incisional hernia with similar long-term effectiveness compared with conventional fundoplication (**chapter 8**). Therefore, laparoscopic fundoplication is the current surgical therapy of choice for GORD. No additional studies are warranted to further illustrate the superiority of laparoscopic anti-reflux surgery. Mainly because, yet another comparative trial will not be feasible for practical and ethical reasons. Such a trial, if at all feasible, would not add any clinically relevant information to current knowledge.

At present, GORD patients with an incomplete response to pharmacological therapy with proton pump inhibitors and unwillingness to take lifelong medication are widely accepted candidates for laparoscopic fundoplication.[1-3] The long-term results of four RCTs will evaluate whether laparoscopic anti-reflux surgery is also the therapy of choice in GORD patients with a complete response to pharmacological therapy.[98] These results will determine whether the higher effectiveness of surgery outweighs its additional costs and increased rate of complications and dysphagia compared with continuing PPI therapy.[98] The difference in costs between both treatment strategies will increase further since PPIs recently came off patent.

At present, the clinical benefits of robot-assisted fundoplication do not justify its higher costs compared with laparoscopic fundoplication.[99] Robotic systems should be preserved for more complex laparoscopic surgery. Robot-assisted myotomy for achalasia reduces for example the risk of oesophageal perforation compared with laparoscopic myotomy.[99] Another possible application is redo fundoplication because its potential for magnification and three-dimensional orientation will probably reduce the risk for oesophageal perforation and vagal nerve damage. This is a recommendation with Level IV evidence and a RCT to prove this point will require an enormous number of patients and an unrealistically long study period.

In addition, studies have yet to demonstrate whether endoluminal EsophyX® fundoplication provides a less invasive alternative for laparoscopic fundoplication in selected patients, with similar reflux control. Initially published favourable results suggested that EsophyX® offers a promising perspective. However, no mid-long term or long-term results have been published yet. The high rate of objective recurrence of reflux disease published so far[78-85] and the high rate of gastric perforations and postfundoplication dysphagia associated with LNF for failed EsophyX® (**chapter 13**), indicate that this endoluminal option will probably not provide a non-operative alternative to candidates for laparoscopic fundoplication.

The five-year results of **chapter 2** to **5** lead to the conclusion that traditional indications for laparoscopic anti-reflux surgery should be broadened. The findings described in **chapter 2** to **5** demonstrate that patients with acid reflux proven on pH-metry and either upright reflux, oesophageal acid hypersensitivity, negative symptom-reflux association or non-erosive reflux disease, benefit from laparoscopic fundoplication. Ambulatory impedance-pH monitoring detects both acid and weakly acidic reflux and the proximal extent of the refluxate. Therefore, new studies will have to evaluate the additional value of this new technique to select candidates for anti-reflux surgery. In the study described in **chapter 4** we found that a negative symptom-reflux correlation during pH-metry in patients with pathological acid exposure, has no impact on outcome after fundoplication. The accuracy of determination of the relationship between reflux and symptoms is higher when reflux is detected with combined impedance-pH monitoring than when detected with pH monitoring alone. Therefore, a larger study using combined impedance-pH monitoring is warranted to reproduce and confirm the results of this study.

As identified in **chapter 6**, patients with poor oesophageal peristalsis and high supine acid exposure have a high risk of recurrent reflux. Prediction models tend to perform better on data on which the model was constructed than on new data. Therefore, a study with an identical design should be performed in another patient population to validate the predictive value of these factors externally.

The study described in **chapter 7** demonstrates that ineffective oesophageal motility as defined by conventional manometry does not predict dysphagia after fundoplication. Currently, a mathematical model is being developed in Adelaide Australia, which combines variables of simultaneous high-resolution manometry and impedance monitoring. Further prognostic studies that evaluate predictors of outcome after fundoplication are needed to evaluate whether this model provides motility parameters before surgery that predict postoperative dysphagia. Identification of these parameters may facilitate tailoring of wrap circumference based on preoperative motility. As a result, future patients with a low risk of developing dysphagia after surgery may be advised to undergo fundoplication with a larger circumference to maximize reflux control and patients with a high dysphagia risk could potentially be counselled to undergo fundoplication with a smaller circumference to reduce postfundoplication symptoms.

In **chapter 9** we describe that surgeon experience has great impact on early outcome of laparoscopic fundoplication. This finding supports the observation that

centralising or concentrating expertise in anti-reflux surgery improves short-term outcome.[100] Three factors can be proposed to define an expert centre for laparoscopic anti-reflux surgery. The first is individual surgeon experience of more than 30 laparoscopic fundoplications (**chapter 9**). The second is an annual volume of more than 40 fundoplications.[100] The third is access to a gastrointestinal motility laboratory for objective diagnosis of reflux disease and oesophageal motility disorders. The role of laparoscopic simulators in surgical training programmes should be further clarified in an attempt to shorten the learning curve to reduce the high rate of adverse outcomes.

The results reported in **chapter 14** and **15** demonstrate that impedance monitoring is a valuable tool to evaluate the development of gas-related symptoms after fundoplication. As identified in **chapter 14**, LNF alters the belching pattern by reducing gastric belches and increasing supragastric belches. It can be hypothesised that the reduction in gastric belches after LNF causes gas bloating, which incites patients to actively increase the number of supragastric belches in a futile attempt to vent air from the stomach. This theory needs to be confirmed by a large study that focuses on impedance patterns and compares symptomatic and asymptomatic postfundoplication patients.

Chapter 10 and **12** compared LTF and 180° LAF to LNF. Compared with LNF, LTF and 180° LAF both reduce dysphagia and gas-related symptoms, with similar reflux control. The results described in **chapter 15** shed light on the physiological origin of the differences in gas-related symptoms between LTF and LNF, with similar short-term reflux control. A subsequent impedance study is currently being conducted to evaluate whether the physiological origin is the same when comparing long-term outcome after 180° LAF and LNF. This study is a randomised comparison of the long-term physiological effects of 180° LAF and LNF. Furthermore, another randomised clinical trial is being carried out in Adelaide, Australia, to provide the final answer to the question of whether LTF or 180° LAF should be regarded the surgical procedure of choice for GORD.

References

(1) Bredenoord AJ, Dent J. Proton pump inhibitor-therapy refractory gastro-oesophageal reflux disease patients, who are they? *Gut* 2007; **56**(4):593-594.

(2) Spechler SJ, Lee E, Ahnen D, Goyal RK, Hirano I, Ramirez F et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. *JAMA* 2001; **285**(18):2331-2338.

(3) Vakil N. Review article: the role of surgery in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2007; **25**(12):1365-1372.

(4) Oelschlager BK, Eubanks TR, Oleynikov D, Pope C, Pellegrini CA. Symptomatic and physiologic outcomes after operative treatment for extraesophageal reflux. *Surg Endosc* 2002; **16**(7):1032-1036.

(5) Lindstrom DR, Wallace J, Loehrl TA, Merati AL, Toohill RJ. Nissen fundoplication surgery for extraesophageal manifestations of gastroesophageal reflux (EER). *Laryngoscope* 2002; **112**(10):1762-1765.

(6) Meyer TK, Olsen E, Merati A. Contemporary diagnostic and management techniques for extraesophageal reflux disease. *Curr Opin Otolaryngol Head Neck Surg* 2004; **12**(6):519-524.

(7) Rakita S, Villadolid D, Thomas A, Bloomston M, Albrink M, Goldin S et al. Laparoscopic Nissen fundoplication offers high patient satisfaction with relief of extraesophageal symptoms of gastroesophageal reflux disease. *Am Surg* 2006; **72**(3):207-212.

(8) Anon. An evidence-based appraisal of reflux disease management: the Genval Workshop Report. *Gut* 1999; **44 (suppl 2)**:s1-s16.

(9) Kahrilas PJ, Quigley EM. Clinical esophageal pH recording: a technical review for practice guideline development. *Gastroenterology* 1996; **110**(6):1982-1996.

(10) DeMeester TR, Johnson LF, Joseph GJ, Toscano MS, Hall AW, Skinner DB. Patterns of gastroesophageal reflux in health and disease. *Ann Surg* 1976; **184**(4):459-470.

(11) DeMeester TR, Bonavina L, Albertucci M. Nissen fundoplication for gastroesophageal reflux disease. Evaluation of primary repair in 100 consecutive patients. *Ann Surg* 1986; **204**(1):9-20.

(12) Eriksen CA, Cullen PT, Sutton D, Kennedy N, Cuschieri A. Abnormal esophageal transit in patients with typical reflux symptoms but normal endoscopic and pH profiles. *Am J Surg* 1991; **161**(6):657-661.

(13) Galmiche JP, Clouse RE, Balint A, Cook IJ, Kahrilas PJ, Paterson WG et al. Functional esophageal disorders. *Gastroenterology* 2006; **130**(5):1459-1465.

(14) Howard PJ, Maher L, Pryde A, Heading RC. Symptomatic gastro-oesophageal reflux, abnormal oesophageal acid exposure, and mucosal acid sensitivity are three separate, though related, aspects of gastro-oesophageal reflux disease. *Gut* 1991; **32**(2):128-132.

(15) Taghavi SA, Ghasedi M, Saberi-Firoozi M, izadeh-Naeeni M, Bagheri-Lankarani K, Kaviani MJ et al. Symptom association probability and symptom sensitivity index: preferable but still suboptimal predictors of response to high dose omeprazole. *Gut* 2005; **54**(8):1067-1071.

(16) Carlsson R, Dent J, Watts R, Riley S, Sheikh R, Hatlebakk J et al. Gastro-oesophageal reflux disease in primary care: an international study of different treatment strategies with omeprazole. International GORD Study Group. *Eur J Gastroenterol Hepatol* 1998; **10**(2):119-124.

(17) Havelund T, Lind T, Wiklund I, Glise H, Hernqvist H, Lauritsen K et al. Quality of life in patients with heartburn but without esophagitis: effects of treatment with omeprazole. *Am J Gastroenterol* 1999; **94**(7):1782-1789.

(18) Venables TL, Newland RD, Patel AC, Hole J, Wilcock C, Turbitt ML. Omeprazole 10 milligrams once daily, omeprazole 20 milligrams once daily, or ranitidine 150 milligrams twice daily, evaluated as initial therapy for the relief of symptoms of gastro-oesophageal reflux disease in general practice. *Scand J Gastroenterol* 1997; **32**(10):965-973.

(19) Wiklund I. Quality of life in patients with gastroesophageal reflux disease. *Am J Gastroenterol* 2001; **96**(8 Suppl):S46-S53.

(20) Dean BB, Gano AD, Jr., Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. *Clin Gastroenterol Hepatol* 2004; **2**(8):656-664.

(21) Galmiche JP, Barthelemy P, Hamelin B. Treating the symptoms of gastro-oesophageal reflux disease: a double-blind comparison of omeprazole and cisapride. *Aliment Pharmacol Ther* 1997; **11**(4):765-773.

(22) Lauritsen K. Management of endoscopy-negative reflux disease: Progress with short-term treatment. *Aliment Pharmacol Ther* 1997; **11 (Suppl 2)**:81-85.

(23) Richter JE, Kovacs TO, Greski-Rose PA, Huang section, Fisher R. Lansoprazole in the treatment of heartburn in patients without erosive oesophagitis. *Aliment Pharmacol Ther* 1999; **13**(6):795-804.

(24) Fuchs KH, Heimbucher J, Freys SM, Thiede A. Management of gastro-esophageal reflux disease 1995; tailored concept of anti-reflux operations. *Dis Esophagus* 1994;(7):250-254.

(25) Hunter JG, Trus TL, Branum GD, Waring JP, Wood WC. A physiologic approach to laparoscopic fundoplication for gastroesophageal reflux disease. *Ann Surg* 1996; **223**(6):673-685.

(26) Kauer WK, Peters JH, DeMeester TR, Heimbucher J, Ireland AP, Bremner CG. A tailored approach to antireflux surgery. *J Thorac Cardiovasc Surg* 1995; **110**(1):141-146.

(27) Watson A, Jenkinson LR, Ball CS, Barlow AP, Norris TL. A more physiological alternative to total fundoplication for the surgical correction of resistant gastro-oesophageal reflux. *Br J Surg* 1991; **78**(9):1088-1094.

(28) Booth MI, Stratford J, Jones L, Dehn TC. Randomized clinical trial of laparoscopic total (Nissen) versus posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. *Br J Surg* 2008; **95**(1):57-63.

(29) Fibbe C, Layer P, Keller J, Strate U, Emmermann A, Zornig C. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized, clinical, and manometric study. *Gastroenterology* 2001; **121**(1):5-14.

(30) NISSEN R. [A simple operation for control of reflux esophagitis.]. *Schweiz Med Wochenschr* 1956; **86**(Suppl 20):590-592.

(31) NISSEN R. Die transpleurael resektion der kardia. *Dtsch Chir* 1937; **249**:311-316.

(32) Dallemagne B, Weerts JM, Jehaes C, Markiewicz S, Lombard R. Laparoscopic Nissen fundoplication: preliminary report. *Surg Laparosc Endosc* 1991; **1**(3):138-143.

(33) Catarci M, Gentileschi P, Papi C, Carrara A, Marrese R, Gaspari AL et al. Evidence-based appraisal of antireflux fundoplication. *Ann Surg* 2004; **239**(3):325-337.

(34) Peters MJ, Mukhtar A, Yunus RM, Khan S, Pappalardo J, Memon B et al. Meta-analysis of randomized clinical trials comparing open and laparoscopic anti-reflux surgery. *Am J Gastroenterol* 2009; **104**(6):1548-1561.

(35) Draaisma WA, Rijnhart-de Jong HG, Broeders IA, Smout AJ, Furnee EJ, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. *Ann Surg* 2006; **244**(1):34-41.

(36) Yang H, Watson DI, Lally CJ, Devitt PG, Game PA, Jamieson GG. Randomized trial of division versus nondivision of the short gastric vessels during laparoscopic Nissen fundoplication: 10-year outcomes. *Ann Surg* 2008; **247**(1):38-42.

(37) Mardani J, Lundell L, Lonroth H, Dalenback J, Engstrom C. Ten-year results of a randomized clinical trial of laparoscopic total fundoplication with or without division of the short gastric vessels. *Br J Surg* 2008; **96**(1):61-65.

(38) Cai W, Watson DI, Lally CJ, Devitt PG, Game PA, Jamieson GG. Ten-year clinical outcome of a prospective randomized clinical trial of laparoscopic Nissen versus anterior 180 (degrees) partial fundoplication. *Br J Surg* 2008; **95**(12):1501-1505.

(39) Jenkinson AD, Kadirkamanathan SS, Scott SM, Yazaki E, Evans DF. Relationship between symptom response and oesophageal acid exposure after medical and surgical treatment for gastro-oesophageal reflux disease. *Br J Surg* 2004; **91**(11):1460-1465.

(40) Lord RV, Kaminski A, Oberg S, Bowrey DJ, Hagen JA, DeMeester SR et al. Absence of gastroesophageal reflux disease in a majority of patients taking acid suppression medications after Nissen fundoplication. *J Gastrointest Surg* 2002; **6**(1):3-9.

(41) Salminen PT, Hiekkanen HI, Rantala AP, Ovaska JT. Comparison of long-term outcome of laparoscopic and conventional nissen fundoplication: a prospective randomized study with an 11-year follow-up. *Ann Surg* 2007; **246**(2):201-206.

(42) Bais JE, Bartelsman JF, Bonjer HJ, Cuesta MA, Go PM, Klinkenberg-Knol EC et al. Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. *Lancet* 2000; **355**(9199):170-174.

(43) Bloechle C, Mann O, Gawad KA, Izbicki JR. Gastro-oesophageal reflux disease. *Lancet* 2000; **356**(9223):69-3.

(44) Booth M, Dehn TC. Gastro-oesophageal reflux disease. *Lancet* 2000; **356**(9223):70-71.

(45) de Beaux AC, Watson DI, Jamieson GG. Gastro-oesophageal reflux disease. *Lancet* 2000; **356**(9223):71-72.

(46) de Brauw LM, Beets GL. Gastro-oesophageal reflux disease. *Lancet* 2000; **356**(9223):69-70.

(47) Gorecki PJ, Hinder RA. Gastro-oesophageal reflux disease. *Lancet* 2000; **356**(9223):70-73.

(48) Pellegrini CA. Gastro-oesophageal reflux disease. *Lancet* 2000; **356**(9223):71-73.

(49) Watson DI, Baigrie RJ, Jamieson GG. A learning curve for laparoscopic fundoplication. Definable, avoidable, or a waste of time? *Ann Surg* 1996; **224**(2):198-203.

(50) Champault GG, Barrat C, Rozon RC, Rizk N, Catheline JM. The effect of the learning curve on the outcome of laparoscopic treatment for gastroesophageal reflux. *Surg Laparosc Endosc Percutan Tech* 1999; **9**(6):375-381.

(51) Deschamps C, Allen MS, Trastek VF, Johnson JO, Pairolero PC. Early experience and learning curve associated with laparoscopic Nissen fundoplication. *J Thorac Cardiovasc Surg* 1998; **115**(2):281-284.

(52) Soot SJ, Eshraghi N, Farahmand M, Sheppard BC, Deveney CW. Transition from open to laparoscopic fundoplication: the learning curve. *Arch Surg* 1999; **134**(3):278-281.

(53) Voitk A, Joffe J, Alvarez C, Rosenthal G. Factors contributing to laparoscopic failure during the learning curve for laparoscopic Nissen fundoplication in a community hospital. *J Laparoendosc Adv Surg Tech A* 1999; **9**(3):243-248.

(54) TOUPET A. [Technic of esophago-gastroplasty with phrenogastropexy used in radical treatment of hiatal hernias as a supplement to Heller's operation in cardiospasms.]. *Mem Acad Chir (Paris)* 1963; **89**:384-389.

(55) Lundell L, Abrahamsson H, Ruth M, Rydberg L, Lonroth H, Olbe L. Long-term results of a prospective randomized comparison of total fundic wrap (Nissen-Rossetti) or semifundoplication (Toupet) for gastro-oesophageal reflux. *Br J Surg* 1996; **83**(6):830-835.

(56) Thor KB, Silander T. A long-term randomized prospective trial of the Nissen procedure versus a modified Toupet technique. *Ann Surg* 1989; **210**(6):719-724.

(57) Granderath FA, Kamolz T, Granderath UM, Pointner R. Gas-related symptoms after laparoscopic 360 degrees Nissen or 270 degrees Toupet fundoplication in gastrooesophageal reflux disease patients with aerophagia as comorbidity. *Dig Liver Dis* 2007; **39**(4):312-318.

(58) Rydberg L, Ruth M, Lundell L. Mechanism of action of antireflux procedures. *Br J Surg* 1999; **86**(3):405-410.

(59) Eubanks TR, Omelanczuk P, Richards C, Pohl D, Pellegrini CA. Outcomes of laparoscopic antireflux procedures. *Am J Surg* 2000; **179**(5):391-395.

(60) Patti MG, Robinson T, Galvani C, Gorodner MV, Fisichella PM, Way LW. Total fundoplication is superior to partial fundoplication even when esophageal peristalsis is weak. *J Am Coll Surg* 2004; **198**(6):863-869.

(61) Fein M, Bueter M, Thalheimer A, Pachmayr V, Heimbucher J, Freys SM et al. Ten-year outcome of laparoscopic antireflux surgery. *J Gastrointest Surg* 2008; **12**(11):1893-1899.

(62) Farrell TM, Archer SB, Galloway KD, Branum GD, Smith CD, Hunter JG. Heartburn is more likely to recur after Toupet fundoplication than Nissen fundoplication. *Am Surg* 2000; **66**(3):229-236.

(63) Horvath KD, Jobe BA, Herron DM, Swanstrom LL. Laparoscopic Toupet fundoplication is an inadequate procedure for patients with severe reflux disease. *J Gastrointest Surg* 1999; **3**(6):583-591.

(64) Fernando HC, Luketich JD, Christie NA, Ikramuddin S, Schauer PR. Outcomes of laparoscopic Toupet compared to laparoscopic Nissen fundoplication. *Surg Endosc* 2002; **16**(6):905-908.

(65) Dallemagne B, Weerts J, Markiewicz S, Dewandre JM, Wahlen C, Monami B et al. Clinical results of laparoscopic fundoplication at ten years after surgery. *Surg Endosc* 2006; **20**(1):159-165.

(66) Kamolz T, Granderath FA, Bammer T, Wykypiel H, Jr., Pointner R. "Floppy" Nissen vs. Toupet laparoscopic fundoplication: quality of life assessment in a 5-year follow-up (part 2). *Endoscopy* 2002; **34**(11):917-922.

(67) Dor J, Humbert P, Paoli JM, Miorclerc M, Aubert J. [Treatment of reflux by the so-called modified Heller-Nissen technic]. *Presse Med* 1967; **75**(50):2563-2565.

(68) Baigrie RJ, Cullis SN, Ndhluni AJ, Cariem A. Randomized double-blind trial of laparoscopic Nissen fundoplication versus anterior partial fundoplication. *Br J Surg* 2005; **92**(7):819-823.

(69) Khan M, Smythe A, Globe J, Stoddard CJ, Ackroyd R. Randomized controlled trial of laparoscopic anterior versus posterior fundoplication for gastro-oesophageal reflux disease. *Aust NZ J Surg* 2010;in press.

(70) Ludemann R, Watson DI, Jamieson GG, Game PA, Devitt PG. Five-year follow-up of a randomized clinical trial of laparoscopic total versus anterior 180 degrees fundoplication. *Br J Surg* 2005; **92**(2):240-243.

(71) Spence GM, Watson DI, Jamiesion GG, Lally CJ, Devitt PG. Single center prospective randomized trial of laparoscopic Nissen versus anterior 90 degrees fundoplication. *J Gastrointest Surg* 2006; **10**(5):698-705.

(72) Watson DI, Jamieson GG, Pike GK, Davies N, Richardson M, Devitt PG. Prospective randomized double-blind trial between laparoscopic Nissen fundoplication and anterior partial fundoplication. *Br J Surg* 1999; **86**(1):123-130.

(73) Watson DI, Jamieson GG, Lally C, Archer S, Bessell JR, Booth M et al. Multicenter, prospective, double-blind, randomized trial of laparoscopic nissen vs anterior 90 degrees partial fundoplication. *Arch Surg* 2004; **139**(11):1160-1167.

(74) Engstrom C, Lonroth H, Mardani J, Lundell L. An anterior or posterior approach to partial fundoplication? Long-term results of a randomized trial. *World J Surg* 2007; **31**(6):1221-1225.

(75) Hagedorn C, Jonson C, Lonroth H, Ruth M, Thune A, Lundell L. Efficacy of an anterior as compared with a posterior laparoscopic partial fundoplication: results of a randomized, controlled clinical trial. *Ann Surg* 2003; **238**(2):189-196.

(76) Nijjar RS, Watson DI, Jamieson GG, Archer S, Bessell JR, Booth M et al. Five-year follow-up of a multicenter, double-blind randomized clinical trial of laparoscopic Nissen vs anterior 90 degrees partial fundoplication. *Arch Surg* 2010; **145**(6):552-557.

(77) Jobe BA, O'Rourke RW, McMahon BP, Gravesen F, Lorenzo C, Hunter JG et al. Transoral endoscopic fundoplication in the treatment of gastroesophageal reflux disease: the anatomic and physiologic basis for reconstruction of the esophagogastric junction using a novel device. *Ann Surg* 2008; **248**(1):69-76.

(78) Cadiere GB, Buset M, Muls V, Rajan A, Rosch T, Eckardt AJ et al. Antireflux transoral incisionless fundoplication using EsophyX: 12-month results of a prospective multicenter study. *World J Surg* 2008; **32**(8):1676-1688.

(79) Testoni PA, Corsetti M, Di Pietro S, Castellaneta AG, Vailati C, Masci E et al. Effect of transoral incisionless fundoplication on symptoms, PPI use, and ph-impedance refluxes of GERD patients. *World J Surg* 2010; **34**(4):750-757.

(80) Cadiere GB, Rajan A, Germay O, Himpens J. Endoluminal fundoplication by a transoral device for the treatment of GERD: A feasibility study. *Surg Endosc* 2008; **22**(2):333-342.

(81) Cadiere GB, Rajan A, Rqibate M, Germay O, Dapri G, Himpens J et al. Endoluminal fundoplication (ELF)--evolution of EsophyX, a new surgical device for transoral surgery. *Minim Invasive Ther Allied Technol* 2006; **15**(6):348-355.

(82) Bell RC, Freeman KD. Clinical and pH-metric outcomes of transoral esophagogastric fundoplication for the treatment of gastroesophageal reflux disease. *Surg Endosc* 2010;in press.

(83) Hoppo T, Immanuel A, Schuchert M, Dubrava Z, Smith A, Nottle P et al. Transoral incisionless fundoplication 2.0 procedure using EsophyX for gastroesophageal reflux disease. *J Gastrointest Surg* 2010; **14**(12):1895-1901.

(84) Repici A, Fumagalli U, Malesci A, Barbera R, Gambaro C, Rosati R. Endoluminal fundoplication (ELF) for GERD using EsophyX: a 12-month follow-up in a single-center experience. *J Gastrointest Surg* 2010; **14**(1):1-6.

(85) Cadiere GB, Van Sante N, Graves JE, Gawlicka AK, Rajan A. Two-year results of a feasibility study on antireflux transoral incisionless fundoplication using EsophyX. *Surg Endosc* 2009; **23**(5):957-964.

(86) Vela MF, Camacho-Lobato L, Srinivasan R, Tutuian R, Katz PO, Castell DO. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. *Gastroenterology* 2001; **120**(7):1599-1606.

(87) Bredenoord AJ, Weusten BL, Curvers WL, Timmer R, Smout AJ. Determinants of perception of heartburn and regurgitation. *Gut* 2006; **55**(3):313-318.

(88) Sifrim D, Castell D, Dent J, Kahrilas PJ. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. *Gut* 2004; **53**(7):1024-1031.

(89) Castell DO, Vela M. Combined multichannel intraluminal impedance and pH-metry: an evolving technique to measure type and proximal extent of gastroesophageal reflux. *Am J Med* 2001; **111 Suppl 8A**:157S-159S.

(90) Frazzoni M, Conigliaro R, Melotti G. Reflux parameters as modified by laparoscopic fundoplication in 40 patients with heartburn/regurgitation persisting despite PPI therapy. A study using impedance-pH monitoring. *Dig Dis Sci* 2010; **in press**.

(91) Roman S, Poncet G, Serraj I, Zerbib F, Boulez J, Mion F. Characterization of reflux events after fundoplication using combined impedance-pH recording. *Br J Surg* 2007; **94**(1):48-52.

(92) del Genio G, Tolone S, del Genio F, Rossetti G, Brusciano L, Pizza F et al. Total fundoplication controls acid and nonacid reflux: evaluation by pre- and postoperative 24-h pH-multichannel intraluminal impedance. *Surg Endosc* 2008; **22**(11):2518-2523.

(93) Bredenoord AJ, Draaisma WA, Weusten BL, Gooszen HG, Smout AJ. Mechanisms of acid, weakly acidic and gas reflux after anti-reflux surgery. *Gut* 2008; **57**(2):161-166.

(94) Smith D, King NA, Waldron B, Cullen PT, Millar B, Fenwick M et al. Study of belching ability in antireflux surgery patients and normal volunteers. *Br J Surg* 1991; **78**(1):32-35.

(95) Johnsson F, Holloway RH, Ireland AC, Jamieson GG, Dent J. Effect of fundoplication on transient lower oesophageal sphincter relaxation and gas reflux. *Br J Surg* 1997; **84**(5):686-689.

(96) Straathof JW, Ringers J, Lamers CB, Masclee AA. Provocation of transient lower esophageal sphincter relaxations by gastric distension with air. *Am J Gastroenterol* 2001; **96**(8):2317-2323.

(97) Tew S, Ackroyd R, Jamieson GG, Holloway RH. Belching and bloating: facts and fantasy after antireflux surgery. *Br J Surg* 2000; **87**(4):477-481.

(98) Wileman SM, McCann S, Grant AM, Krukowski ZH, Bruce J. Medical versus surgical management for gastro-oesophageal reflux disease (GORD) in adults. *Cochrane Database Syst Rev* 2010;(3):CD003243.

(99) Maeso S, Reza M, Mayol JA, Blasco JA, Guerra M, Andradas E et al. Efficacy of the Da Vinci surgical system in abdominal surgery compared with that of laparoscopy: a systematic review and meta-analysis. *Ann Surg* 2010; **252**(2):254-262.

(100) Wang YR, Dempsey DT, Richter JE. Trends and perioperative outcomes of inpatient antireflux surgery in the United States, 1993-2006. *in press Dis Esophagus* 2010.

17

Summary in Dutch
(Nederlandse samenvatting)

Review committee
Acknowledgements (Dankwoord)
List of publications
Curriculum vitae auctoris

Summary in Dutch (Nederlandse samenvatting)

De slokdarm-maag-overgang is een functionele klep tussen de maag en de slokdarm met een drietal functies (zie figuur 1, hoofdstuk 1). De eerste functie is passage van vloeistoffen en vaste stoffen van de slokdarm naar de maag. Ten tweede zorgt de overgang voor ontluchting van de maag naar de mond (boeren). De derde functie van de slokdarm-maag-overgang is het voorkomen van terugstromen van vloeibare maaginhoud naar de slokdarm (gastro-oesofageale reflux). Deze drie functies lijken elkaar uit te sluiten en vereisen een delicaat evenwicht. Enerzijds resulteert een incompetente overgang in excessieve gastro-oesofageale reflux. Anderzijds leidt een overcompetente overgang tot dysfagie (slikklachten) en het onvermogen te boeren.

Gastro-oesofageale refluxziekte (GORZ) is een chronische ziekte gekenmerkt door symptomen en beschadigingen door het terugstromen van maaginhoud naar de slokdarm. De belangrijkste symptomen van GORZ zijn zuurbranden en regurgitatie (terugstromen van maaginhoud naar de mond) en tien à twintig procent van de Westerse bevolking ervaart deze klachten wekelijks. Naast chronische klachten veroorzaakt GORZ vaak ontsteking van de distale slokdarm (oesofagitis). Zuurremmers zijn de eerstelijns therapie voor patiënten met refluxziekte en bieden afdoende vermindering van refluxklachten bij 95% van de patiënten. Patiënten die onvoldoende baat hebben bij maagzuurremmers,[1-3] niet levenslang maagzuuremmers wensen te gebruiken[1-3] of manifestaties buiten de slokdarm hebben,[4-7] zijn kandidaten voor antirefluxchirurgie. Fundoplicatie (operatie waarbij de top van de maag als een manchet om de slokdarm wordt gehecht, zie figuur 2 tot en met 5, hoofdstuk 1) is de chirurgische behandeling van keuze voor GORZ.

De studies beschreven in dit proefschrift zijn gericht op de huidige chirurgische therapie van GORZ. Het proefschrift beoogt op te helderen welke patiënten baat hebben bij antirefluxchirurgie, de chirurgische benadering en het voorkeurstype fundoplicatie te bepalen en de fysiologische effecten van fundoplicatie te onderzoeken. Het eerste deel onderzocht indicaties voor laparoscopische fundoplicatie (fundoplicatie via kijkoperatie), voorspellers van recidiverende refluxziekte en de invloed van slokdarmperistaltiek op dysfagie na fundoplicatie. Het tweede deel vergeleek de langetermijn-uitkomsten van laparoscopische en conventionele antirefluxchirurgie (fundoplicatie via bovenbuikincisie) en het effect van ervaring van de chirurg op het resultaat. De effectiviteit en de bijwerkingen van

verschillende fundoplicatie-typen werden ook bestudeerd. Het derde deel richtte zich op de fysiologische effecten van fundoplicatie.

Hoofdstuk 1 geeft een algemene introductie in de fysiologie van de slokdarm-maag-overgang en de pathofysiologische achtergrond van GORZ. Daarnaast worden de geschiedenis en huidige rol van antirefluxchirurgie in de behandeling van GORZ beschreven, inclusief de klassieke en potentiële additionele indicaties voor fundoplicatie. Vervolgens worden chirurgische benaderingen en fundoplicatie-typen geïntroduceerd. Tot slot wordt het belang van intraluminale impedantie-metrie (slokdarmmeting waarbij passage van gas en zure en zwak-zure vloeistoffen wordt bestudeerd) voor de evaluatie van fysiologische effecten van antirefluxchirurgie uiteengezet.

Deel I - Indicaties

Kandidaten voor antirefluxchirurgie met oesofagitis bij gastroscopie en/of pathologische liggende reflux met een positieve relatie tussen symptomen en reflux tijdens 24-uurs slokdarm-pH-meting hebben een klassieke indicatie voor antirefluxchirurgie. Gastroscopie is onderdeel van het onderzoek voorafgaand aan antirefluxchirurgie. Hierbij blijkt ongeveer helft van de patiënten erosieve refluxziekte the hebben (ERZ, refluxziekte met oesofagitis) en de andere helft van de patiënten niet-erosieve refluxziekte (NERZ, refluxziekte zonder oesofagitis).[8] Ambulante 24-uurs pH-metrie met symptoom-associatie-analyse is de gouden standaard voor het objectief vaststellen van GORZ indien erosies afwezig zijn.[9] Patiënten kunnen op basis van de lichaamshouding waarin pathologische reflux optreedt tijdens 24-uurs pH-metrie worden ingedeeld in geïsoleerde staande reflux, geïsoleerde liggende reflux en bipositionele reflux.[10] Traditioneel worden patiënten met de twee laatstgenoemde refluxpatronen geschikt geacht voor antirefluxchirurgie.[10;11] Geïsoleerde staande reflux, wordt daarentegen gezien als een minder ernstigere vorm van refluxziekte en daarom wordt deze patiënten chirurgie doorgaans onthouden.[10;11] **Hoofdstuk 2** vergelijkt de verschillen in uitkomsten na fundoplicatie bij patiënten met geïsoleerde staande reflux (*n*=81) ten opzichte van patiënten met geïsoleerde liggende (*n*=55) en bipositionele reflux (*n*=98). Patiënten met geïsoleerde staande reflux en patiënten met geïsoleerde liggende reflux hadden even ernstige objectieve manifestaties van refluxziekte voor operatie en vergelijkbare 5-jaars resultaten. Patiënten met bipositionele reflux hadden echter ernstigere refluxziekte in vergelijking met unipositionele reflux en hadden een hoger percentage recidiverende oesofagitis (respectievelijk 3.5 *vs* 9.4 *vs* 16.0%), recidiverende pathologische zuurexpositie (respectievelijk 10.7 *vs* 18.8

vs 40.9%) en reoperaties (respectievelijk 8.9 *vs* 4.1 *vs* 20.0%). Ondanks deze verschillen in ernst van de ziekte, reageerde alle drie de refluxpatronen op lange termijn gunstig op Nissen fundoplicatie. Derhalve dient het preoperatieve refluxpatroon gebruikt te worden bij het informeren van patiënten met bipositionele reflux ten aanzien van chirurgische uitkomst en niet om af te zien van chirurgie bij patiënten met geïsoleerde staande reflux.

Traditionele kandidaten voor fundoplicatie hebben zowel een pathologische zuurexpositie als een positieve symptoom-reflux-correlatie tijdens 24-uurs pH-metrie. Naar schatting 10-15 procent van de GORZ patiënten heeft echter een fysiologische zuurexpositie.[12] **Hoofdstuk 3** evalueert de 5-jaars resultaten van patiënten met fysiologische zuurexpositie, maar een positieve relatie tussen symptomen en reflux-episoden (zuurovergevoeligheid van de slokdarm).[13] Het resultaat van antirefluxchirurgie bij deze patiënten (*n*=28) werd direct vergeleken met een controlegroep die bestond uit patiënten met pathologische zuurexpositie en positieve symptoom-reflux-associatie (*n*=126). Subjectieve en objectieve resultaten en het aantal reoperaties waren niet verschillend. Derhalve werd aannemelijk gemaakt dat patiënten met zuurovergevoeligheid van de slokdarm evenveel baat hebben bij Nissen fundoplicatie als patiënten met pathologische zuurexpositie.

Bij meer dan de helft van de patiënten met pathologische zuurexpositie ontbreekt een positieve associatie tussen symptomen en reflux-episoden tijdens 24-uurs pH-metrie.[14] In **hoofdstuk 4** wordt de invloed van symptoom-reflux-associatie op de langetermijn-resultaten van Nissen fundoplicatie vastgesteld. Subjectieve resultaten en objectieve refluxcontrole van patiënten met pathologische zuurexpositie waren vergelijkbaar voor patiënten met een positieve (*n*=109) en negatieve symptoom-reflux-correlatie (*n*=29). Deze resultaten lijken in tegenspraak met de conclusie van hoofdstuk 3, waarin wordt geconcludeerd dat patiënten met fysiologische zuurexpositie en een positieve symptoom-associatie baat hebben bij antirefluxchirurgie, in tegenstelling tot patiënten met een fysiologische zuurexpositie en een negatieve symptoom-associatie. Deze ogenschijnlijke contradictie kan verklaard worden door de hoge positief voorspellende waarde en lage negatief voorspellende waarde van symptoom-reflux-correlatiescores.[15] Daarom werd geconcludeerd dat patiënten met een pathologische zuurexpositie baat hebben bij fundoplicatie, ongeacht de aanwezigheid van een positieve of negatieve symptoom-reflux-correlatie.

Tot voor kort werd NERZ gezien als een mildere vorm van GORZ en beschouwd als een relatieve contra-indicatie voor fundoplicatie. Eind jaren negentig toonden studies echter aan dat de kwaliteit van leven en ernst van symptomen vergelijkbaar zijn voor patiënten met NERZ en ERZ.[16-19] Bovendien is aangetoond dat medicamenteuze therapie minder effectief is bij NERZ patiënten,[16;20-23] wat een grotere rol voor antirefluxchirurgie zou impliceren. **Hoofdstuk 5** vergelijkt daarom preoperatieve refluxparameters en langetermijn-resultaten van Nissen fundoplicatie bij NERZ en ERZ. Preoperatieve refluxpatronen waren vergelijkbaar in de twee groepen. De subjectieve en objectieve resultaten na fundoplicatie en het aantal reoperaties waren ook vergelijkbaar. Op basis hiervan werd geconcludeerd dat afwezigheid van slokdarmerosies bij gastroscopie bij kandidaten voor antirefluxchirurgie met een pathologische zuurexpositie, geen reden is om af te zien van fundoplicatie.

Recidiverende refluxziekte en dysfagie zijn de belangrijkste indicaties voor reïnterventie na fundoplicatie. In 2009 rapporteerde een systematisch review naar voorspellers van het resultaat van fundoplicatie dat de kwaliteit en consistentie van vorige studies varieert. Daarom werd geconcludeerd dat studies met betere methodologie noodzakelijk zijn. **Hoofdstuk 6** beschrijft een studie die de methodologische aanbevelingen van het review heeft opgevolgd en voorspellers van recidiverende refluxziekte na fundoplicatie heeft vastgesteld. Multivariate binaire logistische regressie toonde aan dat zwakke slokdarmperistaltiek (odds ratio per cent 0.97 [0.95- 0.99]; P = 0.004) of excessieve liggende zuurexpositie (odds ratio per cent 1.03 [1.00-1.07]; P = 0.025) onafhankelijke voorspellers zijn van recidiverende pathologische zuurexpositie. Excessieve liggende zuurexpositie was ook een onafhankelijke voorspeller van reoperatie voor recidiverende refluxziekte (odds ratio per cent 1.05 [1.01-1.08]; P = 0.006). Gezien het feit dat fundoplicatie waarschijnlijk de grootste winst kan behalen bij patiënten met excessieve liggende zuurexpositie, zou antirefluxchirurgie deze groep niet onthouden moeten worden. Chirurgie moet echter gelimiteerd worden in deze groep, aangezien de helft van de patiënten met beide voorspellers recidiverende pathologische zuurexpositie ontwikkelt.

Patiënten met zwakke slokdarmperistaltiek vóór operatie worden vaak verondersteld een hogere kans te hebben om dysfagie te ontwikkelen na fundoplicatie.[24-27] Daarom raadden veel centra deze patiënten een fundoplicatie “op maat” aan, waarbij van een partiële in plaats van een totale fundoplicatie wordt verricht.[25] Twee gerandomiseerde klinische onderzoeken (RCTs) hebben echter niet kunnen aantonen dat het resultaat van fundoplicatie slechter is bij patiënten

met een zwakke slokdarmperistaltiek, dan bij patiënten met een normale slokdarmperistaltiek.[28;29] **Hoofdstuk 7** beschrijft de resultaten van de grootste cohort studie die de invloed van preoperatieve slokdarmperistaltiek op de incidentie van dysfagie na fundoplicatie onderzoekt. De deze studie toonde aan dat preoperatieve peristaltiek bij standaard manometrie (drukmeting van de slokdarm) geen invloed had op postoperatieve dysfagiescores en dilataties (oprekking ter behandeling van slikklachten) en reoperaties voor dysfagie. Daarom werd geconcludeerd dat een fundoplicatie "op maat" op basis van preoperatieve peristaltiek waarschijnlijk niet noodzakelijk is.

Deel II - Technieken

In 1956, verrichtte Rudolph Nissen de eerste fundoplicatie voor GORZ[30] na zijn ***serendipistische*** ontdekking van het antireflux-effect van een totale manchet waarbij de top van de maag over 360° achter de slokdarm langs wordt geplaatst (figuur 3, hoofdstuk 1).[31] Na de eerste beschrijving van laparoscopische Nissen fundoplicatie (LNF, Nissen fundoplicatie via kijkoperatie) heeft deze benadering de conventionele Nissen fundoplicatie (CNF, Nissen fundoplicatie via bovenbuikincisie) snel vervangen, ondanks het feit dat bewijs voor equivalentie destijds ontbrak.[32] Vervolgstudies hebben de kortetermijn-voordelen van LNF ten opzichte van CNF aangetoond, zoals reductie van ziekenhuiscomplicaties, opnameduur en ziekteverlof,[33;34] met een vergelijkbare refluxcontrole na 5 jaar.[35] Maar bevestiging van de superioriteit van LNF ten aanzien van effectiviteit of reoperatie percentage door niveau 1 bewijs ontbreekt. In **hoofdstuk 8** beschrijven wij de 10-jaars resultaten van een RCT die CNF (n=69) en LNF (n=79) vergelijkt. Er waren geen verschillen in langetermijn-refluxcontrole en patiënt tevredenheid. Na CNF ondergingen echter tweemaal zoveel patiënten reoperatie dan na LNF (24 [34.8%] *vs* 12 [15.2%]; P = 0.006), inclusief een hoger aantal littekenbreukcorrecties (9 *vs* 2; P = 0.015). Correctie van een littekenbreuk van een bovenbuikincisie vergt hospitalisatie en heeft een hoog recidiefrisico. Deze studie is de eerste RCT die aantoont dat, bij niet-obese patiënten, laparoscopische operatie de incidentie van littekenbreuken en het aantal littekenbreuken vermindert in vergelijking met bovenbuikincisie. In lijn met de 10-jaars resultaten van andere grote RCTs,[36-38] nam het aantal patiënten dat zuurremmers gebruikte in beide groepen langzaam toe in de tijd. Echter tweederde van de patiënten die zuurremmers gebruikten na 10 jaar, had geen recidiverende zure of niet-zure reflux bij pH-impedantie-meting. Deze bevinding bevestigt eerdere studies die concludeerden dat slechts een klein deel van de patiënten die postoperatief zuurremmers gebruiken, abnormale zuurexpositie hebben tijdens 24-uurs pH-

metrie[35;39;40] of ontmanteling van de fundoplicatie bij gastroscopie.[41] De hypothese tijdens de introductie van LNF - een lager aantal reoperaties voor littekenbreuken en gelijk effectiviteit - wordt sterk ondersteund door deze studie en dit onderzoek levert niveau 1 bewijs voor het gebruik van laparoscopische antirefluxchirurgie als chirurgische benadering van keuze voor GORZ.

De kortetermijn-resultaten van deze RCT[42] riepen vragen op ten aanzien van het effect van ervaring van de chirurg op de resultaten van laparoscopische antirefluxchirurgie.[43-48] In **hoofdstuk 9** onderzoeken we de invloed van ervaring van de chirurg op de langetermijn-resultaten van LNF. De 5-jaars resultaten van de CNF (*n*=74) en LNF (*n*=93) arm van het onderzoek werden vergeleken met de 5-jaars resultaten van een vervolgcohortstudie (*n*=121) die werd verricht nadat de leercurve was verlengd van minimaal 5 LNFs[49] tot minimaal 30 LNFs per chirurg, in lijn met nieuwe inzichten.[50-53] Operatieduur, complicaties, hospitalisatie, vroege dysfagie, dilataties voor dysfagie en het aantal vroege reoperaties, verbeterden significant met ervaring van de chirurg. De kortetermijn-refluxcontrole en klinische uitkomst na 5 jaar verbeterden echter niet met ervaring. In ervaren handen reduceert LNF ziekenhuiscomplicaties en hospitalisatie in vergelijking met CNF, met vergelijkbare 5-jaars effectiviteit en aantal reoperaties. Derhalve concludeerden wij dat deze analyse het effect van ervaring op de kortetermijn-resultaten van laparoscopische antirefluxchirurgie duidelijk illustreert en pleit voor centralisatie van expertise.

De slokdarm-maag-overgang dient zorg te dragen voor passage van vloeibare en vaste stoffen van de slokdarm naar de maag, ontluchting van gas van de maag naar de mond en preventie van het terugstromen van vloeibare maaginhoud naar de slokdarm. Het doel van antirefluxchirurgie is het herstellen van de derde functie, zonder de eerste twee mechanismen te beperken. Derhalve zou de ideale antirefluxoperatie langetermijn-refluxcontrole bieden, met minimale postoperatieve dysfagie en gasgerelateerde symptomen. LNF herstelt de antirefluxbarrière, met excellente 10-jaars refluxcontrole. De ingreep resulteert echter in een overcompetente klep, die de twee andere functies van de slokdarm-maag-overgang neigt te beperken. De belangrijkste bijwerkingen van LNF zijn derhalve dysfagie en gasgerelateerde symptomen die veroorzaakt worden door het onvermogen lucht te ventileren vanuit de maag (onvermogen te boeren).

In 1963 stelde André Toupet een partiële posterieure fundoplicatie (gedeeltelijke fundoplicatie waarbij de top van de maag over 270° achter de slokdarm langs wordt geplaatst) voor ter behandeling van GORZ, in een poging klachten na

fundoplicatie te verminderen (figuur 4, hoofdstuk 1).[54] Enkele studies hebben bevestigd dat Toupet fundoplicatie de prevalentie van postoperatieve dysfagie[55;56] en gasgerelateerde symptomen vermindert.[57;58] Ondanks deze potentiële voordelen, is laparoscopische Toupet fundoplicatie (LTF) geen gemeengoed, waarschijnlijk omdat ongecontroleerde studies minder effectieve refluxcontrole in vergelijking met LNF hebben gerapporteerd.[59-66] **Hoofdstuk 10** beschrijft een systematisch review en meta-analyse van zeven RCTs die LNF (*n*=404) vergelijken met LTF (*n*=338). Deze meta-analyse heeft aangetoond dat de prevalentie van postoperatieve dysfagie, dilataties en reoperaties voor dysfagie na LNF hoger is. De prevalentie van onvermogen te boeren en een opgeblazen gevoel waren ook hoger na LNF, met een gelijke subjectieve en objectieve refluxcontrole. Deze resultaten bieden niveau 1a steun voor het gebruik van LTF als de posterieure fundoplicatie van keuze voor GORZ.

In 1967 introduceerde Jacques Dor anterieure partiële fundoplicatie (gedeeltelijke fundoplicatie waarbij de top van de maag over 90° of 180° voor de slokdarm langs wordt geplaatst) om de hoge prevalentie van post-fundoplicatie-symptomen na Nissen fundoplicatie terug te dringen (figuur 5, hoofdstuk 1).[67] Laparoscopische anterieure fundoplicatie (LAF) is voorgesteld als een alternatieve operatie om postoperatieve symptomen te reduceren. Sindsdien hebben verschillende RCTs bevestigd dat LAF dysfagie[68-73] en gasgerelateerde symptomen[70;71;73] vermindert, in vergelijking met posterieure fundoplicatie. Enkele RCTs suggereren dat hier een hoger risico op recidiverende reflux tegenoverstaat,[68;69;71;73-76] hoewel andere RCTs vergelijkbare refluxcontrole rapporteren.[38;70;72] **Hoofdstuk 11** is een systematisch review en meta-analyse van zeven RCTs die de resultaten van 90°, 120° en 180° LAF (*n*=345) heeft samengevoegd en vergeleken met de samengevoegde resultaten van 180°, 200° en 360° posterieure fundoplicatie (*n*=338). De totale zuurexpositie tijd en de prevalentie van zuurbranden waren hoger na LAF. Op korte termijn werd dit afgewogen tegen minder dysfagie. Dysfagiescores werden echter vergelijkbaar op lange termijn, met een blijvend hogere prevalentie van zuurbranden en gebruik van zuurremmers na LAF. Het aantal reoperaties was ook tweemaal zo hoog na LAF, voornamelijk door reoperaties voor recidiverende refluxziekte. Wij concluderen daarom dat de samengevoegde resultaten van posterieure fundoplicatie superieure refluxcontrole bieden in vergelijking met de samengevoegde resultaten van anterieure fundoplicatie, met gelijke langetermijn-dysfagiescores.

De meta-analyse van hoofdstuk 11 heeft 90°, 120° en 180° LAF samengevoegd en vergeleken met de resultaten van 180°, 200° en 360° posterieure fundoplicatie. De

studie die in **hoofdstuk 12** wordt beschreven heeft de twee meest toegepaste anterieure fundoplicatie-typen gestratificeerd en vergeleken met de resultaten van de meest frequent uitgevoerde posterieure fundoplicatie, om potentiële verschillen tussen de anterieure fundoplicatie-typen te identificeren. Daarom stratificeerde de studie de 90° en 180° LAF groep en vergeleek deze fundoplicatie-typen uitsluitend met LNF. Wij evalueerden de originele 5-jaars resultaten van twee RCTs die 90° LAF met LNF vergeleken en twee RCTs die 180° LAF *versus* LNF randomiseerden. De studie was een gerandomiseerde vergelijking van 90° LAF (*n*=90) *versus* LNF (*n*=82*)* en 180° LAF (*n*=121) *versus* LNF (*n*=132). Er waren geen significante verschillen in het aantal reoperaties en dilataties gedurende de follow-up periode tussen 90° en 180° LAF *versus* LNF. Na vijf jaar resulteerde 90° en 180° LAF in een vergelijkbare reductie van dysfagie en gasgerelateerde symptomen ten opzichte van LNF. Controle van refluxsymptomen was minder goed na 90° LAF, maar gelijk na 180° LAF en LNF. Samenvattend bracht stratificatie aan het licht dat 180° LAF duurzame controle van refluxsymptomen geeft, met minimale post-fundoplicatie-symptomen. Daarentegen is refluxcontrole na 90° LAF minder goed dan na LNF en heeft LNF meer bijwerkingen dan 180° LAF.

Onlangs is endoluminale fundoplicatie (fundoplicatie vanuit de binnenkant van de maag) met behulp van het EsophyX® apparaat voorgesteld als een minder invasief, gastroscopisch alternatief voor laparoscopische fundoplicatie. De anatomische en fysiologische resultaten van endoluminale fundoplicatie zijn veelbelovend.[77] Echter, de kortetermijn-resultaten van klinische studies hebben aangetoond dat ongeveer de helft van de patiënten recidiverende pathologische zuurexpositie[78-84] en persisterende oesofagitis heeft[78;80;85] na endoluminale fundoplicatie. Laparoscopische fundoplicatie is het laatste redmiddel voor patiënten met recidiverende refluxklachten die niet reageren op zuurremmers na endoluminale fundoplicatie. De uitkomst van laparoscopische fundoplicatie na voorafgaande endoluminale fundoplicatie wordt beschreven in **hoofdstuk 13**. Subjectieve en objectieve refluxcontrole van LNF na mislukte endoluminale therapie zijn adequaat. Voorafgaande endoluminale therapie heeft echter een hoog risico op maagperforatie tijdens LNF (27%) en dysfagie na fundoplicatie.

Deel III – Fysiologische effecten

Het is noodzakelijk de fysiologische effecten van antirefluxchirurgie te evalueren om de werkingsmechanismen van fundoplicatie en de verschillen in refluxcontrole en post-fundoplicatie-symptomen tussen verschillende fundoplicatie-typen te

begrijpen. Ten aanzien van refluxcontrole hebben eerdere studies bewezen dat zwak-zure reflux GORZ symptomen kan veroorzaken[86] en dat de proximale uitbreiding bepaalt of een patiënt een reflux-episode als symptoom ervaart.[87] 24-uurs gecombineerde pH-impedantie-meting van de slokdarm speelt een bijzondere rol in de evaluatie van de fysiologische effecten van fundoplicatie, aangezien dit onderzoek zowel zure reflux, zwak-zure reflux[88] als proximale uitbreiding kan bepalen.[89] Het is controversieel of fundoplicatie met name zure reflux vermindert en dat persisterende zwak-zure reflux postoperatieve refluxsymptomen veroorzaakt,[90;91] of dat zure en zwak-zure reflux vergelijkbaar worden gereduceerd.[92;93] Ten aanzien van gasgerelateerde symptomen is het effect van fundoplicatie alleen indirect bestudeerd middels metingen van volumes van opgeboerd gas[94] of manometrische evaluatie.[58;95-97] Het was onduidelijk waarom patiënten na fundoplicatie vaak rapporteren te kunnen boeren, terwijl gastrische boeren (maagboeren) afwezig zijn bij manometrie.[95;97]

De studie beschreven in **hoofdstuk 14** evalueert het effect van LNF op reflux en boeren tijdens 24-uurs pH-impedantie-metrie. LNF controleerde zure en zwak-zure vergelijkbaar na zes maanden, maar de reductie van gasvormige reflux was kleiner. Persisterende refluxsymptomen werden niet veroorzaakt door zure noch zwak-zure reflux. De resultaten toonden aan de LNF het boerpatroon wijzigt door het reduceren van gastrische boeren (ontluchting van gas vanuit de maag; 68.5 → 23.9; $P < 0.001$) en toename van slokdarmboeren (geen ontluchting van gas vanuit de maag; 20.8 → 46.0; $P = 0.036$). Dit verklaart de toename van boeren die door sommige patiënten na LNF wordt ervaren, ondanks de reductie van gastrisch boeren. Reductie van gastrische boeren na LNF doet een opgeblazen gevoel en flatulentie toenemen. Daarom werd gehypothetiseerd dat het opgeblazen gevoel geïnduceerd door de vermindering van gastrisch boeren na LNF, patiënten aanzet tot het actief verhogen van het aantal slokdarmboeren, in een vergeefse poging lucht te ventileren vanuit de maag.

De resultaten van de meta-analyse beschreven in hoofdstuk 10 tonen aan dat LTF een vergelijkbare refluxcontrole biedt als LNF, met minder dysfagie en gasgerelateerde symptomen. Derhalve werd in hoofdstuk 15 gehypothetiseerd dat LTF en LNF vergelijkbaar zure en zwak-zure reflux verminderen en dat LTF gastrische boeren minder reduceert dan LNF. Het effect van LTF en LNF op gastrische boeren is eerder onderzocht, maar deze studies waren beperkt tot evaluatie middels manometrie en rapporteerden tegenstrijdige resultaten.[58;96] Om de hypothese te toetsen werd pH-impedantie-metrie toegepast om het effect van LTF (n=14) op refluxkarakteristieken en boeren te vergelijken met een congruente

LNF groep (*n*=28). Na 6 maanden veranderden zowel LTF als LNF het boerpatroon door reductie van gastrische boeren (ontluchting van gas vanuit de maag) en toename van slokdarmboeren (geen ontluchting van gas vanuit de maag). Gasvormige reflux en gastrische boeren werden echter minder gereduceerd na LTF, wat resulteerde in meer ontluchting van gas vanuit de maag en minder opgeblazen gevoel en flatulentie, terwijl een vergelijkbare inhibitie van reflux werd bewerkstelligd op korte termijn. Deze resultaten leveren de fysiologische rationale voor de klinische bevindingen van de meta-analyse en ondersteunen de conclusie dat LTF de posterieure fundoplicatie van keuze is.

Naschrift

Het onderzoek beschreven in dit proefschrift heeft opgehelderd welke patiënten baat hebben bij antirefluxchirurgie en er werd geconcludeerd dat de indicaties voor fundoplicatie kunnen worden uitgebreid. Er werd aangetoond dat laparoscopische antirefluxchirurgie de chirurgische benadering van keuze is. Partiële laparoscopische fundoplicatie, ofwel LTF dan wel 180° LAF, reduceert dysfagie en gasgerelateerde symptomen, met gelijke refluxcontrole ten opzichte van LNF. Bovendien gaf het onderzoek geen ondersteuning voor een fundoplicatie “op maat” op basis van preoperatieve slokdarmperistaltiek. Deze resultaten leveren niveau 1 bewijs voor een partiële fundoplicatie via kijkoperatie als de chirurgische behandeling van keuze voor refluxziekte. Momenteel wordt een RCT uitgevoerd in Adelaide, Australië om het finale antwoord te geven op de vraag of LTF dan wel 180° LAF gezien moet worden als chirurgische therapie van keuze voor GORZ.

Referenties

Vide pagina 322

Review committee

Prof.dr. Y. van der Graaf
Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht
Utrecht, the Netherlands

Prof.dr. P.D. Siersema
Department Gastroenterology and Hepatology
University Medical Center Utrecht
Utrecht, the Netherlands

Prof.dr. D.C. van der Zee
Department of Paediatric Surgery
Wilhelmina Children's Hospital, University Medical Center Utrecht
Utrecht, the Netherlands

Prof.dr. H.W. Tilanus
Department of Surgery
Erasmus Medical Center
Rotterdam, the Netherlands

Dr. L.P.S. Stassen
Department of Surgery
Maastricht University Medical Center
Maastricht, the Netherlands

Further member of the review committee
Prof.dr. G.G. Jamieson
Discipline of Surgery
Royal Adelaide Hospital
Adelaide, Australia

Acknowledgements (Dankwoord)

Hierbij wil ik eenieder danken die heeft bijgedragen aan de totstandkoming van dit proefschrift. De volgende personen verdienen een speciaal woord van dank:

De promotiecommissie

Prof.dr. HG Gooszen, geachte promotor, beste professor, dit proefschrift is voortgekomen uit uw email aan Werner Draaisma in mijn vierde studiejaar. In minder dan tien woorden beschreef u de hypothese van de eerste studie van dit proefschrift en verzocht u hem dit project te begeleiden. Dit illustreert uw vermogen om het schip met minimale bijsturing op koers te houden. Vroeg in mijn promotietraject heeft u mij gedegen studies toevertrouwd die een stevige basis voor dit proefschrift vormden. Het is een eer om deel uit te maken van de groep promovendi die onder uw hoede hun proefschrift hebben geschreven.

Prof.dr. AJPM Smout, geachte promotor, beste André, jij bent vanaf de eerste studie bij mijn proefschrift betrokken. Jouw kennis en faam op het gebied van de fysiologie van de refluxziekte zijn met name in het tweede deel van dit proefschrift onmisbaar gebleken. Het is buitengewoon dat je contacten in Adelaide hebben geleid tot een fantastisch jaar in Australië, waardoor mijn leven is veranderd.

Dr. WA Draaisma, beste Werner, net voordat jijzelf promoveerde, begon je met het begeleiden van mijn wetenschappelijk onderzoek. Het is uniek dat ik door jouw uitgevoerde studies heb mogen voorzetten en daarmee in je voetsporen ben getreden. Het onderzoek is beter geworden door ons getouwtrek in de afgelopen jaren.

Dr. EJ Hazebroek, beste Eric, de kennis over partiële fundoplicatie die jij vanuit Australië naar Utrecht bracht, heeft dit proefschrift een nieuwe impuls gegeven. Voorafgaand aan jouw komst werd in Utrecht standaard een totale fundoplicatie verricht, maar op basis van ons onderzoek heeft partiële fundoplicatie een belangrijke plaats in de chirurgische behandeling van refluxziekte gekregen.

De leden van de beoordelingscommissie: dank voor uw interesse in dit proefschrift.

De onderzoeksgroep

Prof.dr. IAMJ Broeders, beste Ivo, toen wij elkaar voor het eerste ontmoetten in mijn vijfde studiejaar, was je van mening dat het tijd werd dat onze naam beter vertegenwoordigd zou worden in de chirurgie. Daarna zijn we samen uitgevaren, maar op volle zee bleken er inderdaad teveel kapiteins en ook teveel schepen te zijn. Ik waardeer het zeer dat je betrokken bent gebleven en vanaf de wal het schip naar een veilige haven hebt geloodst. Goede stuurlui aan wal blijken belangrijker dan het spreekwoord doet vermoeden!

Dr. AJ Bredenoord, beste Arjan, mijn wetenschappelijk denken is door jou geprikkeld en aan jouw keukentafel heb je me de interpretatie van hoge-resolutie manometrie en impedantiemetingen bijgebracht.

Ir. HG Rijnhart-de Jong, beste Hilda, jij hebt me het gebruik van door jouw verzamelde data gegund. Pas toen ik in andere datacentres keek, realiseerde ik me hoe zorgvuldig jij de Utrechtse fundoplicatie patiënten volgt.

DJHG Roks, beste David, tijdens jouw geneeskunde studie hebben we samen drie hoofdstukken van dit proefschrift geschreven. We hebben zowel in als buiten het ziekenhuis een fantastische tijd gehad in Adelaide. Jij kan hard werken èn Bourgondisch genieten. Dank voor het 'paranimfen'.

Drs. U Ahmed Ali, beste Usama, jouw epidemiologische expertise was essentieel voor de methodologie van de meta-analyses. Daar ben ik je erg dankbaar voor.

Dr. EJB Furnée, beste Edgar, het was waardevol dat wij gelijktijdig promotieonderzoek deden naar antirefluxchirugie. We wisten elkaar te vinden.

Dr. DR de Vries, beste Durk, hartelijk dank voor je hulp bij mijn prille onderzoek.

EABJ Broeders, zusje, het zegt genoeg dat wij het beiden wel zagen zitten dat jij drie maanden onderzoek voor mij zou komen doen in Australië. Je hebt je project met glans afgerond en ik kijk uit naar de eerste Broeders, Broeders publicatie! Dat jij in het kleine bekken wil gaan opereren, zij je vergeven.

Drs. FA Mauritz, beste Femke, ik ben trots dat jouw wetenschappelijke stage bij mij, heeft geresulteerd in promotieonderzoek naar antirefluxchirurgie bij kinderen.

IG Sportel, beste Irene, door inzet, inzicht en humor heb je ruim 2000 Australische fundoplicatie patiënten geanalyseerd. Je kan trots zijn op het eindresultaat.

J Oors en J van de Scheur, Beste Jac. en Joke, jullie hebben de slokdarmmetingen verricht voor alle Nederlandse patiënten beschreven in dit proefschrift. Ik wil jullie met name bedanken voor de extra patiënten die jullie hebben gemeten voor de Manchet studie en de impedantie studies. Jullie vonden altijd wel een oplossing!

Drs. RK Stellato, beste Rebecca, hartelijk dank voor je gedegen statistisch advies.

Prof.dr. LMA Akkermans, Dr. MGH Besselink, Dr. HC van Santvoort, drs. OJ Bakker en Dr. WR Renooij: als "reflux-wees" mocht ik zo nu en dan het wekelijkse overleg van de pancreatitis werkgroep verstoren. Hartelijk dank voor jullie ideeën en commentaren ten aanzien van mijn studies.

Verder wil ik de onderstaande co-auteurs danken voor hun hulp:
Prof.dr. JJB van Lanschot, Drs. PJJ van Rijn, Dr. MP Schwartz, Dr. ALM Vlek, Dr. JP Ruurda, Drs. RS Nijjar, Drs. N Granchi.

Mede-promovendi van de afdeling Heelkunde en Maag-, Darm-, en Leverziekten: dank voor de goede sfeer.

The Adelaide research group
Prof.dr. GG Jamieson, *father* of oesophageal surgery in Australia. It is an honour that you have agreed to be a member of the 'review committee' of this thesis. I am looking forward to picking grapes at Mosquito Hill and coming back to Adelaide to work for your group. It is very special to be part of the Eleanor Harrald family.

Prof.dr. DI Watson, dear professor, you have trusted me with high-quality randomised trials and provided quick revisions. I have enjoyed working for you and hope that I will have the privilege to continue this collaboration in the future.

Associate Professor PG Devitt, dear professor, your sharp questions and classical music in the hallway kept me focussed. Thanks for supervising Emily's internship.

Prof.dr. RH Holloway, dear professor, thank you for accommodating my research in your Gut Function Laboratory. It is a pleasant research environment.

Drs. SK Thompson, dear Sarah, we are two of a kind and we work well together. Thank you for your critical opinion and for sharing your insight into upper GI surgery in Australia.

Drs. RJ Baigrie, dear Robert, thanks for sharing the results of your Cape Town trial.

JC Myers, dear Jenny, thank you for providing the data for our manometry study.
M Tippett, dear Marcus, thank you for sharing your knowledge of manometries with Irene and myself.

L Smith, dear Lorelle, thank you for teaching the Dutch students how to work with the Adelaide database and providing the follow-up of the trail patients.

Vrienden en familie

Martijn Verhagen, het afgelopen decennium hebben wij studie, cultuur en sport op een fantastische manier gecombineerd! Het siert je dat je het zo regelde dat je kan 'paranimfen'. Dat jij boven de schedelbasis gaat opereren, zij je vergeven.

Ivo Verhagen, het is gewaagd om een patiënt tijdens een craniotomie bloot te stellen aan twee vijfdejaars scholieren. Sinds die dag ambieer ik een chirurgisch vak.

Sailay Siddiqi en Wouter Hazen, vanaf ons tweede studiejaar hebben wij elkaar wetenschappelijk uitgedaagd. Dat jullie respectievelijk aan de verkeerde kant van het diafragma en endoscopisch gaan opereren, zij jullie vergeven.

De heren van Inter Pares: voor tijden van "drank en gezang".

Wintersportvrienden Joep v.d. Leeuw, Bart v.d. Munckhof en Gerbrand Zoet.

Zeilvrienden van de Utrechtse Studentenzeilvereniging Histos.

Sjoerd Nauta, een proefschrift schrijven is als onze tocht naar Spitsbergen: vlakke zeeën maken geen goede schippers. Ik hoop dat we samen nog veel mooie zeiltochten mogen maken.

Gerard, Marie-José, Nicole en Suzanne Berkelmans: het was fantastisch om 'parttime' bij jullie op te groeien.

Chris, Alan and Grace Whyatt: it is great to have a second home “down under”.

Dear Holly, you have fully supported me during the process of writing this thesis. The waves have built up during the past year, but I am very happy that we kept right on course! You are the love of my dreams and our trip to Europe will only be the start of what lies on the horizon for us.

Vader en moeder, de combinatie van geneeskunde en onderwijskunde is me met de paplepel ingegeven en resulteerde in mijn eerste academische stappen in de geneeskunde. Daarom draag ik dit proefschrift aan jullie op. Het afgelopen jaar ontwikkelde zich een ogenschijnlijke paradox, waarbij vergroting van de afstand leidde tot intensiever contact. Dank voor jullie onvoorwaardelijke ondersteuning van mijn beslissingen.

List of relevant publications

1. Broeders JA, Draaisma WA, Bredenoord AJ, de Vries DR, Smout AJ, Gooszen HG. The preoperative reflux pattern as prognostic indicator for long-term outcome after Nissen fundoplication.
American Journal of Gastroenterology 2009; 104(8):1922-30.

2 Broeders JA, Draaisma WA, Bredenoord AJ, de Vries DR, Rijnhart-de Jong HG, Smout AJ,Gooszen HG. Oesophageal acid hypersensitivity is not a contraindication to Nissen fundoplication.
British Journal of Surgery 2009; 96(9):1023-30.

3. Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. Ten-year outcome of laparoscopic and conventional Nissen fundoplication: randomized clinical trial.
Annals of Surgery 2009; 250(5):698-706.

4. Broeders JA, Draaisma WA, Bredenoord AJ, Smout AJ, Broeders IA, Gooszen HG. Long-term outcome of Nissen fundoplication in non-erosive and erosive gastro-oesophageal reflux disease.
British Journal of Surgery; 2010;97(6):845-52.

5. Broeders JA, Mauritz FA, Ahmed Ali U, Draaisma WA, Ruurda JP, Gooszen HG, Smout AJ, Broeders IA, Hazebroek EJ. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) *versus* Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease.
British Journal of Surgery;2010; 97(9):1318-30.
British Journal of Surgery; 2011; 98(2):316; author reply 316-7.

6. Broeders JA, Draaisma WA, Bredenoord AJ, Smout AJ, Broeders IA, Gooszen HG. The impact of symptom-reflux association analysis on long-term outcome after Nissen fundoplication.
British Journal of Surgery 2011; 98(2):247-54.

7. Broeders JA, Draaisma WA, Rijnhart-de Jong HG, Smout AJ, van Lanschot JJ, Broeders IA, Gooszen HG. Impact of surgeon experience on 5-year outcome of laparoscopic Nissen fundoplication.
Archives of Surgery 2011; 146(3):340-6.

8. Broeders JA, Roks DJ, Draaisma WA, Hazebroek EJ, Broeders IA, Smout AJ. Predictors of objectively identified recurrent reflux after primary Nissen fundoplication.
British Journal of Surgery 2011; Epub.

9. Broeders JA, Roks DJ, Ahmed Ali U, Draaisma WA, Smout AJ, Hazebroek EJ. Systematic review and meta-analysis of randomised clinical trials comparing laparoscopic anterior versus posterior fundoplication for gastro-oesophageal reflux disease.
Annals of Surgery 2011; in press.

10. Broeders JA, Bredenoord AJ, Hazebroek EJ, Broeders IA, Gooszen HG, Smout AJ. Effects of anti-reflux surgery on weakly acidic reflux and belching.
Gut 2011; Epub.

11. Broeders JA, Bredenoord AJ, Hazebroek EJ, Broeders IA, Gooszen HG, Smout AJ. Reflux and belching after laparoscopic Toupet versus Nissen fundoplication.
Annals of Surgery; revision.

12. Broeders JA, Sportel IG, Jamieson GG, Nijjar RS, Granchi N, Myers JC, Thompson SK. Impact of ineffective oesophageal motility and wrap circumference on dysphagia after laparoscopic fundoplication.
British Journal of Surgery 2011; in press.

13. Broeders JA, Roks DJ, Jamieson GG, Devit PG, Baigrie RJ, Watson DI. Five-year outcome after laparoscopic anterior partial *versus* Nissen fundoplication: 4 randomized trials.
Submitted.

14. Broeders JA, Mauritz FA, Ahmed Ali U, Draaisma WA, Ruurda JP, Gooszen HG, Smout AJ, Broeders IA, Hazebroek EJ. Systematische review en meta-analyse van laparoscopische Nissen (posterieure totale) *versus* Toupet (posterieure partiële) fundoplicatie voor gastro-oesofageale refluxziekte.
Nederlands Tijdschrift voor Heelkunde 2011; in press.

15. Furnée EJ, Broeders JA, Draaisma WA, Schwartz MP, Hazebroek EJ, Smout AJ, van Rijn PJ, Broeders IA. Laparoscopic Nissen fundoplication after failed EsophyX endoluminal fundoplication.
British Journal of Surgery 2010; 97(7):1051-5.

16. Furnée EJ, Broeders JA, Draaisma WA, Schwartz MP, Hazebroek EJ, Smout AJ, van Rijn PJ, Broeders IA. Symptomatic and objective results of laparoscopic Nissen fundoplication after failed EndoCinch gastroplication for gastro-esophageal reflux disease.
European Journal of Gastroenterology & Hepatology 2010; 22(9):1118-22.

Curriculum vitae auctoris

Joris Broeders was born on 30 March 1984 in Tilburg, the Netherlands. He graduated cum laude from Gymnasium (St.-Odulphuslyceum, Tilburg) in 2002 and subsequently matriculated into Utrecht University School of Medicine. Throughout the first four years of his studies, he worked as a member of the Medical Students Team of the Department of Neurosurgery. As a student in 2006, he joined the research group of Prof.dr. H.G. Gooszen and Prof.dr. A.J.P.M. Smout at the Department of Surgery and the Department of Gastroenterology of the University Medical Center Utrecht. Throughout his forth, fifth and sixth year of Medical School, he performed the first studies of his thesis on laparoscopic antireflux surgery and presented this work to annual meetings of the European Surgical Association. In 2008, he completed his medical degree at Utrecht University. From July 2008 till May 2011, he continued his doctoral program as a full-time PhD student. For the first year of this program, he was appointed as the research fellow of the Stichts Gastroenterologisch Genootschap. The second year, he successfully applied for a two-year Alexandre Suerman MD/PhD grant for the Board of Directors of the University Medical Center Utrecht. During 2008 and 2009 he worked at the weekly outpatient clinic of his supervisors. Throughout the third year, he continued his research on antireflux surgery with Prof.dr. G.G. Jamieson and Prof.dr. D.I. Watson at the Departments of Surgery of the Royal Adelaide Hospital and Flinders Medical Center in Adelaide, Australia.