New insights into esophago-gastric junction physiology

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New insights into esophagogastric junction physiology

Nieuwe inzichten in de fysiologie van de onderste slokdarmsfincter

(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. W.H. Gispen, ingevolge het besluit van het College voor Promoties in het openbaar te verdedigen op donderdag 11 november 2004 des ochtends om 10.30 uur.

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In dienst van de verwondering

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1

Introduction

Gastroesophageal reflux disease

In 1935, Winkelstein described the disease entity that is known as gastro-esophageal reflux disease (GERD). [1] GERD is a clinical disorder defined by the occurrence of gastroesophageal reflux through the esophago-gastric junction (EGJ) into the esophagus or oropharynx to cause symptoms and/or injury to the esophageal epithelium, or both. The prevalence of typical reflux symptoms such as heartburn and/or regurgitation is 10-20%. [2-11] The majority of GERD patients have mild to moderately severe complaints and 30-40% of patients have esophagitis. [12,13] Apart from esophagitis, increased exposure of the esophageal mucosa to gastric content may lead to peptic strictures, Barrett's esophagus and eventually esophageal adenocarcinoma. [14-16] As GERD is a chronic disorder, the majority of GERD patients require long-term administration of antacids and/or antisecretory agents. [17] The efficacy of medical therapy in the control of acid reflux and reflux symptoms has been reported to range from 80-95 per cent. [18-23]

Esophago-gastric junction physiology

The positive abdomen-to-thorax pressure gradient favours retrograde flow of gastric content across the EGJ toward the distal esophagus (i.e. gastroesophageal reflux). Physical activity and inspiration further increase this pressure gradient. Therefore, a dynamic high-pressure zone compensating this pressure variation is necessary, i.e. EGJ. [24] Whilst the EGJ permits esophago-gastric transit during swallow-induced relaxation of the lower esophageal sphincter (LES) and venting of gas during transient sphincter relaxation, it simultaneously must prevent gastroesophageal reflux. This physiological balance is accomplished by the interplay of several anatomical structures. The intrinsic muscles of the distal esophagus, the LES, along with the gastric oblique fibres, constitute the internal sphincter whilst the crural diaphragm constitutes the external sphincter. [24] The LES is characterized by thickened muscles compared to those of the adjacent tubular esophagus. [25,26] The crural diaphragm, specifically the right crus, forms the hiatal canal through which the esophagus enters the abdomen. [27] The EGJ, hence, exists of two sphincter mechanisms (LES and crural diaphragm), illustrated in Figure 1. In addition, there are several other components whose significance is incompletely understood, i.e., the 'flap valve' mechanism at the gastroesophageal junction and the proportion of the EGJ located intra-abdominally. [24] Physical principles dictate that the efficacy of the antireflux barrier is highly dependent on the EGJ pressure. Using a reversed-perfused Dent sleeve device, it is possible to measure the contribution of the

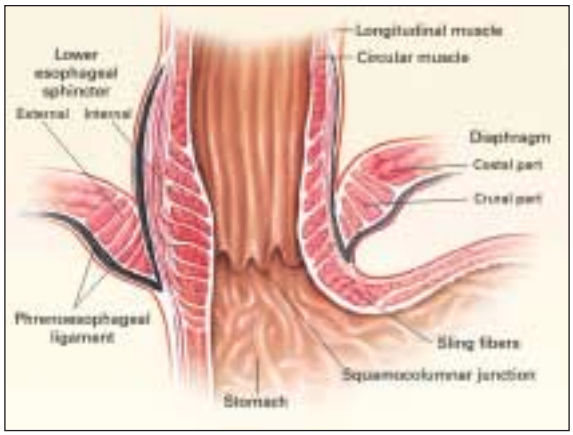

Figure 1
Anatomy of the esophagogastric junction (EGJ). The lower esophageal sphincter and the crural diaphragm, representing the intrinsic and extrinsic sphincter respectively, act in concert to establish EGJ pressure. N Engl J Med. 1997;336(13):924-32. With permission.

two components of the EGJ (i.e., LES and crural diaphragm). [28] End-expiratory EGJ pressure at rest is mostly caused by the intrinsic LES whereas the increase in EGJ pressure with inspiration is caused by the contraction of the crural diaphragm. The contribution of each component is highly variable over time as is the abdomen-to-thorax pressure gradient, which is the driving force of gastroesophageal reflux. In the resting state, this end-expiratory pressure gradient across the EGJ ranges from 4 to 6 mmHg. [24] In healthy volunteers the LES creates a tonic pressure > 10 mmHg, hence, sufficient to prevent reflux. [29] LES pressure variations are coupled to gastric physiology. [30] During phase III of the migrating motor complex, the gastric contractions increase the abdomino-to-thorax pressure gradient, hence, facilitating gastroesophageal reflux. However, via reflex pathways LES pressure increases simultaneously to an extent of 40-80 mmHg, thereby preventing reflux to occur. [30] On the other hand, the pinchcok-like crural diaphragm pressure variations are related to the depth of inspiration as well as to other physical activity i.e. coughing, vasalva maneuver. [24] Of the two sphincters, the crural diaphragm is able to increase EGJ pressure up to 200 mmHg and is substantially more powerful than the LES. [31] From the above it can be concluded that the interplay of the two sphincters (i.e., LES and crural diaphragm), is pivotal in maintaining the antireflux barrier. [31-36]

The EGJ anatomy is changed in patients with a hiatal hernia. Hiatal hernia appears on endoscopical or radiological examination in 50-90% of GERD patients whilst the prevalance ranges from 10-60% in controls. [37-40] With hiatal hernia (type I), widening of the diaphragmatic hiatus and/or laxity of the phrenoesopahgeal ligament allows a part of gastric cardia to herniate upward into the thoracic cavity. Consequently, the intrinsic LES and extrinsic crural diaphragm are physically separated resulting in an over-all decrease in EGJ pressure and a change of the topographic EGJ pressure profile. [33,41] In silico reduction of the hernia by superimposing the two high-pressure zones, representing the LES and crural diaphragm, normalized the EGJ pressure profile. Apart from reduced EGJ pressure, accumulation of gastric content within the hiatal hernia facilitates reflux during swallow-induced LES relaxation impairing esophageal clearance. Several studies have demonstrated that TLESRs account for up to 90% of reflux episodes in asymptomatic controls and in symptomatic GERD patients without hiatus hernia. [42-44] In contrast, GERD patients with hiatus hernia exhibit a more heterogeneous reflux pattern, with reflux episodes frequently occurring during periods of low LES pressure, straining, and even swallow-induced LES relaxation. [44,45] A new approach to study the link between this distinct reflux profile and the anatomical phenomena, i.e. hiatal hernia, was made very recently. Pandolfino et al. [46,47] showed that the EGJ opened at lower pressures and to greater diameter during LES relaxation in hiatal hernia patients as opposed to non-hiatal hernia patients and asymptomatic controls. Thus, in the presence of a large hiatal hernia, resting LES pressure is reduced, esophageal clearance is impaired, and EGJ compliance is increased explaining the higher reflux incidence.

Gastric physology

Functionally, the stomach is divided into a proximal reservoir and distal antral pump on the basis of distinct differences in motility. Functional regions do not correspond to anatomic regions. The reservoir consists of the fundus and approximately one third of the corpus and the antral pump includes the caudal two thirds of the corpus and the antrum. Whilst the proximal stomach exerts a continuous contractile tone, the antral pump contracts phasically to triturate and reduce particle size and to episodically propagate food toward the duodenum. [48] The gastric reservoir has two primary functions. One is to accommodate the arrival of a meal. Gastric accommodation to a meal is a vagally mediated reflex, triggered by antral filling and the entrance of nutrients into the duodenum. [49-51] It results in an adaptive relaxation of the proximal stomach wall, providing the meal with a reservoir without inducing symptoms and/or

intragastric pressure increase. [52] The second function is to maintain a constant compressive pressure on the reservoir content to force it into the 3 per minute motor activity of the antral pump. [48]

From a physiological perspective, gastric motility is related to EGJ function. It has been established that gastric interdigestive contractions are accompanied by marked LES pressure increases, specifically during the late phase II and phase III of the migrating motor complex. [30] In contrast, a significant decrease in LES pressure occurs following a meal, inducing meal-induced adaptive relaxation of the proximal stomach. [53, 54] A similar 20-60% decrease in LES pressure was observed after glucagon adminstration, known to induce augmented fundus relaxation. [55-58] On the other hand, erythromycine reduces fundic volume after a meal and accelerates gastric emptying, which is accompanied by a 25-80% lower LES tone. [58-60] Another important relation between gastric and EGJ physiology, is the role of the proximal stomach, especially the cardiac area, in triggering TLESRs. Distension of the proximal stomach with free air, balloon, or a meal stimulates the reflex pathway underlying TLESRs. [61-63] Zerbib et al. [54] showed that nutrient-induced hormonal factors, i.e. CCK, is involved in TLESR elicitation. After an orally or intraduodenally administered meal, variations in gastric tone relate to the rate of TLESRs. Moreover, after an intraduodenally administered meal, loxiglumide, a CCK-A antagonist, inhibited both postprandial gastric relaxation and TLESR elicitation, implicating a role of both CCK and fundic relaxation in EGJ function. [54]

Pathophysiology of gastroesophageal reflux disease

Gastroesophageal reflux is a physiological phenomenon regularly present, up to 50 times per day, in healthy subjects. [64] Acid reflux is considered pathological when the esophageal acid exposure time with pH < 4 exceeds 5.8% during 24 hour pH-metry. [65] However, in a subset of GERD patients, acid reflux remains physiological. [66-69] In patients with more severe mucosal damage and/or inflammation the esophageal acid exposure time tends to be higher, with most reflux occurring in patients with Barrett's mucosa. [15,70] Critical in GERD is the acid reflux exposure depending on reflux frequency and esophageal acid exposure time. The interplay of offence and defence mechanisms is pivotal in cause and prevention of esophageal mucosal damage in GERD. The noxious quality of the refluxate is determined by pH, i.e. concentration of H^+-ions, and the concentration of pepsin, bile salts and pancreatic enzymes. The defense to reflux is multifactorial: Firstly, the antireflux

barrier (i.e. EGJ), normally prevents acid reflux into the esophagus. Secondly, an intra-esophageal bolus regularly triggers esophagal primary or less frequently secondary peristalsis resulting in esophageal clearance. [42,71] Finally, the epithelial resistance consists of acid buffering and/or dilution by bicarbonate (400 μmol/hour/10cm) and mucous secreted by submucosal glands and tight junctions mechanically preventing the influx of H^+-ions play an important role. [72-74] In GERD, the epithelial barrier function is suggested to be impaired. [24] Consequently, the increased influx of H^+ -ions will stimulate vagal afferents eliciting symptoms and causing cell damage, necrosis and secondary inflammation. Moreover, GERD patients have impaired acid clearance, particularly when recumbent, which is related to the grade of esophagitis. [75] Apart from impaired clearance ability, low LES pressure was believed to be a key factor causing frequent reflux in GERD. However, in 1980, Dent et al. [42] showed that virtually all reflux events in healthy subjects are associated with complete transient relaxations of the LES that are not induced by swallowing (TLESRs). In 1982, Dodds et al. [76] reported that most of the acid reflux events observed in GERD patients also occurred during TLESRs.

TLESR is manometrically defined as an abrupt decrease in LES pressure to the level of intra-gastric pressure that is not associated with a swallow (Figure 2). Criteria are defined by Holloway et al.: 1) absence of swallowing for 4 s before to 2 s after the onset of LES relaxation, 2) relaxation rate of $\geq$ 1 mmHg. s^{-1}, 3) time from onset to complete relaxation of $\leq$ 10 s, 4) nadir pressure of $\leq$ 2 mmHg. TLESRs typically last 10-60 seconds and are frequently accompanied by a common cavity, the manometrically identified mechanism of gastric venting. [77] During a TLESR, the activity of the crural diaphragm is inhibited, facilitating gastroesophageal reflux. [78] Furthermore, other phenomena which regularly accompany a TLESR are a common cavity, esophageal peristalsis and an after-contraction (Figure 2). [79,80] TLESRs are caused by a vagally mediated reflex, organized in the brain stem. In dogs, TLESRs are completely abolished by cooling the cervical vagus. [81,82] Gastric distension, particularly of the cardiac region, is a major stimulus for TLESRs through activation of gastric mechanoreceptors. [82,83] These receptors play a pivotal role in the occurrence of TLESRs and gastroesophageal reflux. On the basis of studies in ferrets [84], two types of mechanoreceptors involved in this reflex arc have been proposed: receptors in series with smooth muscle fibres, responding to wall tension variation (tension receptors) and receptors in parallel to smooth muscle fibres, responding to elongation of the gastric wall (stretch receptors). Although these

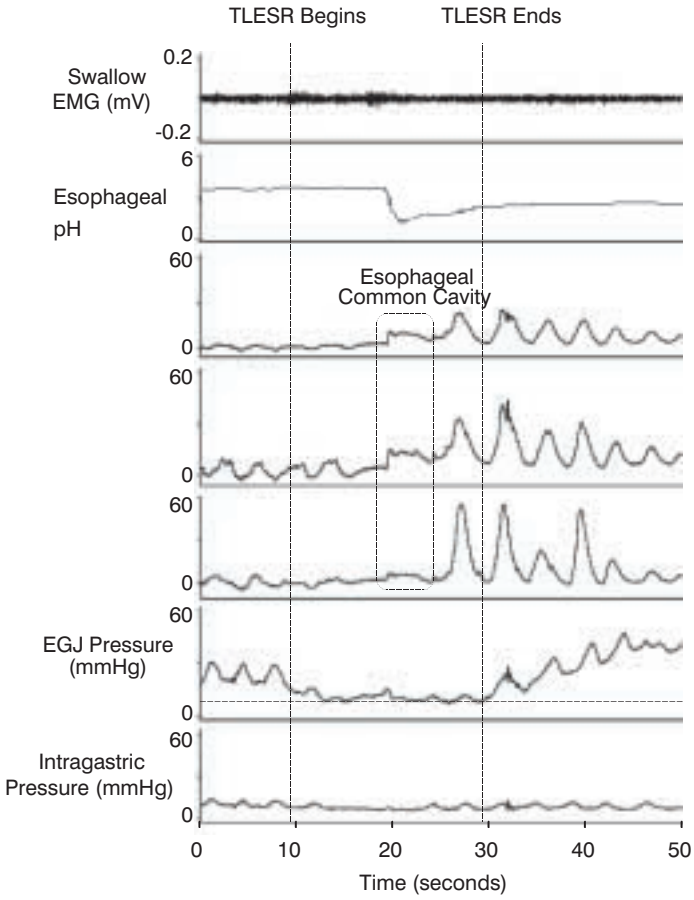

Figure 2
Manometric tracing showing an example of a transient lower esophageal sphincter relaxation (TLESR) accompanied by acid reflux (pH drop to below 4). A common cavity phenomenon can be observed in the manometric tracing as an abrupt increase in esophageal body pressure to intragastric pressure levels.

receptors seem to play a pivotal role in triggering TLESRs and acid reflux, the stimulus–effect relationship between the different biomechanical stimuli activating these receptors and the resulting TLESR rate has not yet been investigated. Meal-induced adaptive relaxation of the proximal stomach is also associated with an increase in TLESR frequency and acid gastroesophageal reflux. [43,62,85] However, whilst mechanical distension leads to intragastric pressure increase

activating both types of receptors, meal-induced adaptive relaxation of the proximal stomach results in an elongation of the gastric wall with minimal intragastric pressure variation. In this thesis we therefore studied the effect of two different biomechanical stimuli, i.e. mechanical distension and a meal, on TLESR frequency in healthy controls.

The neural circuit of TLESRs is not yet completely clear. A neural circuit underlying TLESRs is suggested, based on studies in animals. [81,83] Vagal afferent fibres activated during distention project to the nucleus tractus solitarius (NTS) and to the dorsal motor nucleus (DMV) of the vagal nerve. [86-88] Neurons in the NTS synapse with motor neurons in the DMV and the nucleus ambiguus, which in turn terminate in the enteric nervous system of the LES and the crural diaphragm. [89,90]

As the majority of reflux episodes are associated with TLESRs, one might assume that GERD patients exhibit more TLESRs. Although conflicting data exist, the majority of evidence, however, suggests that in GERD, TLESRs occur as frequent as in healthy controls. [43,62,91-94] Interestingly, intraluminal electrical impedance studies showed that almost all TLESRs are associated with any form of reflux, either gas, mixed (gas & liquid) or liquid reflux in both GERD patients and controls. [95] However, Sifrim et al. [95] observed that GERD patients have more acid reflux and less non-acid reflux than controls. Whilst 60-70% of TLESRs was accompanied with acid reflux in GERD patients, 40-50% was found in controls. [31,43,62,85,96] To date, it is unexplained why TLESRs in GERD patients are more frequently associated with acid reflux. Impaired gastric emptying and augmented storage of nutrients in the gastric fundus might play a role. [97,98] In line with this hypothesis, studies utilizing the barostat, reported prolonged and/or increased proximal gastric accommodation after a meal. [99,100] However, this invasive technique affects intragastric distribution and accelerates gastric emptying. [101] To date, the relationship between fundic volume assessed noninvasively and the rate of TLESRs has not yet been investigated. Therefore, we elected to combine a noninvasive 3D ultrasonographic imaging technique with high-resolution manometry to assess the relationship between proximal gastric volume and the rate of both TLESRs and gastroesophageal reflux in patients with GERD and healthy controls.

Apart from TLESRs, other motor mechanisms such as swallow-associated LES relaxation, absent LES pressure, deep inspiration and straining also contribute to acid reflux exposure, especially in hiatal hernia patients. [44] As for TLESRs, their contribution is markedly different between various time periods. Whereas

their contribution is negligible in the postprandial setting, they underlie approximately 40% and 25% of acid reflux at daytime and nighttime respectively in non-hernia patients with GERD. The approximate comparative figures for hiatal hernia patients with GERD are 54% and 65%. [44] Thus, whilst it is established that TLESRs account for the majority of acid reflux episodes, the relationship between the esophageal acid exposure and the various motor mechanisms underlying gastroesophageal reflux has not yet been investigated. In this thesis we therefore assessed the relationship between the esophageal acid exposure time and the underlying motor events, especially TLESRs, in non-hernia patients with GERD.

Medical therapy

GERD therapy focuses on reduction of esophageal acid exposure. This can be achieved by reducing gastric acid secretion. The H_2-receptor antagonists offer a therapeutic gain of 10 to 24% relative to the placebo for healing esophagitis. [102] Numerous studies, however, demonstrated the superiority of the proton pump inhibitors (PPIs) to H_2-receptor antagonists in both healing erosive esophagitis and symptom relieve. In a meta-analysis, complete relief from heartburn occurred at a rate of 11.5% per week with a proton pump inhibitor compared to 6.4% per week with an H_2-receptor antagonist. [103]

Another approach in GERD therapy is reducing TLESR frequency, the main motor mechanism underlying gastroesophageal reflux. A first step in drug development targeting TLESRs is to get insight into the neurotransmitters involved in this vagal reflex. At present, studies have shown that acetylcholine, cholecystokinin (CCK), γ-aminobutyric acid (GABA), glutamate, nitric oxide (NO) and opoids are involved. [54,104-115] Atropine was the first drug which significantly reduced the rate of TLESRs in both healthy subjects and GERD patients. [108, 109,111,112] Recently, studies have mainly focused on the effect of $GABA_B$ agonist baclofen. Postprandial studies in healthy subjects [110] and GERD patients [114,115] have shown a reduction of the numbers of reflux events up to 50% and in the numbers of TLESRs of up to 60% whereas the effect on the acid exposure time was less [114] or even non-significant [110,115]. Thus, pivotal information, i.e. the contribution of TLESRs to esophageal acid exposure, is up to now lacking. This lack hampered a reliable assessment of TLESR reducing agents on esophageal acid reflux exposure. Therefore we present a study in this thesis assessing the relationship between TLESRs and esophageal acid exposure time.

Anti-reflux surgery

In 1956, Rudolf Nissen (1896 –1981) published his description of gastric fundoplication as a surgical remedy for gastroesophageal reflux. [116] Important parameters believed to affect the functional outcome of this procedure are repositioning of the LES into the abdominal cavity, approximating the crural sling, performing a floppy fundoplication and anchoring the LES below the diaphragm. [117,118] With the recent advent of the laparoscopic techniques, antireflux surgery, especially Nissen fundoplication, has become increasingly advocated for the treatment of refractory GERD. [119,120] Antireflux surgery has to meet high requirements. Firstly, it should effectively reduce reflux symptoms by safely restoring EGJ function without inducing side effects or damage to neural control (vagal nerve). Second, the efficacy of the procedure has to compete with high-quality PPI therapy. Finally, the restored EGJ has to permit seemingly contradictory actions: during swallow induced LES relaxation it must prevent gastroesophageal acid reflux facilitated by the positive abdomen-to-thorax pressure gradient. [121] Furthermore, whilst TLESRs are the mechanism underlying gastric venting of gas, i.e. belching, gastroesophageal reflux of liquids or mixed gas and liquids (acid reflux) during TLESRs has to be prevented.

The long-term efficacy of the procedure in the control of acid reflux and reflux symptoms has been repeatedly reported to be as high as 90%. [18,22] To date, the priniciple mechanism of efficacy of the procedure is still unclear. Potential underlying mechanisms include an increased pressure at the level of the EGJ, a decreased incidence of TLESRs and incomplete EGJ relaxation on swallowing or during transient sphincter relaxation. [122-124] Interestingly, a topographic study by Kahrilas et al. [125] assessing the postoperative EGJ pressure profile suggested that the resultant EGJ pressure is mainly a function of extrinsic compression of the crural diaphragm. Although recent studies have identified that TLESRs play a pivotal role in the pathogenesis of GERD, reports on the effect of a fundoplication on TLESRs are limited. [126,127] After 360° fundoplication, a substantial reduction in TLESRs is reported as well as in the percentage of TLESRs accompanied with acid reflux. [126] As stated above, TLESRs are mainly triggered by distension of the proximal stomach, especially in the area of the gastric cardia. [61] With fundoplication, a fundic wrap is created surrounding this area possibly limiting such distension. Therefore, it is reasonable to hypothesize that the anatomic alterations after fundoplication presumably increase the threshold for eliciting TLESRs. In line with this hypothesis, it has recently been reported that the rate of TLESRs after fundoplication was reduced following a

meal [126] or short-lasting distension with air. [128-130] However, utilizing these stimuli, gastric distension diminishes over time due to gas escape and gastric emptying, making the stimulus intensity variable over time. In this thesis, we present a study assessing the effect of long-lasting isobaric fundic distension on TLESR eliciation after fundoplication. [80]

Primary peristalsis removes and neutralizes (by swallowed saliva) refluxed acid and is therefore crucial to prevent esophagitis. [131] Peristalsis facilitates bolus transport effectively when contraction amplitudes are greater than 30 mmHg. [131] In GERD, impaired esophageal motility (contraction amplitude less than 30 mmHg) is a common finding, with a prevalence of 25% in patients with mild disease and 50% in patients with severe disease. [132,133] It is still controversial whether esophageal dysmotility is a cause or a consequence of reflux disease. [134] No change in esophageal motility has been reported with medical therapy, despite healing of the mucosal injury, indicating that impaired motility in reflux esophagitis is either an irreversible or a contributing factor in its pathogenesis. [135-137] Although recent studies have established that both nadir EGJ pressure and intrabolus pressure increase after Nissen fundoplication, suggesting a restricted passage through the EGJ, there have been few reports addressing the effects on esophageal dynamics. [126,138,139] From these studies, some reported an increased amplitude exclusively in patients with impaired esophageal contractility prior to fundoplication [140], whereas others found no change in esophageal motility. [140,141] Thus, it is so far unclear whether fundoplication restores esophageal motility and whether altered EGJ dynamics are related to motor function of the esophageal body after operation. In this thesis we will provide insight into the relationship between esophageal motility and EGJ function by studying patients with GERD before, at 3 months after and 2 years after successful Nissen fundoplication.

Despite the successful control of reflux following fundoplication, this procedure is in associated with complicating symptoms such as dyspepsia, postprandial fullness, nausea, bloating and upper abdominal pain/discomforts in 10-40%. [122-124,142] The origin of most of these symptoms is still incompletely understood. Recently, it has been established that impaired fundus accommodation is associated with dyspeptic symptoms in a variety of conditions including functional dyspepsia [143-149], postfundoplication dyspepsia [150,151], diabetes mellitus [152], and postvagotomy/gastric surgery. [153] Studies utilizing scintigraphy reported abnormal intragastric distribution of food after fundoplication, with an augmented accumulation in the distal stomach, and an accelerated gastric

emptying. [154] Likewise, in patients with functional dyspepsia, a wider antrum than in healthy controls has been repeatedly reported. [155,156] In this thesis we utilized a noninvasive 3D ultrasonographic imaging technique for the investigation of gastric volumes. We aimed to determine to what extent fundoplication changes postprandial intragastric volume distribution, and whether these altered volumes play a role in postoperative dyspeptic symptoms.

Another frequent complaint after Nissen fundoplication is long-lasting dysphagia reported in between 10-90%. [123,157-159] The underlying mechanical correlate of postoperative dysphagia is still incompletely understood. Hypothesized involved mechanisms include incomplete deglutative esophagogastric junction (EGJ) relaxation, reduced axial motion at the EGJ and an increased esophagogastric transit time, particularly across the EGJ. [80,121,160] Although esophageal bolus transit is mainly a function of esophageal peristalsis, bolus transit across the EGJ is more complex. [131] During swallowing, the esophageal body shortens, a phrenic ampulla is formed [161-163] and the intrinsic LES relaxes with partial inhibition of the crural diaphragm. [78] Whilst fundoplication renders deglutative EGJ relaxation incomplete [80,129] and limits hiatal opening [121], EGJ transit characteristics are likely to be affected by fundoplication. However, the relationship between EGJ transit and symptoms of dysphagia is still incompletely understood. To elucidate the origin of pre- and postoperative dysphagia symptoms, in this thesis, we present a prospective study on the relationship between EGJ transit efficacy and symptoms of dysphagia.

To circumvent or resolve the potential draw backs of a total 360° fundoplication like dysphagia, dyspepsia and/or gas bloat several alternative partial fundoplication techniques have been developed including the Toupet procedure [164], the Belsey Mark IV [165,166], and the Dor operation [120], all less frequently performed than the Nissen fundoplication. Lundell et al. [167], who compared the manometric outcome of partial fundoplication (Toupet) with that after total fundoplication (Nissen-Rosetti) reported a higher EGJ pressure after the latter procedure. While there has been some concern that partial fundoplication fails to control gastroesophageal reflux sufficiently [168], most studies reported good long-term results. [169,170] Moreover, a similar attenuation of meal-induced gastric adaptive relaxation [171,172] and a decreased rate of TLESRs [173] after partial fundoplication have been reported. Watson et al. [174], comparing partial with Nissen fundoplication, found less postoperative dysphagia at 6 months in the former. Furthermore, a comparative study of the effect of partial and complete fundoplication on EGJ physiology could provide pivotal information on the mechanism

of action of fundoplication. Therefore, in this thesis, we will present a study combining non-invasive 3D ultrasonography with high-resolution EGJ manometry and pH-metry, to compare the effects of partial (Belsey Mark IV) and complete (Nissen) fundoplication on fundic volume and EGJ physiology.
From the above we may conclude that despite great progress in the field of GERD pathophysiology since the last two decades, many questions remained unanswered and new questions have arisen. In particular, the effects of fundoplication on EGJ function are still incompletely understood. Therefore, we elected to exclusively focus on the effect of surgical anti-reflux therapy on EGJ function and postulated four theses, which we aimed to answer in this thesis.

Aims and outline of this thesis

The chapters presented in this thesis comprise studies that have been performed 1) to gain more insight into the genesis of transient lower esophageal sphincter relaxations (TLESRs) in health, gastroesophageal reflux disease (GERD) and after fundoplication, 2) to evaluate the effect of fundoplication on esophageal motility, bolus transit across the EGJ and intragastric distribution, 3) to shed more light on the origin of post-operative dyspepsia and dysphagia and 4) to explore the role of pressure gradients across the esophagogastric junction (EGJ) on acid reflux during TLESRs.

Chapter 2 describes a study that aimed to assess whether meal-induced changes in fundic volume are a more powerful trigger for TLESRs than the biomechanical changes during mechanical gastric distension. In this study EGJ manometry was combined with fundic distension using the barostat. In the first part of the study the effect of graded artificial distension of the proximal stomach on the rate of TLESRs was assessed. Thereafter, the effect of a high caloric meal on fundic volume and TLESRs was measured. Wall tension was calculated under both experimental conditions and related to the TLESR frequency.

Chapter 3 aimed to determine the effect of a successful laparoscopic fundoplication on TLESR frequency both at rest and during persistent gastric distension. The efficacy of TLESRs in facilitating gastric venting after fundoplication was compared with GERD patients and healthy controls. The

effect of fundoplication on another vagally mediated reflex, gastric accommodation to barostat distension, was also evaluated.

In Chapter 4 a prospective study is presented aiming to determine whether a successful Nissen fundoplication affects esophageal contractile activity and, if so, whether altered esophageal contractility is correlated to postoperative symptoms of dysphagia and/or odynophagia, alterations in EGJ dynamics (basal and nadir pressure) and radiological outcome.

The study in Chapter 5 is the first to report on non-invasive 3D ultrasonographic imaging of the stomach allowing the calculation of stomach volume and to relate these volumes to postoperative dyspeptic symptoms in patients after fundoplication. This study aimed to assess to what extent fundoplication affects total, proximal, and distal gastric volumes after a liquid nutrient, and whether these altered volumes are related to postoperative dyspeptic symptoms.

The aim of the study presented in Chapter 6 was to assess the relationship between the esophageal acid exposure time, esophageal clearance and the underlying manometric motor mechanisms, especially TLESRs, in non-hernia patients with GERD. Although esophageal acid reflux exposure time depends both on the incidence of reflux episodes and the duration of each reflux event, the relationship between the motor events underlying acid reflux and the acid exposure time has not yet been established.

Chapter 7 presents a prospective study that aimed to determine the effect of a successful laparoscopic fundoplication on the efficacy of EGJ transit for both liquids and solids, the EGJ opening mechanics, and the relation between EGJ transit and symptoms of dysphagia in patients studied both before and after fundoplication.

Chapter 8 describes a prospective study that aimed to assess the role of fundic volumes measured with the non-invasive 3D ultrasonographic technique on eliciting TLESRs and acid reflux in GERD patients studied before and after laparoscopic fundoplication. In this study we hypothesize that the pressure gradient across the EGJ (ΔEGJ pressure), might play an important role in facilitating reflux. Therefore, we compared ΔEGJ pressures and the EGJ pressure profile for TLESRs with and without acid reflux for all subject groups.

The aim of the study in Chapter 9 was to compare the effect of the Nissen and Belsey Mark IV fundoplications on fundic volume, using a non-invasive real-time 3D ultrasound technique, and to assess the relationship between fundic volume and the rate of TLESRs after a liquid nutrient. Utilizing topographic high-resolution manometry, also the pressure gradient across the EGJ and the EGJ pressure profile during TLESRs were determined.

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2

Elicitation of transient lower esophageal sphincter relaxations in response to gastric distension and meal ingestion

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Abstract

The aim of this study was to compare the effect of graded gastric barostat distension and meal-induced fundic relaxation on the elicitation of transient lower esophageal sphincter relaxation (TLESR). In 15 healthy subjects, stepwise fundic distension and esophageal manometry were performed simultaneously. Next, the effect of meal ingestion on proximal stomach volume and lower esophageal sphincter function was studied. During stepwise barostat distension of the proximal stomach, a significant linear correlation between intragastric pressure ($r = 0.91$; $P < 0.01$) and the TLESR rate during inflation and subsequent deflation ($r = 0.96$; $P < 0.01$) was found. A similar relationship was found for volume. In addition, after meal ingestion, the TLESR rate increased significantly from 1.4 ± 3.0 to 5.4 ± 1.5 h^{-1} ($P < 0.01$) and 5.2 ± 1.7 h^{-1} ($P < 0.01$), respectively, during the first and second 30-min postprandially. However, at similar calculated intragastric volumes, barostat distension led to a significantly higher TLESR rate than the meal. Similarly, distension-induced increase in gastric wall tension, estimated from the measured bag pressure and volume using Laplace's law, was associated with significantly higher TLESR rates ($P < 0.01$). In conclusion, the rate of TLESRs in healthy volunteers is directly related to the degree of proximal gastric distension and pressure-controlled barostat distension is a more potent trigger of TLESRs than a meal. The latter finding suggests that tension receptor activation is an important stimulus for TLESRs.

Introduction

In recent years several studies have provided more information on the role of the lower esophageal sphincter (LES) in causing gastroesophageal reflux disease (GERD). It is now generally accepted that in healthy volunteers as well as patients with GERD, transient lower esophageal sphincter relaxations (TLESRs) are the most important underlying mechanism of gastroesophageal reflux in the setting of a normal LES pressure. [1–6] The TLESRs are caused by a vagally mediated reflex, organized in the brain stem. In dogs, TLESRs are completely abolished by cooling the cervical vagus. [7,8] Gastric distension, particularly of the cardiac region, is a major stimulus for TLESRs [7,9] through activation of gastric mechanoreceptors. These receptors play a pivotal role in the occurrence of TLESRs and gastroesophageal reflux. However, the stimulus–effect relationship between the different biomechanical stimuli activating these receptors and the resulting TLESR rate remains unknown.

Meal-induced adaptive relaxation of the proximal stomach is related to an increase in TLESR frequency and gastroesophageal reflux. [3,5,6,10–13] It is now clear that gastric distension, accomplished by inflating an intragastric bag [9] or by gas introduction, is an effective trigger for TLESRs. [14,15] However, the mechanism through which distension leads to induction of TLESRs may be quite different from the activation during meal-induced adaptive relaxation of the proximal stomach. During adaptive relaxation, the proximal stomach accommodates to a meal volume, which mostly results in an elongation of the gastric wall with minimal pressure changes, [14,16] whereas gastric distension results in an intragastric pressure increase. Moreover, during gastric distension an elongation of the gastric wall and a significant tension increase within the gastric wall are expected. Whether meal-induced changes in fundic volume are a more powerful trigger for TLESRs than the biomechanical changes during gastric distension remains to be elucidated.

The aims of the present study therefore were to compare the effects of graded artificial gastric distension and a liquid meal on TLESR frequency, and to assess the stimulus–effect relationship under both experimental conditions.

Materials and methods

Subjects

Fifteen healthy volunteers (8 men, 7 women) with a mean ± SEM age of 23.6 ± 3.4 years (range 19–36) years and a mean ± SEM body mass index of 21.6 ± 1.25 kg m^{-2}, without gastrointestinal symptoms, participated in this study. They did not take any medication known to alter esophageal motor function. Each volunteer gave written informed consent prior to the study and the protocol was approved by the medical ethics committee of University Medical Center Utrecht.

Catheter and system

The catheter, a 150-cm silicone assembly, contained 12 water-perfused channels with a diameter of 0.4 mm, a reversed perfused sleeve device to measure LES pressure, and a central air lumen (Dentsleeve Pvt. Ltd, Wayville, South Australia). Four sideholes of the water-perfused channels were situated 20, 15, 10 and 5 cm proximal to the centre of the sleeve and used to record esophageal activity preceding a fall in LES pressure. A 6-cm-long sleeve sensor with six sideholes at 1-cm intervals opposite the sleeve was positioned in the LES. The most distal perfusion channel was positioned in the stomach and used to record intra-gastric pressure. The catheter was connected to a low-compliance pneumohydraulic capillary perfusion system (pressure of 1 atmosphere) and channels were perfused with distilled water (0.3 mL min^{-1}). Each lumen was connected to an external pressure transducer (DPT-200; Medisize, Hillegom, The Netherlands) and data were stored in a digital data logger (MMS, Enschede, The Netherlands) using a sample frequency of 8 Hz. The central air lumen, an oval channel (1.9 ·2.4 mm), was used to insufflate and deflate the intragastric bag. The polyethylene barostat bag (maximal capacity 850 mL) was mounted on the tip of the catheter 2 cm distal to the sleeve device. Swallowing was monitored with a separate solid-state catheter (P.P.G. Hellige, Best, The Netherlands) positioned in the pharynx.

Electronic barostat

Proximal gastric function was measured with an electronic barostat (Model Distender Series II; G & J Electronics Inc., Custom Biomedical Systems, Toronto, Canada). This barostat measures the volume of air within an intragastric bag maintained at a constant preselected pressure by an electronic feedback mechanism. When the intrabag pressure, measured in the cylinder of the barostat, differed from the preselected pressure by more than 0.2 mmHg, the barostat was triggered to inject or aspirate air from the barostat bag. The maximal air flow the barostat could accomplish was 2.4 L min^{-1}. The barostat was used to measure the intragastric volume during graded distension using stepwise increasing pressures and to measure volume changes in response to a liquid meal at a constant low pressure level.

Meal

The meal, a 300-mL lactose- and fibre-free milk drink contained, per 100 mL, 6.0 g proteins, 18.4 g carbohydrates, and 5.8 g fat, 450 kcal (Nutridrink; Nutricia, Zoetermeer, The Netherlands).

Experimental design

The study was performed after an overnight fast of at least 10 h. Participants were comfortably seated in upright position on an ergonomic chair with knee support (Stokke, Skodej, Norway). Subjects were asked not to move or talk during the experiment to reduce intra-abdominal pressure variation. After calibration of the system, the manometry assembly was introduced through the mouth. To unfold the bag and to assure that it was positioned correctly, it was inflated with 200 mL air manually and thereafter the catheter was pulled back carefully until its passage was restricted by the LES. The bag was then completely deflated and then connected to the barostat. In three subjects we verified the correct position of the intragastric bag by taking an upright upper abdominal X-ray after the experiment, both with the bag empty and after manual inflation of 300 mL air. After manometrical detection of the high pressure zone the sleeve sensor was then carefully positioned in the LES. The assembly was then fixed in this position by taping it to the corner of the mouth. Next, the solid state catheter was introduced through the nose and positioned in the pharynx. After insertion of the catheters subjects were allowed to accommodate for a 15-min period. Minimal distending pressure (MDP) was determined next, followed by barostat and meal stimulation, respectively.

Minimal distending pressure

Firstly, the MDP was determined. This is the intraluminal pressure needed to overcome the extra-luminal (intra-abdominal) pressure. Using the barostat device, we determined the MDP by increasing the intrabag pressure in 1-mmHg steps, from 0 mmHg (atmospheric pressure) to the pressure level that first provided an intragastric bag volume of more than 30 mL of air. [13] During the experiment, the intragastric bag volume and intragastric bag pressure were recorded continuously by the barostat-linked computer.

Barostat stimulation

Starting at MDP, pressure was increased stepwise by 2 mmHg every 5 min until participants reported intolerable discomfort or the intragastric bag reached a volume of 650 mL. From that pressure level, pressure was decreased stepwise by 2 mmHg every 5 min until MDP was reached again. Esophageal manometry was performed simultaneously during each upward and downward pressure step. The duration of this procedure was approximately 70 min. After this procedure, the subjects were allowed to rest for a 10-min period during which the intragastric bag was kept at atmospheric pressure (0 mmHg).

Meal stimulation

During a 45-min baseline recording period, the intrabag pressure was set and maintained at 1 mmHg above MDP. [17,18] After the baseline recording period all subjects drank the meal at a rate of 100 mL min^{-1}, using a straw. Volume changes after meal ingestion were then recorded and esophageal manometry was performed simultaneously over a period of 2 h.

Data analysis

Intragastric volume recordings were averaged for each 5-min distending period with a constant pressure. Starting from the MDP level, mean ascending and descending volume–pressure curves were constructed for each individual subject. Gastric compliance (dV/dP) for each individual was taken as the regression coefficient of the steepest part of the ascending part of the compliance curve. All measured volumes were corrected for the effects of air compressibility using Boyle's law ($P \times V = K$). Furthermore an estimation of the gastric wall tension was calculated by applying Laplace's law [$T = 1/2\ (P(3\ V/4\pi)^{1/3})$] to quantify the combined effect of both volume and pressure on TLESR incidence. [19,20]

Table 1
Relationship between intragastric pressure, intragastric volume, wall tension and transient lower esophageal sphincter relaxation (TLESR) frequency during barostat distension.

P (mmHg) above MDP	Barostat bag volume (mL)	Wall tension (N m $^{-1}$)	TLESR freq (n h $^{-1}$)
MDP	28 ± 6	0	2.8 ± 1.5
2	92 ± 16	2.8	6.4 ± 1.7
4	184 ± 25	7.1	7.4 ± 1.7
6	291 ± 23	12.3	9.2 ± 2.0
8	417 ± 30	18.5	10.2 ± 3.3
10	483 ± 24	24.3	10.3 ± 2.7
12	597 ± 35	31.3	14.4 ± 2.4
10	585 ± 27	25.9	12.0 ± 2.8
8	566 ± 25	20.5	9.2 ± 2.4
6	527 ± 22	15.0	8.3 ± 2.1
4	402 ± 28	9.2	4.8 ± 1.6
2	256 ± 33	3.9	3.6 ± 1.6
MDP	62 ± 12	0	2.8 ± 1.4

Means ± SEM volume data pooled for each pressure step.

By using Laplace's law we assumed the proximal stomach to be spherical, very thin-walled, and in static-force equilibrium. We calculated a radius assuming the fundus to be perfectly spherical. Based on this calculated radius and the transmural gastric pressure (intragastric minus intra-abdominal pressure) we calculated wall tension and performed a correlation analysis with the TLESR rate. We did not take the issue of active vs passive tension into account as both types of tension seem to activate tension receptors. [21]

For the pre- and postprandial recordings, the mean barostat volume was determined at 5-min intervals. The intragastric meal volume was calculated using the gastric emptying rate, which was not measured but instead estimated based on the energy density (1.5 kcal mL $^{-1}$) of the meal, the initial volume (300 mL) and the time interval after consumption as reported by Hunt et al. [22] According to these data the gastric emptying rate was 4.0 kcal min $^{-1}$ during the first 30-min interval; 2.7 kcal min $^{-1}$ during the second 30-min interval and 2.4 kcal min $^{-1}$ in the second hour postprandially. A rough estimate of the total

gastric volume was calculated by adding the approximate intragastric meal volume and the barostat bag volume for each 30-min interval postprandially (Table 1).

The LES manometric recordings were analysed for basal pressure and the occurrence of TLESRs, according to the criteria of Holloway et al. [23] The TLESR incidence during distension was assessed in each 5-min period with a constant pressure. In 15 volunteers this resulted in a total observation time of 75 min at each pressure level. After meal ingestion the TLESR rate (n h^{-1}) was assessed at 30-min intervals and compared with the TLESR rate during fasting. Basal end-expiratory LES pressure (end-expiratory sleeve pressure minus fundic pressure) was determined at 5-min intervals during distension and at 30-min intervals pre- and postprandially.

Statistical analysis

All pooled data are presented as means ± SEM. Pearson's correlation test was used to calculate correlation coefficients. Statistical analyses of changes in basal LES pressure before and after the meal, and before and after distension, were performed using Student's *t*-test for paired data. Differences in the number of TLESRs were calculated using analysis of variance (ANOVA). $P < 0.05$ was taken as statistically significant.

Results

Response to barostat distension

Distension of the proximal stomach was well-tolerated by all volunteers. The MDP (mean ± SEM) was 6.3 ± 0.8 mmHg. At the start of the inflation (pressure 0 mmHg above MDP), 28 ± 6 mL was already present in the bag. At each pressure level, the mean intragastric bag volumes were significantly larger during stepwise deflation of the barostat bag, from 12 to 0 mmHg above MDP, compared with inflation, from 0 to 12 mmHg above MDP, creating a hysteresis graph (Figure 1). Stepwise distension of the proximal stomach was associated with a rising TLESR rate. A significant linear relation was found between the intragastric bag pressure and the TLESR rate ($r = 0.91$; $P < 0.01$) during inflation.

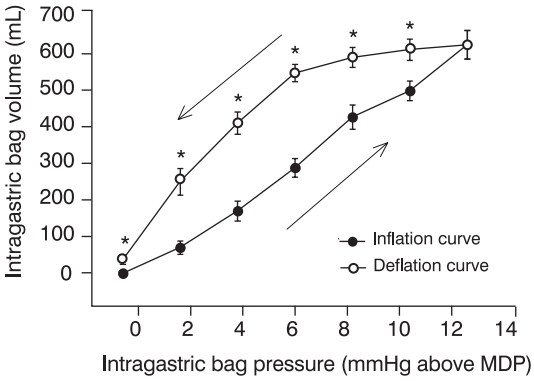

Figure 1
Pressure–volume relationship during graded gastric distension with a barostat in 15 healthy subjects. Data correspond to means ± SEM. The delay in the return of the gastrics volume towards the value at minimal distending pressure (MDP) during stepwise deflation of the barostat bag represents hysteresis. *$P < 0.05$ compared with volume during inflation.

Subsequently, deflation of the proximal stomach resulted in a decrease in TLESR frequency and a significant correlation between the intragastric pressure and the TLESR rate was found ($r = 0.96$; $P < 0.01$) (Figure 2). Similarly, Figure 3 shows a linear correlation between TLESR frequency and the resulting volumes during inflation ($r = 0.90$; $P < 0.01$) and subsequent deflation of the barostat bag ($r = 0.87$; $P < 0.05$). The mean intrabag volumes for the inflation and deflation curve and the resultant TLESR frequencies are depicted in Table 1. No relationship between the compliance, calculated for each individual subject, and the TLESR incidence was found ($P > 0.05$).

Gradual isobaric distension of the stomach resulted in an increasing gastric wall tension from 0 N m^{-1} at MDP to a maximum of 31.3 N m^{-1} during the last distension step. Data on gastric wall tension are also provided in Table 1. A linear correlation between the calculated wall tension during the upward and downward pressure steps and the TLESR rate ($r = 0.89$, $P < 0.01$ and $r = 0.98$, $P < 0.01$, respectively) was found.

Gastric distension had no effect on LES pressure as the mean basal LES pressure at rest (10 ± 4 mmHg) was similar to the mean LES pressure during distension (9 ± 4 mmHg). No significant relation was found between the distension pressure and basal resting LES pressure ($P < 0.05$). Mean swallow frequency at atmospheric pressure, 4.0 ± 25 min^{-1} , was not significantly different ($P < 0.05$) from the frequency measured during the sequential distension episodes.

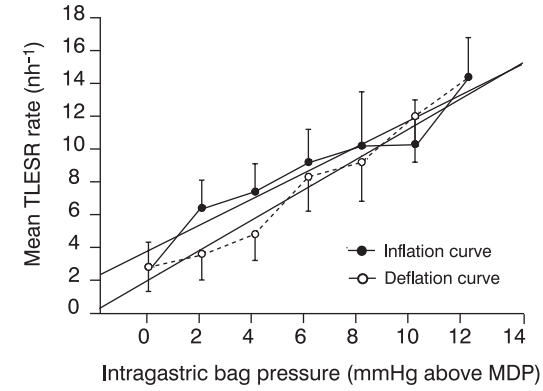

Figure 2
Effect of intragastric pressure on transient lower esophageal sphincter relaxation (TLESR) frequency during graded pressure increments (•) and decrements (○). Data correspond to means ± SEM. The straight solid line represents the correlation (r = 0.91) between pressure and TLESRs during increasing the pressure stepwise (inflation). The straight dashed line represent this correlation (r = 0.96) during graded pressure decrease (deflation).

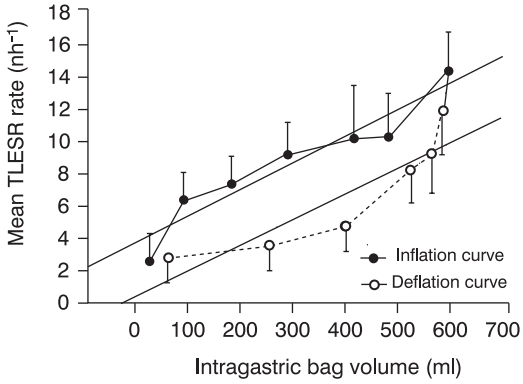

Figure 3
Relationship between the intragastric bag volume and transient lower esophageal sphincter relaxation (TLESR) during inflation (•) and deflation (○). Data correspond to mean ± SEM.
The straight solid line represents the correlation (r = 0.90) between volume and TLESRs during inflation. The straight dashed line represents this correlation (r = 0.87) during deflation.

Response to meal ingestion

The preprandial intragastric bag volume at MDP + 1 mmHg was 90 ± 7 mL. In all volunteers meal ingestion caused an immediate proximal gastric relaxation reflected by an increase in bag volume. Mean intragastric bag volume was already significantly ($P < 0.05$) enlarged during the first 5 min after meal ingestion and stayed significantly increased until 100 min postprandially. On average, the maximal postprandial volume (349 ± 61 mL) was reached at 40 min postprandially and decreased gradually during the remaining 80-min recording period (Figure 4). The total gastric volume based on the estimated meal volume and the intragastric bag volume for each 30-min interval is shown in Table 2. After meal ingestion TLESR incidence increased significantly from 1.4 ± 0.3 h^{-1} to 5.4 ± 1.5 h^{-1} ($P < 0.01$) and to 5.2 ± 1.7 h^{-1} ($P < 0.01$) during

the first and second 30-min postprandial intervals, respectively. During the third 30-min interval, TLESR incidence was still elevated but this did not reach statistical significance ($P < 0.06$). During the fourth postprandial 30-min interval, the TLESR rate returned to baseline level (Figure 4, Table 2).

The effect of mechanical distension with the barostat on TLESR frequency appeared to be greater than that of a liquid meal: isobaric distension at 8 mmHg during deflation with an intragastric volume of ~ 550 mL resulted in a TLESR frequency of 9.2 h^{-1} (Table 1), while during the first 30-min interval after meal ingestion with a similar total gastric volume only 5.4 TLESRs h^{-1} were scored (Table 2). Preprandially, gastric wall tension was 1.4 N m^{-1} . During the first 30 min after the meal, maximum gastric wall tension was 2.5 N m^{-1} , being significantly lower ($P < 0.01$) than the maximum tension calculated during barostat distension. In the following 30-min periods mean gastric wall tension gradually decreased (Table 2).

The preprandial mean basal LES pressure was 11 ± 4 mmHg. After ingestion of the meal LES pressure was significantly decreased during the first (8 ± 3 mmHg, $P < 0.05$) and second postprandial hour (9 ± 4 mmHg, $P < 0.05$). Mean swallow frequency during fasting (3.0 ± 1.05 min^{-1}) was not significantly different ($P > 0.05$) from the frequency measured during each postprandial interval.

Table 2

Relationship between pre- and postprandial total intragastric volume, wall tension and transient lower esophageal sphincter relaxation (TLESR) frequency.

Time interval	Barostat bag volume (mL)	Meal volume (mL)	Total gastric volume (mL)	Wall tension (Nm^{-1})	TLESR freq. (nh^{-1})
First 30 min	290 ± 42	260	550	2.54	5.4 ± 1.5
Second 30 min	323 ± 48	193	516	2.49	5.2 ± 1.7
Third 30 min	258 ± 42	142	400	2.29	4.2 ± 1.4
Fourth 30 min	137 ± 33	94	231	1.90	1.1 ± 1.4
Fasting	90 ± 7	–	90	1.39	1.4 ± 0.3

The total gastric volume is equal to the summation of the intragastric barostat bag volume and the intragastric meal volume which is calculated based on a gastric emptying rate reported by Hunt et al. [22]

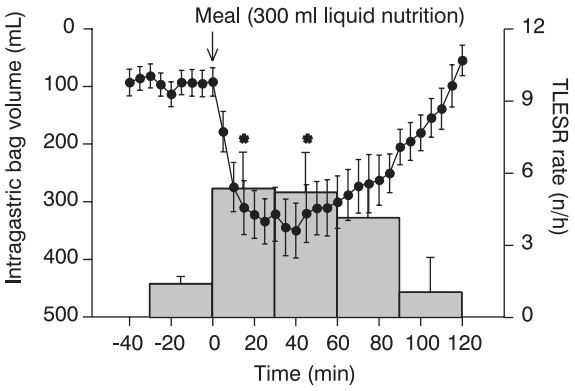

Figure 4
Mean (SEM) pre- and postprandial intragastric bag volume curve (•). After 45-min baseline recording, the liquid meal (300 mL, 450 kcal) was ingested during a 3-min period. After the meal, there was a large rapid and sustained volume increase, i.e. a proximal gastric relaxation, to a maximal value followed by a slow return to fasting level. The bar plot shows that transient lower esophageal sphincter relaxation (TLESR) frequency was significantly increased ($P < 0.01$) during the first and second 30-min postprandial interval. In the third and fourth 30-min intervals, the TLESR rate gradually diminished.

Discussion

This study compared the effect of graded gastric distension and meal-induced gastric relaxation on TLESR elicitation in healthy human subjects. Our results clearly indicate that the TLESR rate in healthy subjects is directly related to the degree of proximal gastric distension and that pressure-controlled distension is a more potent trigger of TLESRs than a meal, which possibly relates to tension receptor activation.

Several studies analysing the mechanism by which TLESRs are elicited have identified proximal gastric distension, especially distension in the area of the gastric cardia, as the dominant mechanism, but pharyngeal stimulation may also contribute. [9] Although the biomechanical stimulus for TLESRs has not been accurately identified yet, volume seems to be an important factor. Almost 2 decades ago, Holloway et al. [9] showed a fourfold increase in the TLESR rate after inflating a balloon with 750 mL CO2 in healthy volunteers. More recently Boulant et al. [24] performing continuous isobaric distension, showed a more

pronounced volume-related TLESR increase. Clearly, the method of distension has a major impact on TLESR frequency. In addition, adaptation of the mechanoreceptors during prolonged distension occurs within the first 15 min, [25] hence, TLESRs do not occur at similar rate during each time interval. Therefore, and as we wanted to measure the effect of a fixed-pressure stimulus on TLESR frequency, a short distension period was most suitable. At the same pressure levels, intragastric volumes during gastric inflation were smaller than during gastric deflation, but the frequencies of TLESRs were similar. Hence, intragastric volume does not seem to be the primary factor that determines TLESRs during fasting.

To further elucidate the combined effect of both volume and pressure as a defining principle, we calculated wall tension. However, as described by Gregerson et al. [20,26,27] use of Laplace's law requires a number of assumptions. The wall of the stomach is assumed to be infinitely thin, the proximal stomach should have a simple ellipsoidal geometry and the intra-abdominal pressure should be evenly distributed. Although not all theoretical factors related to Laplace's law were fulfilled, estimated wall tension during stepwise distension was found to increase significantly and to be positively correlated to the TLESR rate.

As depicted in Figure 1, pressure–volume curves during inflation were different from the curves during deflation of the intragastric bag, a phenomenon called hysteresis. It is still unclear whether the observed hysteresis is caused by the passive properties of the gastric wall or by the slow active contraction of the lengthened active smooth muscle. [28] However, a relationship with the compliance (taken as the slope of the steepest part of the inflation curve) and TLESR incidence could not be demonstrated.

Previous studies have reported that the LES resting pressure increases significantly during gastric distension. [24,29] Our data however, showed no significant alterations in basal LES resting pressure during gastric distension, confirming findings observed by Holloway et al. [9,24,29] Although the basal LES pressure was referenced to the rising intragastric pressure, the LES pressure remained constant. Hence, we may conclude that the pressure in the sphincter region adapted to the rising intragastric pressure, thereby maintaining its antireflux barrier function.

The barostat technique used to monitor postprandial gastric relaxation has already been validated by Azpiroz and Malagelada. [13] In the fasting state and after consumption of a liquid meal, a volume increase in the barostat bag has been shown to reflect relaxation of the proximal stomach. [18] No effect of

previous distensions on postprandial TLESR rate was expected because the remaining volume after distension was low, resulting in a TLESR rate similar to that observed before distension. Furthermore, a 55-min interval was used after distension before the meal was given, in order to exclude such an effect. Our investigations demonstrated an immediate, significant and sustained volume increase occurring after meal ingestion in concordance with the results observed by others. [17,18,30–32] The mechanisms through which meal ingestion leads to relaxation of the proximal stomach are probably complex. It is likely that the adaptive response to a meal is mainly the result of the release of hormones, including cholecystokinin (CCK), after the arrival of nutrients in the duodenum. However, this mechanism does not provide an adequate explanation for the rapid onset of the relaxation. An immediate increase in proximal gastric volume is also seen after intraduodenal installation of a caloric meal. [32] Zerbib et al. [32] observed that the CCK-A receptor antagonist loxiglumide had no effect on fundic tone after an oral meal, but strongly inhibited fundic relaxation elicited by duodenal infusion of this meal. From these data we may conclude that not only hormonally induced adaptive relaxation, but also other factors, including neurally mediated reflexes, may be involved in the immediate volume increase observed during postprandial gastric relaxation.

After the meal, intragastric pressure was kept constant by the barostat. Postprandial gastric relaxation was accompanied by a decrease of LES pressure, but intragastric volume, gastric wall tension and the rate of TLESRs increased. These results are in line with studies demonstrating an increased TLESR rate and more gastro esophageal reflux associated with fundus relaxation induced by sumatriptan. [33] The increase in TLESRs in the first and second 30-min interval was 4.0 h^{-1}, which was similar to the data reported by Zerbib et al. [32,34] Lidums et al. [30] however, studying the effect of atropine on the number of TLESRs, found a higher TLESRs rate during the first and second hour postprandially. The discrepancy in the methodology used may account for the higher rates found by Lidums et al. [30] including the use of a soft mixed-nutrient meal instead of a liquid meal as used in the present study.

The return of the proximal gastric volume to the fasting level was accompanied with a gradual decrease in TLESR frequency and therefore it seems likely that, as the intragastric pressure remained constant, changing volume due to gastric relaxation became an important factor in triggering TLESRs. In fact, as Penagini et al. [35] showed that GERD patients have a larger proximal gastric volume in the late postprandial period, it is likely that the delayed recovery of proximal gastric

tone in GERD patients is related to the higher TLESR rates observed in these patients. [15] Other factors that may contribute to the observed postprandial increase in TLESR rate are the release of gut hormones such as CCK, because the effect of a meal on TLESR frequency is decreased by a CCK-A receptor antagonist. [32]

The increase of the bag volume after the meal reflected gastric accommodation. However, to approximate reality better, the intrinsic meal volume was also taken into account. As gastric emptying was not measured, an estimation was made based on Hunt's data. [22] According to these data, and those provided by others, [36,37] gastric emptying is mainly dependent on the energy density of the meal, the initial volume and the time interval after consumption. Both the energy density and the initial volume of the meal used in the present study were identical to a meal used by Hunt et al. [22] hence we believe that the gastric emptying data used were reliable. In addition, as published by Azpiroz et al. [38] gastric emptying rates for a liquid meal with a barostat bag present in the stomach are only marginally increased.

Although the receptive field for triggering TLESRs is not completely clear, this is believed to be a vagally mediated response to gastric distension, as TLESRs are eliminated after vagotomy. [7] The nature of the mechanoreceptors involved is still incompletely understood. Based on animal studies, two types of mechanoreceptors involved have been proposed. Receptors in series to smooth muscle fibres, responding to wall tension, were called 'tension' receptors. Receptors in parallel, activated by elongation of the gastric wall (muscle), were called 'elongation' receptors. [39,40]

When comparing the effects of gastric distension with a barostat and a liquid meal on TLESR frequency we may conclude that, at similar intragastric volumes, barostat distension leads to a significantly higher TLESR rate (Tables 1 and 2). Barostat distension in this study resulted in an elongation of the stomach wall as well as in a significantly increased wall tension, hence both types of receptors involved in triggering TLESRs could be activated. Although the simplified Laplace formula used in this study provides a crude estimation of tension, a greater cross-sectional area in combination with constant pressure during meal induced adaptive relaxation at least corresponds to a higher wall tension. However, the Leuven group [41,42] suggested that in meal-induced gastric relaxation, series receptors could actually be less active or inactive, because of relaxation of the smooth muscles. Consequently, it is reasonable to assume that mainly elongation receptors were activated after meal ingestion, which

accounts for a less pronounced TLESR increase than during mechanical distension.

In summary, both gastric distension and meal-induced gastric relaxation were potent stimuli for TLESRs in healthy subjects but meal ingestion tended to result in a smaller TLESR rate increase compared with mechanical gastric distension. This observation can be explained by the fact that the mechanical distension of the stomach leads to a higher wall tension, resulting in an additional stimulation of the in series 'tension' receptors triggering TLESRs.

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3

Reduced TLESR elicitation in response to gastric distension in fundoplication patients

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Abstract

Transient lower esophageal sphincter relaxations (TLESRs) are vagally mediated in response to gastric cardiac distension. Nine volunteers, eight gastroesophageal reflux disease (GERD) patients, and eight fundoplication patients were studied. Manometry with an assembly that included a barostat bag was done for 1 h with and 1 h without barostat distension to 8 mmHg. Recordings were scored for TLESRs and barostat bag volume. Fundoplication patients had fewer TLESRs (0.4 ± 0.3/h) than either normal subjects (2.4 ± 0.5/h) or GERD patients (2.0± 0.3/h). The TLESRs rate increased significantly in normal subjects (5.8 ± 0.9/h) and GERD patients (5.4 ± 0.8/h) during distension but not in the fundoplication group. All groups exhibited similar gastric accommodation (change in volume/change in pressure) in response to distension. In conclusion, fundoplication patients exhibit a lower TLESR rate at rest and a marked attenuation of the response to gastric distension compared with either controls or GERD patients. Gastric accommodation was not impaired with fundoplication. This suggests that the receptive field for triggering TLESRs is contained within a wider field for elicitation of gastric receptive relaxation and that only the first is affected by fundoplication.

Introduction

Laparoscopic Nissen fundoplication is increasingly advocated for the treatment of gastroesophageal reflux disease (GERD), and its efficacy for the control of acid reflux and reflux symptoms has been well established. Long-term success rates as high as 90% have been reported. [1,2] At present, the principal underlying mechanism of action of a successful antireflux operation is still incompletely understood. [3,4] Hypothesized mechanisms of efficacy include increased intraluminal pressure at the site of the esophagogastric junction (EGJ), incomplete EGJ relaxation, and a decreased transient lower esophageal sphincter relaxation (TLESR) frequency. [5,6,7]

Although recent studies have established that TLESRs play a pivotal role in the pathogenesis of GERD, reports to date on the effect of a fundoplication on TLESR elicitation are limited. [5,6,8] Animal data indicate that TLESRs are a vagally mediated reflex and can be abolished by experimentally cooling the cervical vagus [9]. Distension of the proximal stomach, especially in the area of the gastric cardia, is a major stimulus for TLESRs to occur. [10] With fundoplication, a fundic wrap of variable length is created surrounding this area and possibly limiting such distension. Therefore, it is reasonable to hypothesize that the anatomic alterations after fundoplication may increase the threshold for eliciting TLESRs. In line with this hypothesis, it has recently been reported that the frequency with which TLESRs occur after fundoplication was reduced following a meal [5] or short-lasting distension with air. [6,8,11] In a recent study [12], it was also demonstrated that the TLESR increase during adaptive gastric relaxation to a meal is mainly due to there release of hormones, including CCK, after the arrival of nutrients in the duodenum. Furthermore, gastric adaptive relaxation was found to be reduced and gastric emptying to be accelerated after fundoplication. [13] However, experiments using a purely mechanical stimulus are, up to now, lacking. To obtain better insight into the effect of persistent mechanical distension applied in the proximal gastric area on TLESR elicitation and gastric accommodation post fundoplication, we employed an experimental technique using simultaneous EGJ manometry and distension by means of a barostat. The aims of this investigation were to determine the effect of a successfull laparoscopic fundoplication on TLESR frequency both at rest and during persistent gastric distension, the efficacy of TLESRs in facilitating gastric venting after fundoplication compared with normal controls and GERD patients, and the effect of fundoplication on another vagally mediated reflex, gastric accommodation to barostat distension.

Material and methods

Esophageal manometry and isobaric distension of the stomach were performed simultaneously in healthy subjects, in patients with uncomplicated GERD, and in patients who had undergone a laparoscopic Nissen fundoplication. The study protocol was approved by the Northwestern University Institutional Review Board, and written, informed consent was obtained from all participants.

Subject groups

Subjects for this study were derived from a pool of normal volunteers, patients with symptomatic reflux disease, and patients who had undergone laparoscopic Nissen fundoplication to treat chronic reflux disease. They included nine healthy volunteers (5 men, 4 women), eight GERD patients (4 men, 4 women), and eight patients (3 men, 5 women) who had undergone fundoplication. All patients with reflux disease had a history of endoscopic esophagitis but were in endoscopic and symptomatic remission as a result of maintenance therapy with a proton pump inhibitor. On endoscopy, no hiatal hernia > 3 cm in axial length was observed at endoscopy in any of these patients. The patients who had undergone fundoplication were at least 6 mo post-operative at the time of the study, were free of heartburn, had no significant dysphagia, and were using no antisecretory medications. The mean ages of the control subjects were 32 ± 7 yr; GERD patients, 44 ± 10 yr; and patients who had undergone fundoplication, 47 ± 9 yr. Before the study, administration of proton pump inhibitors was discontinued for at least 5 days, and drugs that could affect esophageal motility were discontinued for at least 24 h. Tobacco use was not permitted on the day of the study.

Laparoscopic fundoplication

All laparoscopic fundoplications were performed by the same surgeon (R. J. Joehl) using the same technique. The gastrocolic and gastrosplenic omentum, including the short gastric vessels, were divided, and the proximal gastric fundus was mobilized. The right diaphragmatic crus was approximated with single 2-0 silk sutures. A 360°C fundoplication was constructed with a 50F Maloney bougie placed in the esophagus and traversing the EGJ. A loose wrap of ~3 cm length was created and secured with two sutures placed ~1 cm apart. The proximal suture was anchored to the esophageal musculature and was placed above the anatomic EGJ. At the time of the experiment, > 6 mo after surgery, all patients were on an unrestricted diet.

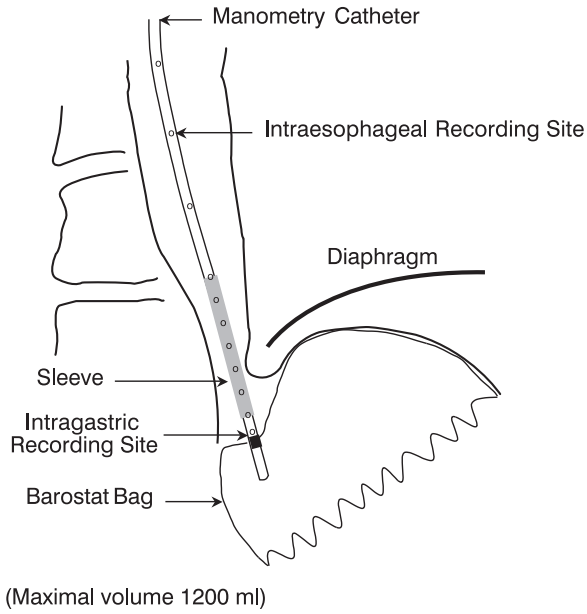


Figure 1
Manometric assembly used in experimental protocols. A sleeve sensor with 7 sidehole recording sites spaced 1 cm apart on the opposite face straddled the esophagogastric junction. The esophageal recording sites were 3, 6, and 9 cm proximal to the sleeve. The intragastric recording site was 1 cm distal to the sleeve. A plastic bag with maximal volume of 1200 ml at the distal end of the catheter was used to distend the stomach.

Manometry assembly and barostat system

A 12-lumen silicone catheter (Dent Sleeve, Wayvill, South Australia) was used for manometry. The assembly incorporated three sidehole recording sites positioned 3, 6, and 9 cm proximal to the sleeve sensor, a 6-cm-long reversed perfused sleeve sensor, 7 sidehole recording sites on the opposite face of the sleeve positioned 1 cm apart, one side hole 1 cm distal to the sleeve to record intragastric pressure, and a large oval channel (1.9 x 2.4 mm inner diameter) lumen for air transit to and from the barostat bag (Figure 1). Each catheter lumen was perfused with sterile water at 0.15 ml/min by using a low-compliance perfusion pump (Dentsleeve, Mark II, 16-channelmodel). Swallowing was monitored with a submental electromyography (EMG) recording obtained by using two disc electrodes positioned under the chin and a grounding patch

attached to the side of a subject's neck. Manometry and swallowing EMG channels were connected to a computer polygraph set at a sampling frequency of 40 Hz for manometry and 200 Hz for EMG (Neomedix Systems, Warriewood, New South Wales, Australia), and processed by using Gastromac software (version 3.5; Neomedix, Warriewood, NewSouth Wales, Australia). The barostat channel was connected to a polyethylene bag (maximal capacity 1200 ml) at one end and an electronic barostat (Janssen, JSI, Beerse, Belgium) at the other. Pressure within the barostat bag was monitored from within the barostat cylinder, and air was injected or aspirated when that pressure differed from the preselected pressure by > 0.2 mmHg. Intragastric bag volume data were stored in a digital data logger (MMS, Enschede, The Netherlands).

Pilot experiment

A pilot study was performed in 10 normal subjects to determine the optimal intragastric pressure associated with an adequate intragastric distension volume stimulus (~400 ml) for triggering TLESRs 10. Beginning at minimal distending pressure (MDP; see below), pressure was increased stepwise by 2 mmHg every 5 min until participants reported intolerable discomfort or the intragastric bag reached a volume of 650 ml. From that pressure level, pressure was decreased stepwise by 2 mmHg every 5 min until MDP was reached again. Mean pooled volume data during inflation and deflation are depicted in Figure 2; 8 mmHg above MDP was chosen as the most suitable fixed-pressure stimulus.

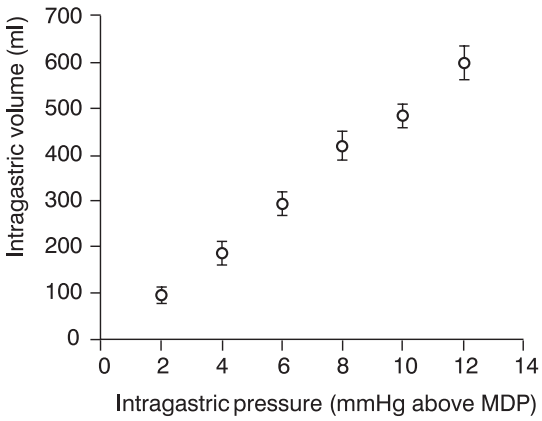


Figure 2
Pilot experiment to determine optimal distension pressure. Mean pooled volume data during inflation and deflation during stepwise gastric distension in 10 healthy subjects. Data illustrated are means ± SE. A pressure of 8 mmHg above minimal distending pressure (MDP) was chosen as fixed-pressure stimulus.

Manometry and barostat recording

Subjects were studied after an overnight fast of at least 10 h. Participants were seated comfortably in an upright position and asked to use a saliva aspirator to minimize swallowing during recording. The manometry assembly, including the lubricated and folded barostat bag, was passed transorally. The bag was then inflated manually with 200 ml of air to unfold it and to assure that it was positioned correctly. The bag was then deflated and connected to the barostat. The catheter was then positioned so that the sleeve was straddling the EGJ high-pressure zone. With the catheter in this position, four to five sidehole recording sites were located in the esophageal body, six to seven sidehole recording sites were within the esophagogastric high-pressure zone, and one side-hole was measuring the intragastric pressure. The MDP was determined after insertion and positioning the catheter by increasing the intrabag pressure, in 1-mmHg steps from 0 mmHg (atmospheric pressure) to the pressure level that first provided an intragastric bag volume of > 30 ml in accordance with the Azpiroz definition [14]. After MDP determination, subjects were allowed to recover for 15 min. This was followed by a 1-h baseline recording period and a 1-h period during which proximal gastric distension was produced with the barostat set to maintain an intrabag pressure at 8 mmHg above MDP.

Data analysis

Intragastric bag volumes during baseline and distension were determined at 10-min intervals. Proximal gastric accommodation was defined as the ratio between the increase in intragastric bag volume during distension and the increment in intragastric bag pressure (8 mmHg) maintained by the barostat [15]. Manometric tracings were analyzed blindly to characterize mean EGJ pressure, swallow-induced EGJ relaxation, TLESRs, and esophageal common cavities (CCs) associated with TLESRs. A CC was defined as an abrupt increase in intraesophageal pressure to intragastric pressure in at least two distal esophageal recording sites [16]. The deglutitive nadir pressure, defined as the swallow-induced (5-ml waterbolus) nadir relaxation pressure, and the nadir EGJ pressure during a TLESR were also measured. Mean end-expiratory EGJ pressure was measured with the sleeve sensor and referenced to intragastric pressure for the entire 1-h interval during baseline and distension ignoring periods with swallowing-related relaxation or contraction and respiratory artifacts. TLESRs were defined by using the criteria of Holloway et al. [17] The completeness of TLESR was evaluated by determining the difference between

intragastric pressure and the nadir pressure during complete relaxation. For the fundoplication patients, TLESRs were scored if the nadir pressure during relaxation was equal to or less than the residual relaxation pressure determined during repeated water swallows.[10] Data were summarized as means ± SE. Averaged data were compared by using one-way ANOVA or Student's *t*-test; $P < 0.05$ was considered significant.

Results

Effect of isobaric distension on proximal gastric volume and EGJ pressure

Minimal distending pressure was similar among the three subject groups: 5.5 ± 0.2 mmHg in the controls, 5.5 ± 0.4 mmHg in the GERD group, and 5.0 ± 0.2 mmHg in the fundoplication group. Gastric accommodation during distension (change in volume/ change in pressure) was also not significantly different among subject groups: 52 ± 21 ml/mmHg among controls, 43 ± 13 ml/mmHg among the GERD patients and 46 ± 19 ml/mmHg among fundoplication patients. Gastric distension at 8 mmHg above MDP significantly increased intra-

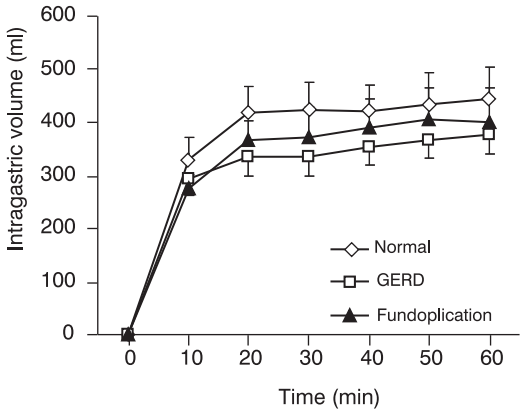


Figure 3
Intragastric volume during distension at a fixed pressure (8 mmHg above MDP) assessed in 10-min intervals in healthy controls, patients after Nissen fundoplication, and gastroesophageal reflux disease (GERD) patients. Intragastric volume during the 60-min distension episode was not significantly different between any of the subject groups ($P \geq 0.5$).

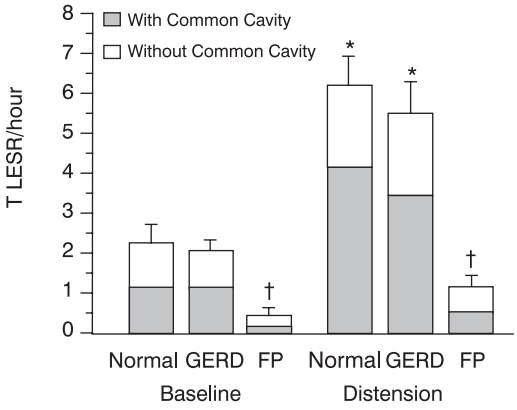


Figure 4
The rate at which transient lower esophageal sphincter relaxations (TLESRs) occurred and the percentage of TLESRs associated with a common cavity during baseline recording and during the period of gastric distension among subject groups. *$P < 0.01$ baseline vs. distension. † $P < 0.01$ fundoplication (FP) vs. normal controls and GERD patients.

gastric volume in normal, GERD, and fundoplication patients as illustrated in Figure 3. Intragastric volume changes were not significantly different among any of the subject groups ($P > 0.5$). EGJ pressure was significantly lower among the GERD patients (18 ± 4 mmHg) compared with either the control subjects (23 ± 3 mmHg) or the fundoplication patients (28 ± 4 mmHg), and this did not change during distension in any subject group: normal, 24 ± 4 mmHg; GERD, 17 ± 3 mmHg; fundoplication, 27 ± 3 mmHg.

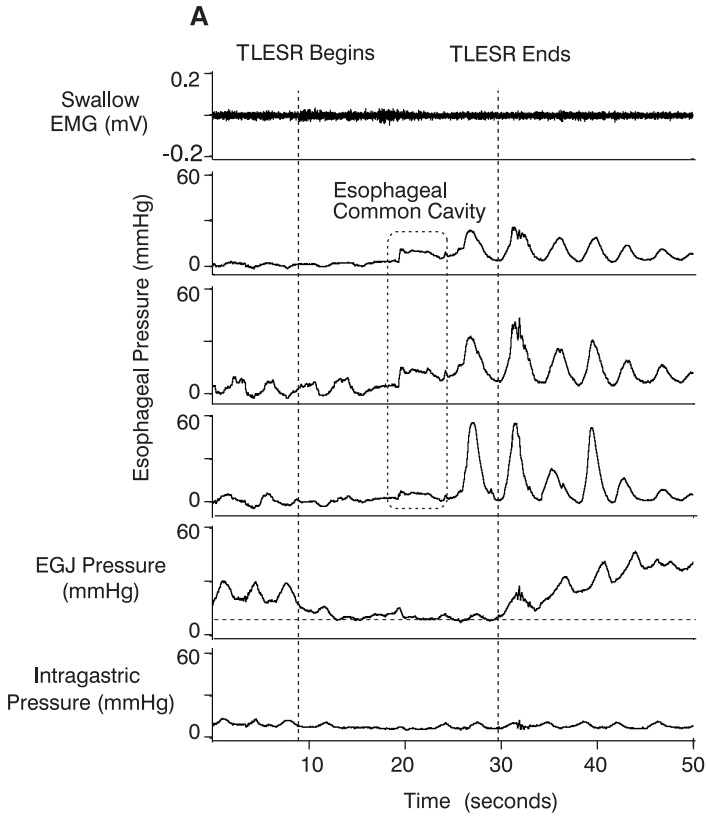
Table 1
Nadir pressure during swallowing and during TLESRs in normal subjects, patients with GERD and patients who had undergone fundoplication.

	Nadir EGJ Pressure mmHg During Swallows	TLESR Nadir Pressure, mmHg	
		Baseline	Distension
Normal controls	3.8 ± 0.4	1.9 ± 0.4	1.4 ± 0.3
GERD	3.6 ± 0.5	1.3 ± 0.4	1.5 ± 0.3
Fundoplication	10.3 ± 1.0*	9.9 ± 2.4*	10.6 ± 0.9*

Values are means ± SE. TLESRs, transient lower esophageal sphincter relaxations; GERD, gastroesophageal reflux disease; EGJ, esophagastric junction. *$P < 0.05$ vs. normal subjects and GERD patients.

Effect of barostat distension on TLESRs

The rate at which TLESRs occurred during each experimental condition for each subject group is illustrated in Figure 4. Normal subjects and GERD patients exhibited similar TLESR rates in the basal state. Fundoplication patients, however, showed a significantly lower TLESR rate during baseline compared with normal controls ($P < 0.01$) and GERD patients ($P < 0.01$). During barostat distension, the TLESR rate increased significantly in both normal ($P < 0.01$) and GERD patients ($P < 0.01$) but not in the fundoplication group. The percentage of TLESRs associated with a CC during the baseline recording was also similar among controls and GERD patients (63 and 65%, respectively) but significantly lower among the fundoplication patients (25%; $P < 0.05$). During barostat distension, the comparative figures were 68% in normal subjects, 66% in GERD patients, and 47% in fundoplication patients. Although the percentage of TLESRs associated with a CC among the fundoplication patients increased during distension, the increase was not significant



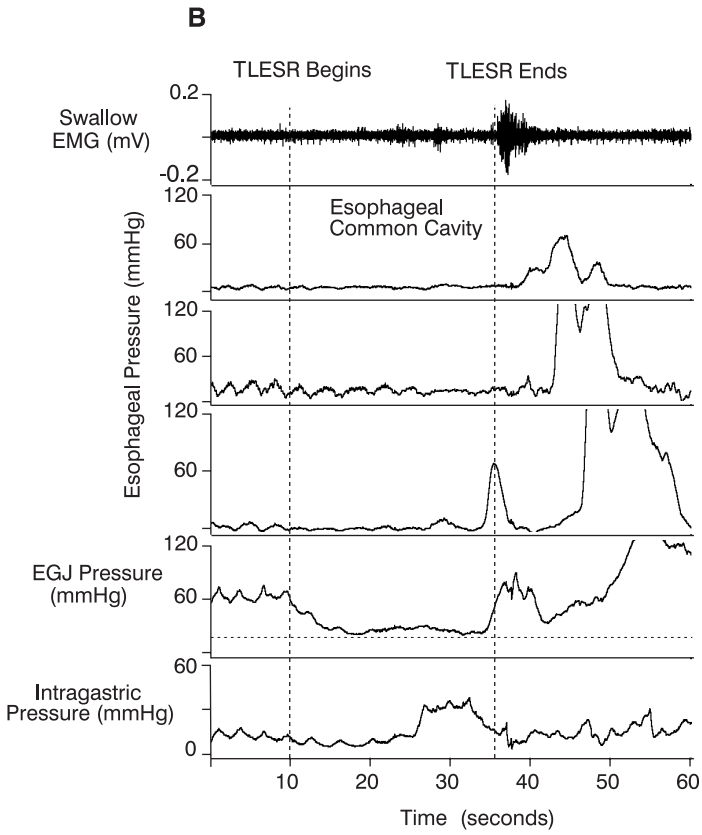


Figure 5

Manometry tracing illustrating an example of a TLESR recorded during the baseline period in a normal control (A) and in a fundoplication patient (B). For clarity, not all manometric channels are depicted. The horizontal dashed line in the esophagastric junction (EGJ) channel represents the corresponding intragastric pressure. Although the subject in B swallowed, as evident in the electomyographic recording, this event occurred after the onset of the TLESR. Note that in A, the EGJ relaxation is complete and accompanied by a common cavity, whereas in B, neither condition is achieved. Also note that, as was often the case, the respiratory effect on the manometric signal was less distinct after fundoplication.

compared with baseline, and the percentage remained significantly less than that observed in either of the other subject groups. In addition to the observed quantitative differences in TLESR rate, significant qualitative differences were observed among the fundoplication subjects. Table 1 compares the nadir relax-

ation pressures observed during swallowing and during TLESRs among the subject groups. Note that in all cases, the relaxation pressure achieved during TLESRs was slightly lower than that achieved during swallowing but was significantly higher in both cases among the fundoplication patients. Only exceptionally was a complete TLESR (nadir pressure of < 2 mmHg) observed in the fundoplication group. The elevated relaxation pressure during TLESRs is exemplified in the manometric tracings illustrated in Figure 5; note that, as was often the case, no CC was observed in the example illustrated. The duration of TLESR was not altered by fundoplication but was similar among the three groups both during baseline and during distension.

Discussion

Although TLESR has been identified as an important physiological mechanism underlying gastroesophageal reflux [18], data on TLESR elicitation and characteristics after a laparoscopic fundoplication are limited. The major finding of this study was that patients who had undergone a successful fundoplication exhibit a lower rate of TLESRs at rest and showed a marked attenuation of the TLESR increase during prolonged gastric distension compared with either healthy controls or GERD patients. Furthermore, most TLESRs in fundoplication patients were characterized by a higher residual pressure (incomplete relaxation) and associated with fewer common cavities. In contrast to TLESR elicitation after operation, the gastric accommodation response to prolonged distension was not impaired after fundoplication. These findings suggest that, in addition to a substantially higher EGJ pressure [7], reflux control after fundoplication is partly attributable to an increased threshold for eliciting the most frequent mechanism of reflux, a TLESR.

In the present experiment, prolonged gastric distension was applied and found to be an effective trigger for TLESRs in normal subjects and GERD patients. In both groups, the TLESR rate increased by about four per hour. However, no significant augmentation in TLESR rate was evident in the fundoplication patients. This observation corroborates earlier reports using 750 ml of intragastric carbon dioxide [6,8,20] or a meal [5,21] to achieve gastric distension that also reported a reduced number of distension-induced TLESRs after fundoplication. However, with bolus gas infusion or with a meal, gastric distension

diminishes over time due to gas escape or gastric emptying, respectively, making the stimulus intensity variable over time. In addition, Zerbib et al. [12] demonstrated that a duodenally administered meal resulted in a similar TLESR rate increase compared with an oral meal, suggesting the involvement of nutrient-induced hormonal factors, especially CCK. [22] We elected to use long-lasting iso-baric distension of the proximal stomach to circumvent these potential limitations. Another advantage of the barostat method is the ability to apply a sustained stimulus for a period of an hour, a major advantage in the study of a physiological event as infrequent and random as a TLESR. At face value, these results seem to contradict a previous study reporting a higher frequency of TLESR in response to gastric air distension in patients with a hiatus hernia. [19] However, there are significant methodological differences between the studies that may explain the discrepancy. First, the definition of hiatus hernia was different. In the previous study, a clip technique was used and axial displacement of the SCJ relative to the hiatus was assessed fluoroscopically, whereas in the present study, endoscopy was used. In our experience, the size of hiatus hernia-estimated endoscopy is always larger than that measured with the clip technique, and several patients thought to have a hiatus hernia on endoscopic grounds will have no demonstrable hernia when the clipping method is used. Because no hiatal hernia ≥ 3 cm in axial length was observed endoscopically in any of the GERD patients investigated in this study, one would anticipate that they would have either no or small hernias if the clipping method was used, making them more comparable with the non hernia group in our previous publication. [11] The second significant methodological difference between the studies was in the method of gastric distension; in the previous study, continuous intragastric air infusion was used, whereas in this case a closed intragastric bag was used.

A key finding in the present study was that gastric accommodation of the stomach to prolonged distension was not impaired with fundoplication. This finding is at variance with recent data [13, 23] demonstrating a reduced gastric accommodation response after a meal. Again, methodological differences may account for the discrepancy. Gastric wall elongation after a meal is due to nutrient-induced hormone release (including CCK) accompanied by minimal intragastric pressure variation. [12] In contrast to this, the present experiment employed isolated and purely mechanical distension at fixed pressure in the proximal stomach. Accommodation to the latter stimulus may be partially dependent on viscoelastic properties of the smooth muscle cells and

connective tissue in the gastric wall. [23] Consistent with the findings of the present study, Vu et al. [13] found gastric compliance unchanged after fundoplication. A major question raised by this and prior investigations is how fundoplication increases the threshold for triggering TLESRs. Present thinking is that TLESR is a vagal reflex elicited mainly by gastric distension. Although the receptive field for triggering TLESRs is not completely clear, mechanoreceptors in the region of the gastric cardia are commonly implicated. [18, 24] On the basis of studies in ferrets [25], two types of mechanoreceptors have been proposed: receptors in series with smooth muscle fibers, responding to wall tension variation, and receptors in parallel with smooth muscle fibers, responding to elongation of the gastric wall. Both types of receptors are activated during gastric distension. [26,27] However the gastric cardia is situated, after fundoplication, within the fundic wrap, presumably with a reduced ability to stretch or elongate [23]. Thus an identical and constant distension stimulus likely results in a diminished cardiac cross-sectional area compared with what would be observed if the same stimulus were applied in normal subjects or GERD patients. Reduced cross-sectional area would, in turn, result in decreased wall tension and elongation, thereby reducing the activation of both types of receptors potentially responsible for triggering TLESRs. Furthermore, because TLESR elicitation and gastric receptive relaxation are both mediated by the vagal nerve and gastric accommodation was not affected by fundoplication in either our experiment or an earlier experiment [13], it is tempting to speculate that the vagal afferent field for triggering TLESRs is either independent of or contained within a larger area responsible for elicitation of gastric receptive relaxation and that only the first is substantially reduced by fundoplication.

Another finding confirmed in the present study was of incomplete relaxation during TLESR, as first described by Ireland et al. [9] Despite the fact that TLESRs scored in the fundoplication patients (Figure 4B) closely resembled the distinctive temporal profile of TLESRs observed in normal subjects (Figure 4A), they technically do not meet the criteria established by Holloway et al. [17] because the nadir pressure was $\geq$ 2mmHg in most instances. However, as was also demonstrated by the Adelaide group, deglutitive lower esophageal sphincter relaxation was incomplete in these patients, justifying the use of the modified criteria defined by Ireland et al. [5] Postprandial epigastric fullness and bloating appear in 10–80% of patients after Nissen fundoplication [28, 29], and an inability to relieve this discomfort by belching is frequently reported. [7]

A TLESR associated with a common cavity is the most relevant manometrically identified mechanism of gastric gas venting [16]. Apart from a fall in the number of TLESRs, a significant reduction of the percentage of TLESRs associated with a common cavity phenomenon was also found in fundoplication patients. These data are in concordance with findings by the Adelaide group, who found a significant reduction in the number of common cavities during gaseous distension of the stomach (10 min) after fundoplication. [6,20] The observed pattern of incomplete relaxation during TLESRs provides a potential explanation for the frequently reported symptoms related to increased amounts of intestinal gas after fundoplication.

In summary, fundoplication patients exhibit a diminished rate of TLESRs both at rest and during isobaric gastric distension compared with both normal controls and GERD patients. Second, TLESRs in fundoplication patients were characterized by a higher residual pressure and a lower efficacy of facilitating gastric venting than was seen in normal subjects or GERD patients. Finally, gastric accommodation was not impaired with fundoplication, suggesting that the vagal afferent field for triggering TLESRs is contained within a wider field for elicitation of gastric receptive relaxation and that only the first is affected by fundoplication.

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4

Long-term effect of fundoplication on motility of the esophagus and esophagogastric junction

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Abstract

This study assessed the long-term effect of Nissen fundoplication on esophageal and esophagogastric junction (EGJ) motility. Symptoms were scored and esophageal manometry performed in 34 consecutive patients with chronic gastroesophageal reflux disease, before, 3 months after and 2 years after surgery. Distal peristaltic amplitude increased from a median of 57 (95 per cent confidence interval (c.i.) 18 to 107) mmHg to 86 (95 % c.i. 54 to 208) mmHg ($P < 0.001$) at 3 months and 92 (45 to 210) mmHg ($P < 0.001$) at 2 years. In four patients the increase was to more than 180 mmHg and three of these patients reported odynophagia. After surgery, a linear relationship was observed between the peristaltic amplitude and nadir EGJ relaxation pressure at 3 months ($r_S = 0.68$, $P < 0.001$) and 2 years ($r_S = 0.64$, $P < 0.001$). A significant correlation was also found between amplitude and both basal EGJ pressure and intrabolus pressure at 3 months ($r_S = 0.58$, $P < 0.001$ and $r_S = 0.63$, $P < 0.001$ respectively) and 2 years ($r_S = 0.71$, $P < 0.001$ and $r_S = 0.49$, $P = 0.024$). There was also a relationship between peristaltic amplitude and the odynophagia score at 2 years ($r_S = 0.60$, $P = 0.017$). In conclusion, within 3 months of fundoplication the amplitude of esophageal peristalsis increased substantially, leading to a nutcracker esophagus and odynophagia in a subgroup of patients. These phenomena did not appear to progress with time.

Introduction

With the advent of laparoscopic techniques, Nissen fundoplication is increasingly advocated for the treatment of gastroesophageal reflux disease (GERD). The long-term efficacy for this procedure in the control of acid reflux and reflux symptoms has been reported to range from 80 to 95 per cent.[1,2] Potential underlying mechanisms include an increased pressure at the level of the esophagogastric junction (EGJ), a decreased incidence of transient lower esophageal sphincter relaxations and incomplete EGJ relaxation on swallowing or during transient sphincter relaxation.[3,4,5] The consequences of these effects on esophageal motility over time are not completely understood.

Although recent studies have established that both nadir EGJ pressure and intrabolus pressure increase after Nissen fundoplication, suggesting a restricted passage through the EGJ, there have been few reports of long-term effects on esophageal dynamics.[3,6,7] It is now generally accepted that GERD is associated with an increased prevalence of impaired esophageal contractile activity, but data regarding esophageal motility after fundoplication are conflicting. Some studies [8,9] have shown an increased amplitude only in patients with impaired preoperative esophageal contractility, whereas others have found no change.[10,11] The relationship between altered EGJ dynamics and the motor function of the esophageal body after operation remains to be elucidated.

The aim of this prospective study was to determine whether a successful Nissen fundoplication affects esophageal contractile activity and, if so, whether altered esophageal motility correlates with postoperative symptoms of dysphagia and odynophagia, alterations in EGJ dynamics and radiological outcome.

Patients and methods

Patients

Thirty-four consecutive patients (20 men and 14 women of median age 53.5 (range 49–58) years) with chronic GERD, established by symptom evaluation, upper gastrointestinal endoscopy, 24-h pH monitoring and esophageal manometry, were included in the study. All of these patients were also participants in a multicentre randomized trial comparing laparoscopic with open Nissen fundoplication [12]. Antireflux surgery was proposed for patients with refractory symptoms of GERD despite antireflux medication (at least 40 mg omeprazole daily) and with pathological 24-h esophageal acid exposure (pH < 4 for more than 6 per cent of the time). Seventeen patients were randomized to undergo the laparoscopic and 17 the open procedure.

Upper gastrointestinal endoscopy and 24-h pH monitoring were performed before and 3 months after operation. Manometry was performed before surgery and at 3 months and 2 years after operation. Clinical assessments were carried out before each manometric investigation and radiography was used to assess the position of the fundic wrap. Patients who needed reoperation were excluded from the study and medication that might affect esophageal motility was stopped at least 72 h before manometry. The medical ethics committee of the University Medical Centre Utrecht approved the study; written informed consent was obtained from all participants.

Operative technique

Both open and laparoscopic Nissen fundoplication were performed using a technique described previously [12]; a floppy 360° fundoplication of 3.0–3.5 cm was created. The wrap and diaphragm were identified with one and two haemoclips (less than 1 cm apart) respectively, for future radiographic images. The clip identifying the fundic wrap was placed in the angle of His before the wrap was constructed, so was located in the wrap after fundoplication.

Clinical assessment

Clinical outcome was assessed prospectively using a standard questionnaire before, at 3 months and 2 years after surgery. Heartburn, dysphagia and odynophagia were scored by means of a Likert scale combining frequency (daily, weekly, monthly or less frequently) and severity (severe, moderate, mild or absent) for each symptom. Dysphagia was defined as an unpleasant sensation of food remaining in the esophagus shortly after food intake. Odynophagia

was defined as a painful sensation behind the sternum during passage of food through the esophagus.

Esophageal manometry

After an overnight fast, an eight-channel silicone assembly with an incorporated sleeve sensor (Dent Sleeve, Belair, South Australia, Australia) was used. The assembly (outer diameter 4.7 mm, inner diameter 0.74 mm) incorporated pharyngeal and hypopharyngeal sideholes (respectively 25 and 20 cm proximal to the proximal border of the sleeve), three esophageal sideholes (5, 10 and 15 cm proximal to the proximal border of the sleeve), a reversed perfused sleeve sensor with one side-hole on its proximal border and one intragastric sidehole (2 cm distal to the sleeve). Each catheter lumen was perfused with degassed water at a rate of 0.45 ml/min using a pneumohydraulic perfusion pump (Arndorfer Medical Specialities, Greendale, Wisconsin, USA) and pressures were recorded with external pressure transducers (DPT-100; Medisize, Hillegom, The Netherlands). Manometry data were stored in a digital data logger set at a sampling frequency of 4 Hz (MMS, Enschede, The Netherlands). All investigations were performed with subjects in a supine position.

The assembly was passed transnasally until the sleeve sensor entered the stomach. A stepwise pull-through using an automated puller (MMS) was performed until the sidehole on top of the sleeve entered the distal esophageal body, so that the sleeve sensor was straddling the EGJ. The manometric response to ten standardized wet swallows (5-ml water bolus) was recorded.

The amplitudes and duration of the esophageal pressure waves at 15 cm (proximal esophagus), 10 cm (mid) and 5 cm (distal) above the upper margin of the EGJ were measured, disregarding non-propagated contractions. Velocity of the peristaltic waves was calculated as the peak-to-peak velocity of the waves between adjacent sideholes. After each swallow the intrabolus pressure, defined as the intraesophageal pressure increase before the steep upstroke of a peristaltic wave [7,13], was assessed from the most distal recording site. Ineffective esophageal motility was defined as more than 30 per cent of pressure waves in the distal esophagus with a contraction amplitude lower than 30 mmHg [14]. When peristaltic contraction amplitudes were 180 mmHg or more, a diagnosis of nutcracker esophagus was made.

Preoperative EGJ pressure is mainly attributable to the intrinsic lower esophageal sphincter (LES) and the extrinsic compression by the crural diaphragm. After surgery, there is the additional component of the fundic wrap.

Mean end-expiratory EGJ pressure, referenced to the end-expiratory gastric baseline pressure, was calculated over a 5-minute period. The nadir EGJ pressure, defined as the lowest mean residual pressure over an interval of at least 3 s during swallow-induced relaxation, was measured for each swallow. Correlations between peristaltic amplitude in the distal esophagus, basal and nadir EGJ pressures, and intrabolus pressure were assessed before, and 3 months and 2 years after fundoplication.

Radiological examination of the esophagus

All patients underwent barium esophagography before and 2 years after operation to obtain information about the position of the fundic wrap and dimensions of the esophageal body. Radiographs were assessed by an independent observer and one of the authors, who were blinded to symptomatic and manometric outcomes. The position of the wrap (abdominal, intrathoracic or abdominothoracic), the width of the esophagus (normal, dilated or constricted), the presence of herniation of the wrap and telescoping of the stomach through the wrap were investigated. Herniation was considered to be complete if the wrap was located above the diaphragm and partial if it was at the level of the diaphragm. Telescoping was defined as migration of the EGJ (mild) or of part of the stomach (severe) above the wrap [15].

Statistical analysis

Results are expressed as median values with the 95 per cent confidence interval (c.i.). Manometric variables measured before, and 3 months and 2 years after Nissen fundoplication were assessed using the non-parametric Friedman test for repeated measures with post hoc adapted Student–Newman–Keuls test. The Mann–Whitney U test was used for statistical comparisons between unpaired patient groups. The Spearman coefficient was used to determine correlations. For all statistical tests $P < 0.050$ was considered significant.

Results

There were no significant differences between patients operated on laparoscopically and those who underwent the open procedure with respect to manometric variables or symptoms at either 3 months or 2 years after operation.

The effect of fundoplication on the function of the esophageal body over time is shown in Table 1. Before surgery three patients had ineffective esophageal motility, with propagating waves for 70 per cent or less of ten wet swallows, but motility was normal at 2 years. After operation there was a significant increase in the amplitude of peristaltic contractions in the distal esophagus (Figure 1 and Table 1). This did not change significantly over time and was unrelated to preoperative amplitude ($r_S = 0.11$, $P = 0.481$). In four patients (two laparoscopic, two open), the amplitude increased to the range of nutcracker esophagus, with contraction amplitudes above 180 mmHg. Even when these four patients were excluded, a significant increase in amplitude was observed at both 3 and 24 months after surgery ($P < 0.001$). No increase in the amplitude of peristaltic contractions was found in the proximal or middle part of the esophagus. Intrabolus pressure also increased after fundoplication (Table 1) and correlated positively with the contraction amplitude at 3 months ($r_S = 0.63$, $P < 0.001$) and 2 years ($r_S = 0.49$, $P = 0.024$). The duration and peak-to-peak velocity of peristaltic contractions were not affected by the operation.

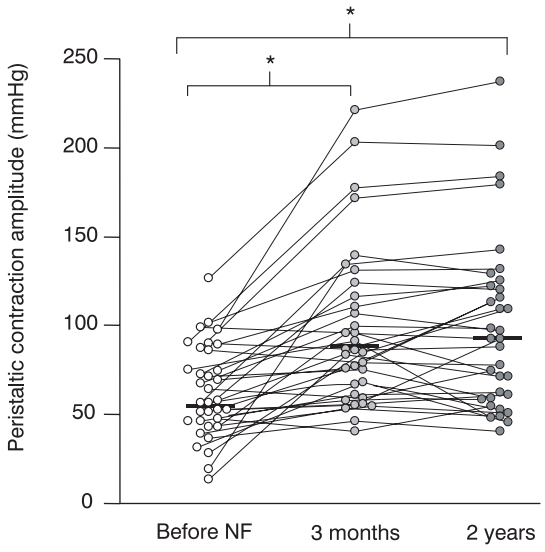

Figure 1
Amplitude of peristaltic contractions in 34 patients measured before, at 3 months and 2 years after uncomplicated Nissen fundoplication. Note that in four patients the amplitudes increased to the range of a nutcracker esophagus (above 180 mmHg). Horizontal bars denote the median amplitude of peristaltic contractions at each time point. *$P < 0.001$ (Student–Newman–Keuls test).

Table 1
Esophageal and esophagogastric junction motility assessed before, and at 3 months and 2 years after Nissen fundoplication.

	Before NF	After NF			
	(n=34)	3 months (n=34)	*P**	2 years (n=34)	*P**; *P*†
Primary peristalsis (%)	100 (50-100)	100 (30-100)	0.939	100 (40-100)	0.422 ; 0.326
Peristaltic amplitude (mmHg)	57 (18-107)	86 (54-208)	<0.001	92 (45-210)	<0.001; 0.124
Intrabolus pressure (mmHg)	9.7 (6.9-13.7)	11.8 (7.2-19.0)	<0.001	12.2 (8.9-18.3)	<0.001; 0.509
EGJ length (cm)	3.5 (1.8-5.0)	4.0 (3.0-5.5)	0.048	4.0 (2.0-6.0)	0.032; 0.740
Basal EGJ pressure (mmHg)	6.8 (2.1-15.0)	11.6 (4.1-24.3)	<0.001	12.0 (2.8-22.8)	<0.001; 0.236
Nadir EGJ pressure (mmHg)	1.2 (0.2-2.3)	6.1 (2.3-12.6)	<0.001	6.8 (1.0-12.3)	<0.001; 0.626

Values are median (95 per cent confidence interval). NF, Nissen fundoplication; EGJ, esophagogastric junction. *Versus before NF; †versus 3 months after NF (Student-Neuman-Keuls test).

Overall EGJ length increased significantly with fundoplication, and was similar at 3 months and 2 years after surgery (Table 1). Basal EGJ pressure increased after fundoplication ($P < 0.001$) but did not change significantly with time after surgery. Deglutitive nadir EGJ relaxation pressure increased to a similar extent as basal EGJ pressure and also did not change with time (Table 1).

Before surgery there was no significant relationship between basal or nadir EGJ pressure and the amplitude of peristaltic contractions, but after fundoplication basal EGJ pressure was related to amplitude at 3 months and two years (Figure 2). Moreover, a significant correlation was found between the deglutitive nadir EGJ pressure and amplitudes of peristaltic contractions at 3 months and 2 years (Figure 3). Patients with high-amplitude peristaltic contractions after operation had significantly higher EGJ basal and deglutitive nadir EGJ relaxation pressures than patients with amplitudes in the normal range (Table 2).

At 2 years, a satisfactory anatomical position of the fundoplication was observed in 23 of the 34 patients. In seven patients the EGJ had migrated upwards (partial herniation), resulting in an abdominothoracic position of the

wrap. Mild telescoping was observed in six patients, two of whom also had partial herniation. Dilatation of the esophagus was not seen in any patient. No correlation was found between radiological outcome and any of the manometric variables.

Adequate symptomatic reflux control (Likert score 0) was obtained in 33 of 34 patients at 3 months and in 30 patients at 2 years after fundoplication. Eleven patients experienced odynophagia (seven mild, two moderate and two severe) at 2 years. A significant correlation was found between peristaltic amplitude and odynophagia at 2 years (r_S=0.60, P=0.017). Three of the four patients with extremely high amplitudes reported odynophagia (two moderate, one severe), resulting in a significantly higher overall odynophagia score in this subgroup than in patients with normal motility (P = 0.042) (Table 2).

Before surgery, dysphagia was present in 15 patients (five mild, five moderate and five severe). There was no relationship between basal or nadir EGJ relaxation pressures, the severity of oesophagitis and the presence or absence of a hiatal hernia. Complete resolution or major improvement of dysphagia was reported by nine patients at 3 months and 12 patients at 2 years. Nine of 19 patients with no dysphagia before operation had developed this symptom (six mild, three moderate) at 3 months after fundoplication. By 2 years, dysphagia had disappeared in three patients (all with mild symptoms), become severe in three and arose de novo in a further three patients (all moderate), so that one

Table 2
Manometric data for patients with normal and high-amplitude peristaltic contractions in the distal esophagus after Nissen fundoplication.

	3 months after NF			2 years after NF		
	Normal (n=30)	High Amplitude (n=4)	*P**	Normal (n=30)	High Amplitude (n=4)	*P**
Primary peristalsis (%)	100 (20-100)	95 (80-100)	0.485	100 (40-100)	95 (90-100)	0.777
Intrabolus pressure (mmHg)	11.4 (6.8-19.2)	15.8 (14.1-17.9)	0.025	11.6 (8.9-17.3)	14.6 (12.9-18.8)	0.037
Basal EGJ pressure (mmHg)	10.9 (3.8-20.7)	19.9 (14.3-25.0)	0.004	10.9 (2.7-20.4)	19.3 (12.8-23.8)	0.010
Nadir EGJ pressure (mmHg)	5.4 (2.2-11.9)	9.9 (8.2-12.9)	0.013	6.3 (1.3-11.6)	10.6 (8.1-12.7)	0.013
Odynophagia score (score 0-3)	-	-	-	0.0 (0.0-1.9)	2.0 (0.0-3.0)	0.042

Values are median (95 per cent confidence interval). NF, Nissen fundoplication; EGJ esophagogastric junction. * Mann-Whitney U test.

patient had mild, five had moderate and three severe dysphagia. At both 3 months and 2 years after operation, deglutitive nadir EGJ pressure was significantly higher in patients with moderate or severe dysphagia than in those with no or mild dysphagia ($P = 0.017$ and $P = 0.004$ respectively). No other discriminative manometric variable was found. In addition, a significant correlation was found between the dysphagia score and nadir EGJ pressure at 2 years after operation ($r_S = 0.50$, $P = 0.003$), which was not observed at 3 months. No significant relationship was found between the amplitude of peristaltic contractions and the dysphagia score.

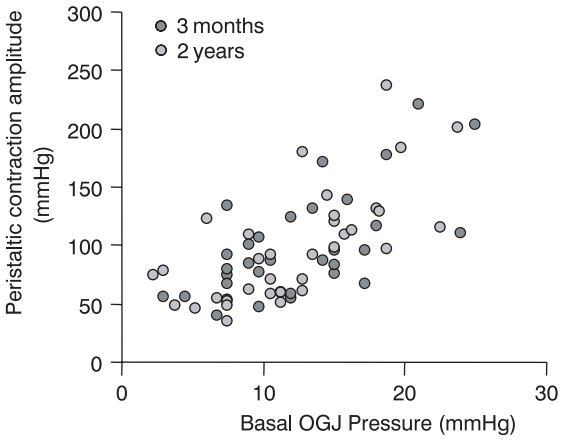

Figure 2
Correlation between basal esophagogastric junction (EGJ) pressure and the amplitude of peristaltic contraction waves in the distal esophagus at 3 months ($r_S = 0.58$, $P < 0.001$) and 2 years ($r_S = 0.71$, $P < 0.001$) after fundoplication.

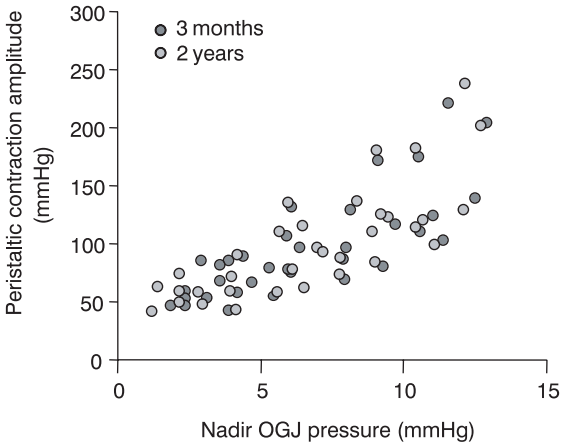

Figure 3
Correlation between nadir esophagogastric junction (EGJ) relaxation pressure during swallowing and the amplitude of peristaltic contraction waves in the distal esophagus at 3 months ($r_S = 0.68$, $P < 0.001$) and 2 years ($r_S = 0.64$, $P < 0.001$) after surgery.

Discussion

Although incomplete EGJ relaxation has been identified as a common effect of Nissen fundoplication [11,16,17], data on the long-term consequences for esophageal motility are limited. The major finding of this study was that successful operation results in a marked increase of peristaltic amplitude in the distal esophagus and that this amplitude correlates significantly with the altered EGJ dynamics, specifically basal EGJ pressure and nadir EGJ relaxation pressure. The amplitude appears not to increase any further after 3 months. Peristaltic amplitudes in the range of a nutcracker esophagus (more than 180 mmHg) were observed in four of 34 patients and three of these patients reported odynophagia. No anatomical correlate was found on barium esophagography at 2-year follow-up. These findings strongly suggest that the creation of a high-pressure zone at the level of the EGJ affects esophageal body motility and may, in a small proportion of patients, lead to the development of a nutcracker esophagus.

The present data corroborate earlier reports describing an increased esophageal contraction amplitude following antireflux surgery. [8,9,11,16] Peristalsis facilitates bolus transport effectively when contraction amplitudes are greater than 30 mmHg. [18] Some reports have described an increased amplitude only in patients with ineffective esophageal motility (contraction amplitude less than 30 mmHg) before operation. [8,9] These findings are at variance with the present finding of an increased amplitude irrespective of that before operation, in line with results reported by others. [16]

A question raised by this and previous investigations is why the contractile activity in the distal esophagus increases after fundoplication. Such an effect is not observed with medical therapy, despite the healing of mucosal injury. [19,20] In a study that combined manometry and videofluoroscopy, Kahrilas et al. [21] found that a restricted hiatal opening after fundoplication decreased the efficacy of transport across the EGJ. A possible hypothesis is that the increase in esophageal contractility is necessary to overcome the increased resistance at the EGJ after operation. Nadir EGJ relaxation and intrabolus pressures, both a measure of resistance across the EGJ, increase with fundoplication [7], as found in the present study. In line with the hypothesis, a statistically significant correlation was found between the postoperative increase in contraction amplitude and the nadir EGJ relaxation pressure, as well as a significant relationship between amplitude and intrabolus pressure. Furthermore, Rydberg et al. [16],

who compared the manometric outcome of a partial fundoplication (Toupet) with that following a total fundoplication (Nissen–Rosetti), reported a higher EGJ pressure after the latter procedure. In addition, an increase in peristaltic amplitude was found only after total fundoplication. These data strongly suggest that the increase in esophageal peristaltic amplitude represents a compensatory mechanism whose purpose is to overcome the increased resistance at the sphincter complex.

After Nissen fundoplication a small subgroup of patients developed peristaltic contractions in the distal esophagus with an amplitude greater than 180 mmHg, resembling a nutcracker esophagus. [14] These extraordinarily high contraction amplitudes were apparent 3 months after surgery and did not increase subsequently. Significantly higher nadir EGJ relaxation and intrabolus pressures were recorded in these patients after operation. In addition, a significant relationship was found between nadir EGJ pressure and contraction amplitude. It is therefore likely that the resistance across the EGJ was higher in this subgroup of patients and induced greater contractile activity in the distal esophagus.

Odynophagia occurred frequently after fundoplication and was related to the postoperative amplitude of contractions in the distal esophagus. Among postoperative symptoms, retrosternal pain is prominent, perhaps owing to a restricted passage or to the recurrence of gastroesophageal reflux. The latter affects only a small proportion of patients, ranging from 2 to 5 per cent during the year or so after surgery as diagnosed by endoscopy and 24-h pH monitoring. [22,23] The present results indicate that in a small proportion of patients odynophagia may be caused by esophageal hypercontractility, resulting in a manometric pattern resembling that of a nutcracker esophagus in combination with normalization of the 24-h pH profile.

In agreement with observations by others [7], the present study found that postoperative dysphagia was related to the deglutitive nadir EGJ relaxation pressure. This relationship was only present 2 years after surgery, suggesting that incomplete EGJ relaxation may play a role in generating long-lasting dysphagia. Apart from manometry, the authors rely mainly on barium esophagography to evaluate postoperative esophageal and EGJ function. In this study, no relationship was observed between the anatomical position of the fundic wrap and an adverse clinical or manometric outcome. Additional techniques, such as combined fluorososcopy and manometry [24] or multichannel intralumi-

nal impedance and manometry [25], might help to shed more light on the pathogenesis of postoperative dysphagia.

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Relationship between partial gastric volumes and dyspeptic symptoms in fundoplication patients
A 3D ultrasonographic study

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Abstract

Impaired gastric accommodation may induce dyspeptic symptoms in post-fundoplication patients. Our aim was to assess the effect of a meal on total and partial gastric volumes in relation to dyspeptic symptoms in both dyspeptic and nondyspeptic fundoplication patients using three-dimensional (3D) ultrasonography. Eighteen postfundoplication patients of whom eight with and ten without dyspeptic symptoms and eighteen controls were studied. Three-dimensional ultrasonographic images of the stomach were acquired and symptoms were scored while fasting and at 5, 15, 30, 45, and 60 min after ingesting of a 500-mL liquid meal. From the 3D ultrasonographic images of the stomach the total, proximal and distal gastric volumes were computed. Dyspeptic and nondyspeptic fundoplication patients exhibited similar total gastric volumes at 5 min postprandially compared to controls, whereas smaller total gastric volumes were observed from 15 to 60 min postprandially ($P = 0.007$ and $P < 0.001$ respectively). Postprandial proximal/total gastric volume ratios were markedly reduced in both dyspeptic (0.39 ± 0.016; $P < 0.05$) and nondyspeptic (0.38 ± 0.016; $P < 0.01$) fundoplication patients compared to controls (0.47 ± 0.008). In contrast, distal/total gastric volume ratios were larger in dyspeptic fundoplication patients (0.14 ± 0.008) compared to both nondyspeptic fundoplication patients (0.11 ± 0.007; $P < 0.05$) and controls (0.07 ± 0.003; $P < 0.001$). Dyspeptic fundoplication patients had a higher postprandial score for fullness, nausea and pain than nondyspeptic patients ($P < 0.05$) and controls ($P < 0.05$). Meal-induced distal gastric volume increase correlated significantly with the increase in fullness ($r=0.68$; $P < 0.01$). In conclusion, after a liquid meal, fundoplication patients exhibit a larger volume of the distal stomach compared with controls. Distal stomach volume was more pronounced in dyspeptic fundoplication patients and related with the increase in postprandial fullness sensations.

Introduction

In recent years, Nissen fundoplication is increasingly advocated as a surgical remedy for gastroesophageal reflux disease (GERD), and its efficacy for the long-term control of acid reflux has been as high as 90%. [1,2] Despite this successful control of reflux, long-lasting dyspeptic symptoms, such as postprandial fullness, nausea, bloating and upper abdominal pain/discomfort, persist in 10-40% of patients. [3-6] To date, the underlying mechanism of post-fundoplication dyspepsia is still incompletely understood.

Gastric accommodation to a meal is a vagally mediated reflex, triggered by antral filling and the entrance of nutrients into the duodenum. [7-9] It results in an adaptive relaxation of the proximal stomach wall, providing the meal with a reservoir without inducing symptoms and/or intragastric pressure increase. [10] Impaired fundus accommodation is associated with dyspeptic symptoms in a variety of conditions including functional dyspepsia [11-17], postfundoplication dyspepsia [18,19], diabetes mellitus [20], and postvagotomy/gastric surgery. [21] Scintigraphy studies have shown an abnormal intragastric distribution of food after fundoplication, with an augmented accumulation in the distal stomach, and an accelerated gastric emptying. [22] Likewise, in patients with functional dyspepsia, a wider antrum than in healthy controls has been repeatedly reported. [23,24] Recent biomechanical studies in health [25] and functional dyspepsia [8] have established that the less compliant antrum is hypersensitive to artificial [8,25] or meal-induced [26] distension. Although the pathophysiology of postfundoplication dyspepsia is likely complex, it is reasonable to hypothesise that impaired control of fundic accommodation may lead to an overload of the sensitive distal stomach with fundoplication, thereby inducing dyspeptic symptoms. However, to date, noninvasive real time experiments directly measuring total and partial gastric volumes in relation to dyspeptic symptoms postfundoplication, are lacking.

Therefore, the aims of this investigation were to determine with a noninvasive real-time 3D ultrasound technique, to what extent fundoplication affects total, proximal and distal gastric volumes after a liquid nutrient and whether these altered volumes are related to postoperative dyspeptic symptoms.

Materials and methods

Patients

Three groups of subjects were studied: (1) 8 patients (5 men, 3 women; mean age 55 (42-66), BMI 27 (24-28) who had undergone a Nissen fundoplication with dyspeptic complaints fulfilling the Rome II criteria; (2) 10 patients (7 men, 3 women; mean age 42 (23-66), BMI 26 (18-34) after fundoplication without dyspeptic complaints and (3) 18 healthy volunteers (11 men, 7 women; mean age 34 (20-54) yrs, BMI 23 (20-29). Antireflux surgery was performed in patients with refractory symptoms of GERD despite at least 40 mg of omeprazole daily and with pathological 24-h esophageal acid exposure (>6%) and a positive association between reflux and symptoms (SAP > 95%). [27] Preoperatively, no dyspeptic complaints were reported in either patient group. At the time of the study, all patients were at least 24 months after surgery and they were free of heartburn, had no significant dysphagia, and were taking no antacids. Except for a slightly higher mean age (55 n 42 yrs; ($P < 0.05$)), which does not affect gastric accommodation [18], dyspeptic patients were not significantly different from nondyspeptic patients regarding sex, weight, length, and BMI. Prior to the study, administration of medication that could affect gastric motility was discontinued for at least 7 days. The study was approved by the medical ethics committee of the University Medical Center Utrecht and written informed consent was obtained from all participants.

Operative technique

NF was performed as follows: The proximal fundus was mobilised by coagulating and dividing the gastrocolic and gastrosplenic omentum, including division of the short gastric vessels. The right crus was approximated and a floppy 360° fundoplication of 3.0-3.5 cm was constructed. Three nonresorbable stitches were used to create the fundic wrap.

Experimental design

Subjects were studied after an overnight fast of at least 10 h. Participants were comfortably seated in a wooden chair leaning slightly backward. The test meal was ingested within 3 min and the end of the ingestion period was defined as time zero. Ultrasonographic data were acquired while fasting and at 5, 15, 30, 45 and 60 minutes after meal ingestion. Occurrence of antral contractions was observed by 2D ultrasound before meal ingestion to evaluate whether participant's interdigestive migrating motor complex was in phase III (regular

contractions with a frequency of 3/min). If a phase III pattern was observed, meal ingestion was postponed until phase I returned.

3D ultrasonography imaging system

The 3D imaging system consisted of a commercially available ultrasound (US) scanner (Esaote-Pie Medical, Maastricht, the Netherlands) with a 3.5 MHz curved US probe and a tracking system (Esaote-Pie Medical, Maastricht, the Netherlands). The tracking system consisted of a transmitter generating a spatially varying magnetic field and a small receiver containing 3 orthogonal coils to sense the magnetic field strength. [28] The receiver was firmly attached to the US probe. Data were transferred to the computer workstation and stored on a 30 GB harddisk. Data processing was done on a Windows-NT version 4.0 workstation equipped with two 233 MHz Pentium processors and 256 MB RAM.

In vitro validation experiment

An in vitro validation experiment was performed to assess air-fluid interfaces utilizing the 3D imaging system. A balloon with a maximal capacity of 1000 mL was filled with 12 randomly chosen volumes between 0 and 600 mL consisting of a mixture of 40% Nutridrink and 60% H_2O and 0, 5, 10, 15, and 20% of air, respectively. Then the balloon was positioned in a water basket and the intra-balloon pressure was measured using a manometer enabling the introduction of a correction factor for air compressibility using Boyle's Law. Thereafter a 3D imaging recording (see below) was performed and two investigators analysed data while blinded for the actual volumes.

Data acquisition

Using the 3D imaging system, the US probe with attached sensor was used to localise the left lateral and superior margins of the stomach and the pylorus. The depth of scanning was adjusted enabling a US scan of the stomach, superior mesenteric vein, aorta, left liver lobe and diaphragm on top of the gastric fundus. A standardised US scanning pattern was used, starting at the left lateral subcostal margin and then moving distally to the pylorus having the US probe in a vertical position. During the scan all participants suspended their breathing in inspiration. For each ultrasound scan approximately 300 - 400 2D ultrasound images were stored with a scan typically lasting 15 - 20 s. The investigator (RS) was blinded to the type of patient (dyspeptic or nondyspeptic) he was scanning. To address the problem of air bubbles in the fundus, the visible

amount of air was estimated according to Tefera et al. [28] (0: no visible air; 1: small amounts; 2: moderate amounts; and 3: great amounts of air, disturbing the quality of the ultrasound, hence, necessitating exclusion from the study).

Test meal

The meal (500 mL) consisted of a 200 mL lactose- and fiber- free milk drink, containing 3.3 gram proteins, 12.0 gram carbohydrates, and 4.3 gram fat, 300 kcal (Nutridrink, Nutricia, Zoetermeer, The Netherlands) mixed with 300 mL H_2O.

Volume estimation

For gastric volume estimation we used software with rendering and volume estimation capability (Invivo, Medcom, Darmstadt, Germany). The 300-400 2D sagital US frames were processed to construct 3D images, containing 60-70 sagittal planes. In the sagittal US scanplanes the inner layer of the stomach wall, corresponding to the interface between the outer profile of the gastric wall mucosa and the liquid nutrition, was outlined in an average of 20-30 planes. The computer using a triangulation technique generates gastric contours in the intermediate frames. Then a 3D reconstructed image and volume of the stomach was obtained. From this 3D reconstruction, the proximal part was separated by a dividing plane 10 cm below the point the fundic top reaches up to the diaphragm, perpendicular to the longitudinal axis of the stomach. Similarly, a distal part was separated, defined as the gastric region between the anatomical landmark AA (the sagital US scanplane in which the antrum, the left liver lobe in cross section with the superior mesenteric vein and the abdominal aorta in a longitudinal section were simultaneously visible [29]) and the gastroduodenal junction. The investigator (RS) was blinded to the order of the tracings in time and to the origin of the tracing (patient or healthy subject).

Symptom evaluation

Subjects were asked to score dyspeptic symptoms (epigastric fullness, nausea, and upper abdominal discomfort/pain) using a 100-mm visual analogue scale (VAS) for each symptom at fasting and at 5, 15, 30, 45 and 60 minutes postprandially. On the VAS scale 0 denotes no symptoms and 100-mm an intolerable symptom.

Statistical analysis

Data were summarized as mean (SEM). Normality was tested using Kolmogorov-Smirnov test. At consecutive time points averaged 3D volume data and averaged symptom scores were compared among controls, dyspeptic and nondyspeptic fundoplication patients using repeated measures analysis of variance (ANOVA). Averaged estimated 3D volumes with different percentages of air in the pilot study were compared using one-way ANOVA. The effect of air injected on the estimated 3D volume in the pilot experiment was measured using multiple regression analysis. The measure of concordance between two different operators was tested using Kendall's W test. Pearson's correlation test was used to calculate correlation coefficients in the in vitro validation study, whereas, partial correlation coefficients were used to calculate correlation coefficients between partial gastric volumes and symptom scores postprandially. A $P < 0.05$ was considered significant. All statistical analysis was performed using commercially available computer software (SPSS 11.0 for Microsoft Windows).

Results

In vitro validation

In the in vitro study a total of 60 3D images were recorded. The 3D system yielded a strong correlation between true and estimated 3D volumes with 0% ($r = 0.995$; $P < 0.01$), 5% ($r = 0.996$; $P < 0.01$), 10% ($r = 0.997$; $P < 0.01$), 15% ($r = 0.997$; $P < 0.01$) and 20% ($r = 0.998$; $P < 0.01$) air present in the balloon. The mean differences (± SEM) between the estimated and true volumes with 0% (–2.0 ± 1.5 mL), 5% (0.1 ± 1.4 mL), 10% (1.8 ± 1.6 mL), 15% (1.6 ± 1.5 mL), and 20% (–1.7 ± 1.2 mL) air present were not significantly different. The difference between the estimated 3D and true volumes, illustrated in Figure 1, did not significantly correlate with the percentage of air injected in the balloon ($r = 0.04$; $P > 0.05$) or with the true volumes ($r = 0.16$; $P > 0.05$). There was a significant measure of agreement between the estimated volumes of the 3D images obtained by two different operators (Kendall's W: 0.997; $P < 0.001$).

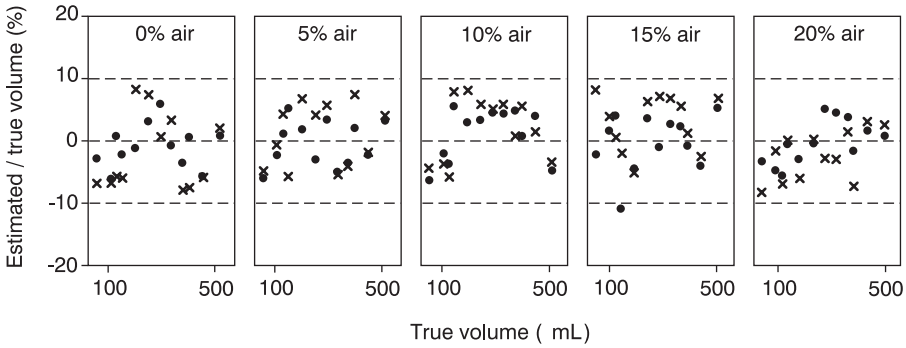

Figure 1

Plot displaying estimated 3D volume data obtained by two different operators (operator 1 (•); operator 2 (x)) of a barostat balloon positioned under water with 0, 5, 10, 15 and 20% air present in the balloon in the volume range 0-600 mL.

Technical aspects of 3D ultrasonography

A total of 5 patients (two grade 3; two grade 2; one grade 1) and 3 controls (grade 1) had visible intragastric air pockets. None of the healthy controls but two of the patients were excluded, one due to large air pockets (grade 3) in the gastric fundus and one due to poor stomach visualisation. Prior to meal ingestion, no fluids were visualised in the proximal stomach in patients and controls.

Total gastric volumes after a liquid meal

Fasting gastric volume was not significantly different among the three subject groups: 43 ± 3 mL in controls, 36 ± 5 mL in the nondyspeptic fundoplication group, and 32 ± 2 mL in the dyspeptic fundoplication group (all $P > 0.05$). At 5 min postprandially, total gastric volumes were similar among all three subject groups (489 ± 6 mL, 470 ± 4 mL and 467 ± 11 mL among controls, nondyspeptic and dyspeptic fundoplication patients respectively; all $P > 0.05$). Between 15 and 60 minutes postprandially, total gastric volumes were significantly larger among the control subjects compared with both dyspeptic ($P = 0.007$) and nondyspeptic fundoplication patients ($P < 0.001$), whereas, gastric volumes among the dyspeptic and the nondyspeptic group were not significantly different ($P > 0.05$) (Figure 2).

Proximal and distal stomach volumes after a liquid meal

After a liquid meal, dyspeptic and nondyspeptic fundoplication patients exhibited reduced proximal stomach volumes compared with normal controls ($P < 0.001$ and $P < 0.01$ respectively), whereas, volumes in the proximal stomach were similar among dyspeptic and nondyspeptic patients ($P = 0.93$) (Figure 3). Similarly, proximal to total gastric volume distribution ratios, correcting volume data for differences in total gastric volume, were significantly smaller in both dyspeptic and nondyspeptic fundoplication patients than in healthy controls (Table 1). Fasting distal stomach volumes were similar among all three subject groups. After meal ingestion, dyspeptic fundoplication patients revealed an increased distal stomach volume compared to nondyspeptic patients ($P < 0.01$) and healthy controls ($P < 0.001$). Nondyspeptic fundoplication patients showed a larger distal stomach volume than controls ($P = 0.02$) (Figure 4). Table 1 compares the distal to total gastric volume distribution ratios between the three subjects groups. The increased distal stomach volume associated with fundoplication, especially in the dyspeptic fundoplication group, is exemplified in the 3D ultrasonographic images illustrated in Figure 5.

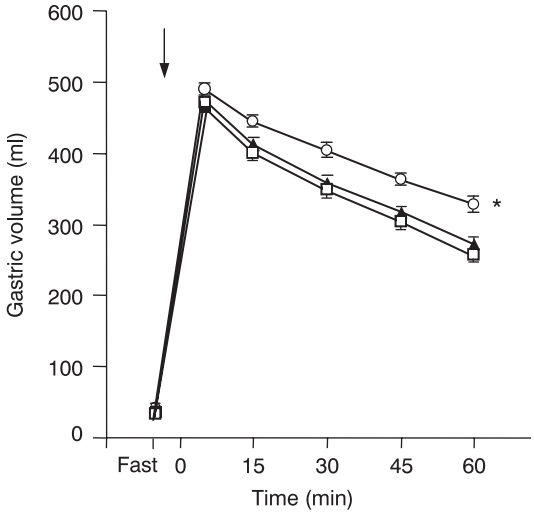

Figure 2
Gastric volume measurements with 3D US imaging system, before and after ingestion of a liquid meal in dyspeptic fundoplication patients (n = 8; ▲), nondyspeptic fundoplication patients (n = 10; □), and healthy controls (n = 18; ○). Arrow indicates start of meal ingestion. *$P < 0.01$ controls *v*s patients.

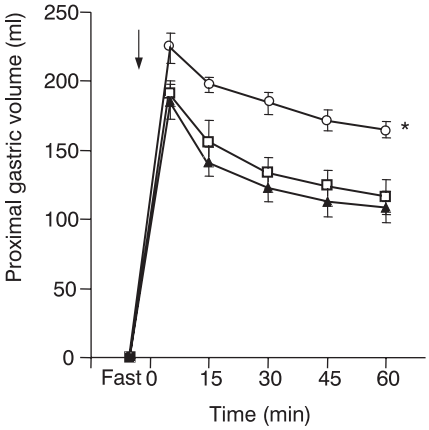

Figure 3
Proximal gastric volume measurements in dyspeptic fundoplication patients (▲), nondyspeptic fundoplication patients (□) and healthy controls (○). Arrow indicates start of meal ingestion. **P* < 0.01 controls *vs* patients.

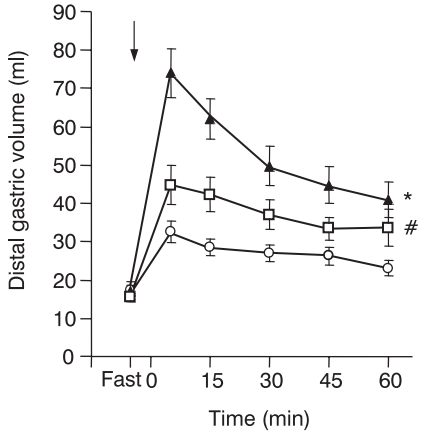

Figure 4
Distal gastric volume measurements in dyspeptic fundoplication patients (▲), nondyspeptic fundoplication patients (□) and healthy controls (○). Arrow indicates start of meal ingestion. **P* < 0.01 dyspeptic *vs* nondyspeptic fundoplication patients and controls. #*P* < 0.05 nondyspeptic patients *vs* controls.

Relationship between proximal and distal gastric volume and postprandial symptoms

Preprandial sensations were similar among all three subject groups (Figure 6). After meal ingestion, a significant increase in fullness was observed in controls ($P < 0.01$), dyspeptic ($P < 0.01$) and nondyspeptic fundoplication patients ($P < 0.01$) whereas, nausea and pain only significantly increased in the dyspeptic group (Figure 6). After the meal, dyspeptic fundoplication patients showed higher epigastric fullness scores at all points in time compared with either nondyspeptic patients ($P < 0.01$) or healthy controls ($P < 0.01$) (Figure 6).

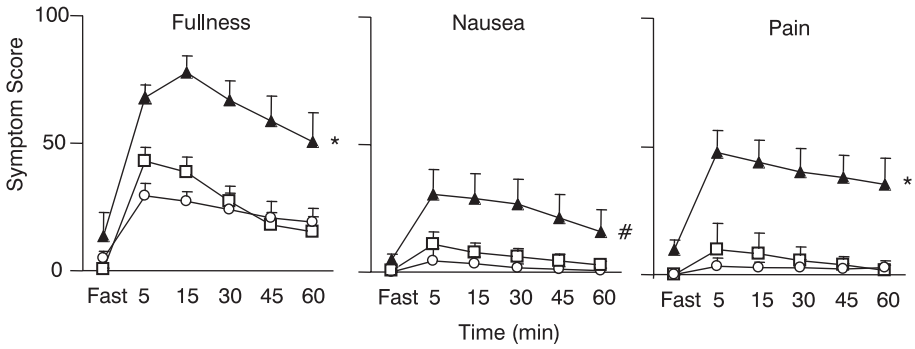

Figure 6

Effect of ingestion of a liquid meal on epigastric fullness, nausea and pain perception in dyspeptic fundoplication patients (n = 8, ▲), nondyspeptic fundoplication patients (n = 10, □) and healthy controls (n = 18, ○). *P < 0.01 dyspeptic *vs* nondyspeptic fundoplication patients and controls. *P < 0.01 and $^{\#}P$ < 0.05 dyspeptic *vs* nondyspeptic fundoplication patients and controls.

Postprandially, nausea and pain scores were significantly higher in the dyspeptic patients compared with nondyspeptic patients (P < 0.05 and P < 0.01 respectively) and controls (P < 0.05 and P <0.01 respectively) (Figure 6). The increase in fullness correlated to the distal gastric volume increase at 5 min (r = 0.68; P < 0.01) (Figure 7), and 15 min (r = 0.62; P < 0.05) min postprandially, whereas, no such relation was present at later stages after meal intake. The increase in fullness did not correlate with the proximal gastric volume increase (r = -0.23; P > 0.05). Furthermore, nausea and pain scores remained low in nondyspeptics and controls, hence, no correlation with either proximal or distal gastric volume increases was observed.

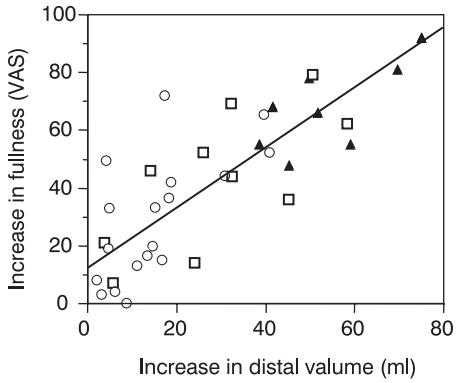

Figure 7

Relation between the increase in distal stomach volume and the epigastric fullness sensation 5 min postprandially in 8 dyspeptic fundoplication patients (▲), 10 nondyspeptic fundoplication patients (□) and 18 healthy controls (○). (r = 0.68, P < 0.01).

Table 1
Postprandial gastric volume distribution ratios in normal subjects, dyspeptic and nondyspeptic fundoplication patients.

	Proximal / Total Gastric Volume Ratio	Distal / Total Gastric Volume Ratio
Normal controls	0.47 ± 0.008	0.07 ± 0.003
Nondyspeptic fundoplication patients	0.38 ± 0.016*	0.11 ± 0.007*
Dyspeptic fundoplication patients	0.39 ± 0.016*	0.14 ± 0.008†‡

Values are means ± SEM. *$P < 0.05$ *vs* normal subjects; †$P < 0.001$ *vs* normal subjects and ‡$P < 0.05$ *vs* nondyspeptic fundoplication patients.

Discussion

This study is the first to report on 3D ultrasonographic imaging for the investigation of gastric volumes in relation to postoperative dyspeptic symptoms in patients after fundoplication. The major finding of this study was that patients with dyspeptic symptoms after fundoplication exhibit a markedly increased distal stomach volume after meal ingestion compared with either nondyspeptic fundoplication patients or healthy controls. Although the meal-induced increase in proximal stomach volume was reduced in fundoplication patients compared with controls, no significant differences between dyspeptic and nondyspeptic fundoplication patients were found. Dyspeptic fundoplication patients had a higher postprandial score for fullness, nausea and pain than nondyspeptic patients and controls. Interestingly, the increase in distal stomach volume correlated significantly to the postcibal epigastric fullness increase. These findings suggest that fundoplication affects proximal stomach accommodation leading to an augmented distal stomach volume, which is associated with the upper gastrointestinal fullness sensation.

Three-dimensional ultrasound imaging is a noninvasive technique based on imaging of the gastric wall, which provides information on gastric accommodation. [30] This 3D US technique allows assessment of the entire stomach and permits partitioning of the stomach into proximal and distal regions, unlike the invasive barostat method, which typically assesses the proximal stomach. A potential limitation of the 3D US technique, however, is intragastric air

entrapment, which could limit gastric outline visualisation, especially in patients after fundoplication. [31] However, the present in vitro experiment clearly demonstrated that amounts of air up to 20% of the total volume do not interfere with 3D US volumetry.

A key finding in the present study was that fundoplication patients exhibit an augmented meal-induced volume increase of the distal stomach compared with healthy controls. This finding is in line with recent scintigraphic data [22], demonstrating a more distal distribution of a meal after fundoplication. Theoretically, the increased volume of the distal stomach could either be the result of impaired proximal gastric accommodation to a meal inducing antral overdistension or increased distal gastric relaxation. In healthy controls, antral distension [8,9] and the entrance of nutrients into the duodenum [32] elicit antrofundic and enterofundic reflex pathways relaxing the proximal stomach to act as a reservoir. Apparently, these reflexes become incomplete or cannot overcome the ensuing alterations in anatomy after fundoplication, as we found meal-induced relaxation of the proximal stomach to be reduced with fundoplication, corroborating earlier reports using a barostat. [33] This results in an augmented passive filling/distension of the distal stomach. However, the possibility that antral relaxation may also be enhanced with fundoplication has not yet been investigated. Furthermore, because antral distension promotes antral peristalsis

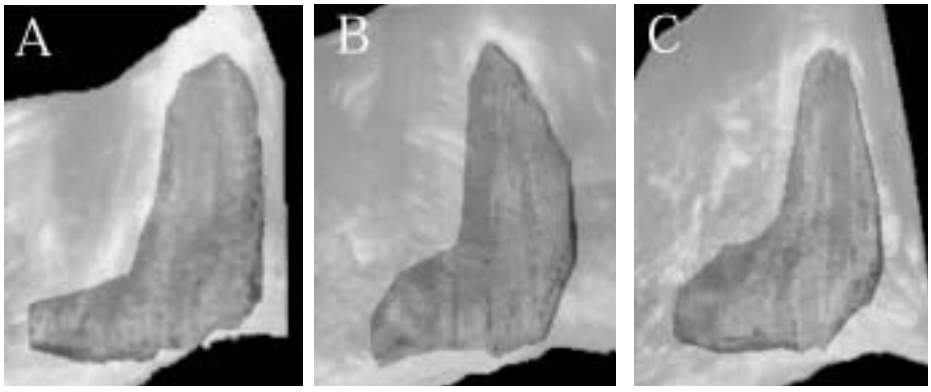

Figure 5
Three 3D ultrasonographic images illustrating an example of a stomach in a healthy volunteer (A), a nondyspeptic fundoplication patients (B), and a fundoplication patient with dyspepsia (C) at 15 min postprandially. Note the augmented distal distribution after fundoplication, being most pronounced in example C.

[34], which is related to gastric emptying [35], it is conceivable that gastric emptying is accelerated after fundoplication, as previously reported. [22] In the present study, the effect of fundoplication on total gastric 3D US volume (Figure 2) was likely to be due to accelerated gastric emptying because it appeared after 15 minutes. Likewise, in a recent study using the SPECT (single photon emission computed tomography) technique, similar total gastric volumes between fundoplication patients and controls were found 15 minutes after meal ingestion. [36] The increase in gastric emptying, however, did not compensate for the increase in distal stomach volume in the present study, at least within 1 h.

Dyspeptic fundoplication patients exhibited a significantly greater postprandial increase in nausea and pain than did the nondyspeptic fundoplication patients or healthy controls, who both reported hardly any increase in these symptoms. This was not the case, however, for fullness, as the nondyspeptic patients and healthy subjects showed a substantial increase in fullness after meal intake. Fullness scores showed a positive correlation with distal stomach volume, exclusively at 5 and 15 minutes after meal intake, that is, during the process of gastric accommodation, which is completely installed at ± 30 minutes after meal intake in both healthy controls [14,37] and fundoplication patients [19,33]. However, differences in distal gastric volumes between dyspeptics, nondyspeptics, and controls were still present at later stages (Figure 4). Apparently differences as small as ± 10 mL did not lead to different sensations in nondyspeptic fundoplication patients (Figure 6). In contrast, dyspeptic fundoplication patients exhibited both higher symptom scores and larger distal gastric volumes at later stages also. This temporal association did not imply a causal role for the distal stomach in symptom generation at later stages, especially as no significant correlation between symptoms and distal gastric volume was observed. Therefore, it is reasonable to hypothesize that other mechanisms such as increased visceral hypersensitivity, as regurlarly reported in functional dyspepsia [8,14,15,38-40], or changes in gastric motility/emptying [22,41] might also be involved in the genesis of postfundoplication dyspepsia.

A question raised by this investigation is how larger volumes in the distal stomach, as measured in the dyspeptic fundoplication patients, induce more symptoms (Figures 4 and 7). Although the pathophysiology of symptom generation is complex, it is established that dyspeptic symptoms can be elicited by mechanoreceptor activation through non-5-HT3 serotonergic pathways by volume-controlled distension of the distal stomach. [25] According to Gregersen et al. [42], these mechanoreceptors directly respond to changes in wall stress rather than volume or pressure alone. Circumferential wall stress ($\Delta Pr/h$) is proportionate to the transmural pressure (ΔP) and the antral radius (r) and

inversely related to the wall thickness (h). [34] Because radius increases and wall thickness reduces with volume increase, we may conclude that in dyspeptic patients the circumferential wall stress is considerably higher compared to nondyspeptic patients, which may explain the augmented sensations in the former.

In summary, fundoplication patients exhibit an attenuated accommodation of the proximal stomach leading to increased distention of the distal stomach. Second, this augmented distal stomach distension appeared more pronounced in dyspeptic fundoplication patients than in either nondyspeptic fundoplication patients or controls. Finally, the increase in distal stomach volume is related to postprandial fullness, suggesting that the altered accommodation response plays an important role in postfundoplication dyspepsia.

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6

Relationship between the mechanism of gastroesophageal reflux and esophageal acid exposure in patients with reflux disease

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Abstract

This study investigated the relationship between the esophageal acid exposure time and the underlying manometric motor events, especially transient lower esophageal sphincter relaxations (TLESRs), in patients with gastroesophageal reflux disease (GERD). In 31 patients, esophageal motility and pH were measured for 3 hours after a test meal with the subjects in sitting position. Ten GERD patients underwent 24-h ambulatory manometry and pH recording. For each patient both the frequency and the duration of pH drops were measured and related to the underlying motor event. In the 3-h postprandial study, of 367 reflux episodes 79% was associated with a TLESR, 14% with absent basal LES pressure and the remaining 7% with other mechanisms, representing 62%, 28% and 10% of the acid exposure time respectively. Acid reflux duration per motor mechanism, hence, was significantly longer for absent basal LES pressure than for a TLESR (189 $\pm$ 23 s and 41 $\pm$ 5 s resp., $P < 0.001$). In the 24-h ambulatory study, the contribution of TLESRs to the reflux frequency vs acid exposure time were 65% vs 54% during the interprandial period and 74% vs 53% after the meal. During the night, absent basal LES pressure accounted for 36% of reflux events representing 71% of the acid exposure time. During all periods, the time from reflux onset until the first clearing motor event was significantly shorter when reflux was associated with a TLESR than with absent basal LES pressure. In conclusion, the duration of esophageal acid exposure following a TLESR is shorter than reflux during absent basal LES pressure. TLESRs are, the major contributor to esophageal acid exposure during the day. At night, however, reflux during absent basal LES pressure is the major contributor to acid exposure.

Introduction

Transient lower esophageal sphincter relaxations (TLESRs) are the most frequent mechanism underlying acid reflux in healthy controls [1 2] as well as patients with gastroesophageal reflux disease (GERD) without hiatal hernia [3-5] and account for approximately 80% of acid reflux episodes. Other motor mechanisms, such as absent lower esophageal sphincter (LES) pressure, swallow induced LES relaxation or straining account for the remaining 20% of the acid reflux episodes [3] and these mechanisms are responsible for the excess of acid reflux in GERD patients with hiatal hernia. [6] The incidence of TLESRs in controls and patients with GERD is similar, whereas, the proportion of TLESRs associated with acid reflux is higher in patients with GERD. [7]

Ambulatory 24-h pH monitoring studies show a direct relationship between the 24-h acid reflux exposure time and the severity of endoscopic esophagitis. [8] Furthermore, the perception of a reflux event is directly related to the duration of an acid reflux episode. [9] Although esophageal acid reflux exposure time depends both on the incidence of reflux episodes and the duration of each reflux event, manometric studies have focussed exclusively on the relationship between these motor events and the frequency of acid reflux events. [1-6] To date, the relationship between the motor mechanisms underlying acid reflux and the duration of an acid reflux episode or the acid exposure time has not yet been established. In addition, the question of how the duration of reflux events caused by the various motor mechanisms is related to the process of acid clearance remained unexplored. Therefore, the aim of this study was to assess the relationship between the esophageal acid exposure time, esophageal clearance and the underlying manometric motor mechanisms, especially TLESRs, in non-hernia patients with GERD.

Patients and methods

Two sets of previously gathered data were analyzed: 1) 4-hour stationary esophageal manometry and pH metry, recorded during 1 hour at baseline and 3 hours postprandially, and 2) 24-hour ambulatory esophageal manometry and pH-metry recordings.

Subjects

Stationary recordings (4h): Studies were performed in 31 symptomatic GERD patients (18 men, 13 women; aged 25-73 years (mean (SEM) 49.3 (2.2) years). At upper endoscopy, 10 had grade B, and 14 had grade A oesophagitis according to the Los Angeles (LA) classification [10], whereas, 7 patients had no mucosal breaks. Of these 31 patients, 13 were studied in the Royal Adelaide Hospital and 18 at the University Medical Center Utrecht. Age and gender distribution were not significantly different between the patient groups.

Ambulatory recordings (24h): Ten symptomatic GERD patients (4 men, 6 women; aged 21-53 years (mean (SEM) 39.8 (3.7) years)), who were all not enrolled in the stationary study, were studied. At upper endoscopy, 4 patients had oesophagitis grade A (LA classification) and the remaining 6 had no mucosal breaks. This study was performed at the University Medical Center Utrecht.

All patients without esophageal erosions had symptoms related to esophageal acid exposure, as demonstrated by 24-hour pH measurements (symptoms association probability index >95% and symptom index >50%). [11] In none of the GERD patients in either group was an hiatal hernia observed endoscopically as defined by the axial separation of the ends of the gastric folds, marking the gastroesophageal junction, and the diaphragmatic impression. Patients with a history of any disease or operation which might influence gastrointestinal motility or gastric acid secretion were excluded. Before each study, medications that affect gastrointestinal motility and/or acid secretion were discontinued for at least 4 days. Each patient gave written informed consent, and the studies were approved by the Medical Ethics Committees of the Royal Adelaide Hospital and/or the University Medical Center Utrecht.

Recording technique

In both protocols a water perfused multilumen silicone assembly with incorporated sleeve sensor (DentSleeve Pty, Ltd, Wayville, South Australia) was used for manometry. Lower esophageal sphincter pressure was measured with a reversed perfused sleeve sensor. [13] Gastric pressure was recorded via a side

hole located 1 cm distal to sleeve sensor. Side holes starting at the proximal margin of the sleeve sensor monitored pressure at four sites along the esophageal body, and the side hole in the pharynx recorded swallowing. Each lumen was perfused with degassed water at a rate of 0.08 mL/min in Utrecht and 0.15 mL/min in Adelaide using hydraulic flow restrictors (DentSleeve Pty, Ltd) and a low compliance pneumohydraulic perfusion pump. In the ambulatory studies this pump was portable and consisted of a small gas cylinder and a water reservoir (350 mL). [2,14]

Esophageal pH was measured with a glass electrode (model LOT 440, Ingold A.G., Urdorf, Switzerland) in Utrecht and with an antimony electrode (Synectics Medical AB, Stockholm, Sweden) in Adelaide, both of which were positioned at 5 cm above the proximal margin of the LES and sampled at a rate of 1 Hz. Data were displayed, stored and analysed using MMS software (MMS, Enschede, The Netherlands) in Utrecht or AcqKnowledge software (Biopac Systems, Goleta, California, USA) in Adelaide.

Study protocols

Stationary recordings (4h): The study protocol has been published previously.[15,16] In short, after an overnight fast, the esophageal pH and manometric catheters were introduced. Esophageal manometric and pH recordings were performed during 1 hour at baseline and 3 hours after consumption of a test meal. At Utrecht, this meal consisted of a McDonald's Quarter Pounder, 47 g potato chips, 485 mL orange juice and 20 g onions; (967 kcal), whilst in Adelaide, it consisted of savoury minced meat, mashed vegetables, 150 mL milk and ice cream, (750 kcal). All patients were studied in an upright position.

Ambulatory recordings (24h): The study protocol has been published previously. [6] In short, after an overnight fast, the esophageal pH and manometric catheters were introduced transnasally. The study started at 7.30 AM and standardized meals were taken at fixed times. The content of the meals was: breakfast, 42.2 g carbohydrate, 27.8 g protein, 20.8 g fat, 458 kcal; lunch, 94.8 g carbohydrate, 30 g protein, 37.2 g fat, 870 kcal; and dinner, 117.5 g carbohydrate, 57.4 g protein, 14.6 g fat, 831 kcal. Patients had a cup of tea or coffee in the afternoon and evening and were free to drink water. During the day patients spent the time sitting and taking short walks. At night, from 11 PM until 7.30 AM the next day, the patients stayed in bed in a recumbent position.

Data analysis

The pH recordings were analysed for the number and duration of reflux episodes and for the total esophageal acid exposure time per motor mechanism. An acid reflux episode was defined as a period with pH < 4 after a drop of at least 1 pH-unit with a velocity ≥ 0.5 pH units/s for a minimum duration of 3 s or, if esophageal pH was already below 4, a further drop in pH of at least 1 pH unit sustained for at least 3 seconds (Figure 1). The end of an acid reflux episode was defined by the return of esophageal pH to at least 80% of baseline for at least 5 s. When superimposed reflux occurred the end of a reflux episode was defined by the start of the new reflux episode. The duration of each reflux event was defined as time with pH < 4 per reflux episode.

TLESRs were defined according to the criteria published previously. [17] Absent basal LES pressure was defined as a period ≥ 30 s with end-expiratory LES pressure ≤ 0.4 kPa. [6] Abdominal straining was defined as a brief elevation in both gastric and esophageal pressure exceeding at least 2 times the normal respiratory pressure excursions. [6,18]

For each reflux episode, the motor event associated with reflux was determined from the patterns of LES pressure and esophageal body activity, and their relationship to swallowing, and the occurrence of abdominal straining. [3,8,19] The motor mechanisms of reflux were categorized as TLESR, swallow induced reflux (including multiple swallows), absent basal LES pressure, straining, and non-interpretable when pressures were obscured by artefacts. When straining induced a reflux event and occurred during normal basal LES pressure it was judged to be the mechanism of reflux. However, when straining occurred during another mechanism, e.g. absent LES pressure or TLESR, straining was deemed to be a process additional to the main mechanism.

The proportion of reflux events and the proportion of the reflux exposure time associated with the motor mechanisms of acid reflux were calculated per patient and thereafter averages were calculated for each group of motor mechanisms. The acid exposure time attributable to each motor mechanism was also calculated per patient. In the 4h-stationary study the preprandial (1-hour) and postprandial period (sum of the 3-hour period after the meal) was analysed. In the ambulatory 24-hour study, the total 24-hour period, the day-time postprandial period (sum of the 3 2-hour periods after each meal), the day-time interprandial period (day-time period without the postprandial periods), and the night-time period (11 PM to 7:30 AM) were analysed.

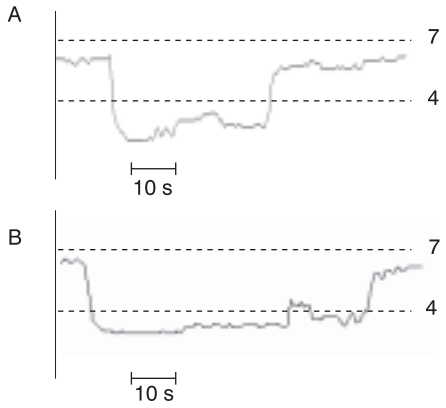

Figure 1
pH-recordings illustrating an example of a reflux episode without (A) and with (B) a transient shift to pH > 4 but < 5 followed by a return to pH < 4 within 5 s. Both episodes were counted as 1 reflux episode.

To investigate the clearing motor mechanisms associated with the motor events underlying acid reflux, the nature and timing of the first clearing motor event after the onset of reflux were determined. Primary peristalsis was defined as esophageal peristaltic activity preceded by pharyngeal contractile activity whereas secondary peristalsis was not. A clearing motor event was defined as peristaltic activity in at least 2 adjacent sideholes and defined to be effective when leading to an increase of distal esophageal pH of at least 0.5 pH unit within 5 s after the start of the distal esophageal contraction.

Statistical analysis

Data are expressed as mean ± SEM. Comparisons between the patients studied in Adelaide and in Utrecht regarding the percentage of the acid reflux associated with the underlying motor events and the acid exposure time per motor event were performed using mulivariate analysis of variance (MANOVA). The duration of acid exposure per motor mechanism was compared using analysis of variance (ANOVA). The nature of and time until first clearing motor event and were compared among motor events using multivariate analysis of variance (MANOVA). Adjustments for multiple comparisons were performed using Bonferroni's procedure. For all statistical tests the significance level was 0.05.

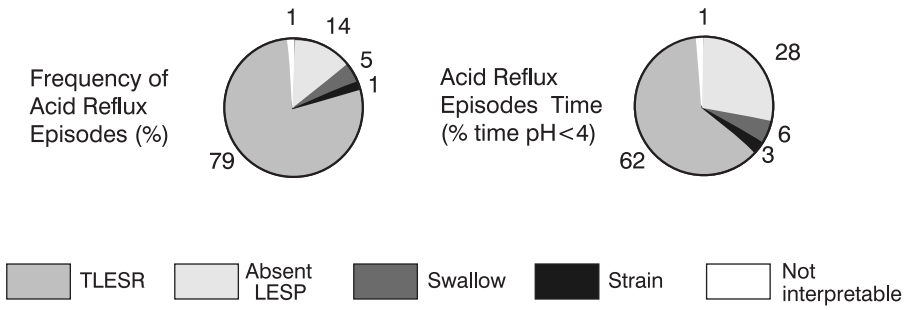

Figure 2
The frequency of acid reflux events and the acid exposure time associated with the motor mechanisms of reflux during the 3-hour postprandial period of the 4-hour stationary study. Note the lower relative contribution of TLESRs when acid reflux exposure time is considered.

Results

The percentages of acid reflux episodes associated with the various motor mechanisms were not significantly different between patients studied in Adelaide and those in Utrecht for any variable (TLESR $P = 0.7$, absent LES pressure $P = 0.9$; swallow-induced $P = 0.4$; strain $P = 0.2$; not interpretable $P = 0.9$). Likewise, the acid exposure time per mechanism was not significantly different between the groups for any variable (TLESR $P = 0.9$, absent LES pressure $P = 0.7$, swallow $P = 0.4$; strain P = 0.3, not interpretable $P = 0.8$), hence, pooling these patient groups was justified.

4-hour stationary study

In the fasting state, only 16 acid reflux episodes occurred in 11 patients. In these 11 patients the majority, 77 ± 12%, of acid reflux episodes were associated with TLESRs and contributed 73 ± 14% of the acid reflux exposure time.

Postprandially, 79 ± 4% of 367 reflux episodes was associated with a TLESR. However, these reflux episodes contributed only 62 ± 6% of the acid exposure time (Figure 2). In contrast, absent basal LES pressure was the mechanism underlying only 14 ± 3% of reflux episodes but these episodes accounted for

Table 1
The nature and time from onset of acid reflux of the first clearing motor event in the postprandial study.

	Time until 1st clearing motor event(s)	Nature of 1st clearing motor event (%)	
		1° Peristalsis	2° Peristalsis
TLESR	19±2†	81±4*	19±4*
Absent LESP	51±7	97±2	3±2
Swallow	27±4†	98±2	2±2
Strain	18±4‡	100	-
Not interpretable	27±9‡	100	-

†$P < 0.01$ *vs* absent LESP; ‡$P < 0.05$ *vs* absent LESP; *$P < 0.05$ *vs* absent LESP, swallow, strain and not interpretable.

Table 2
The frequency of acid reflux episodes (a) and the acid exposure time (b) associated with the motor events of reflux during the postprandial study according to the severity of oesophagitis.

a

Esophagitis grade	Frequency of acid reflux episodes (%)				
	TLESR	Absent LESP	Swallow	Strain	Not interpretable
0 (n=7)	77±7	12±6	9±5	2±2	0±0
A (n=14)	80±6	13±5	4±1	1±1	2±1
B (n=10)	76±9	17±7	4±2	2±1	1±1

b

Esophagitis grade	Acid reflux exposure time (%time pH<4)				
	TLESR	Absent LESP	Swallow	Strain	Not interpretable
0 (n=7)	57±13	23±12	11±6	9±9	0±0
A (n=14)	68±9	24±8	5±2	1±1	2±1
B (n=10)	57±11	36±11	3±2	1±1	2±1

28 ± 6% of the acid exposure (Figure. 2). Both swallow and strain-induced reflux occurred infrequently, 5 ± 1% and 1 ± 1% respectively, and the contribution to the reflux exposure time was proportionately small (Figure 2). The duration of acid reflux episodes associated with an absent basal LES pressure (189 ± 23 s) lasted significantly longer compared with acid reflux episodes associated with a TLESR (41 ± 5 s, $P < 0.001$), swallow (67 ± 12 s, $P < 0.001$), or straining (77 ± 24 s, $P = 0.018$) (Figure 3).

The most common clearing event was primary peristalsis. Secondary peristalsis occurred mainly after reflux during a TLESR (Table 1). Most (85 ± 3 %) first clearing motor mechanisms were effective. The time from onset of an acid reflux episode until the first clearing motor event was significantly shorter when reflux was associated with a TLESR, swallow or straining than when the mechanism of reflux was absent basal LES pressure (Table 1). No differences were found in either the spectrum of reflux mechanisms or their contribution to the gastroesophageal acid exposure time among patients with basal LES pressure < 5 mmHg at the start of the study (n=4) or with LA grade 0, grade A, or grade B oesophagitis (Table 2).

24-hour ambulatory study

During the postprandial period, esophageal acid exposure was significantly higher compared to all other periods (Table 3). A total of 344 reflux episodes were scored with a mean of 34 ± 3 per patient. Over the total 24-h period, TLESRs accounted for the majority (69 ± 7%) of the reflux episodes as well as the majority but smaller proportion (51 ± 11%) of the acid exposure time (Figure 4). Absent basal LES pressure accounted for only 20 ± 7% of the reflux episodes but 38 ± 10% of the acid exposure. Reflux during swallow-induced LES relaxation or straining was uncommon and contributed only a minor proportion of the acid exposure.

Table 3

Esophageal acid exposure during the total 24-hour, the day-time interprandial period, the day-time postprandial period, and the night-time period.

	Time with pH < 4 (%)
Total 24-hour	3.3±1.0
Day-time inter-prandial period	1.4±0.7
Day-time postprandial period	7.3±0.5*
Night-time period	2.1±1.1

*$P < 0.05$ *vs* total 24-hour, day-time inter-prandial and night-time period.

Table 4
The nature of the first clearing motor event in the 24-hour ambulatory study.

	Nature of 1st clearing motor event							
	Total 24-hour		Day-time inter-prandial period		Day-time postprandial period		Night-time period	
	1° p	2° p	1° p	2° p	1° p	2° p	1° p	2° p
TLESR	77±6	23±6	66±8	34±7	73±9	27±9	68±8	32±7
Absent LESP	93±4	7±4	93±7	7±7	89±7	11±7	100	0
Swallow	81±4	19±4	67±22	33±21	89±6	11±5	100	0
Strain	100	0	100	0	100	0	100	0
Not interpretable	70±8	30±6	67±19	33±9	100	0	100	0

1° p = primary peristalsis, 2° p = secundary peristalsis

The majority of the reflux episodes occurred post-prandially (55%) or during the day between meals (27%) and only a small proportion (17%) of reflux episodes occurred during the night. TLESR was the dominant mechanism of reflux in all three periods and contributed the majority of the acid exposure during the day (Figure 4). At night, however, whilst absent basal LES pressure contributed only 36% of the reflux episodes, it contributed 71% of the acid exposure (Figure 4). The duration of acid reflux episodes that occurred during absent basal LES pressure was significantly longer than that during TLESR for all periods (Figure 5). Additionally, acid clearance following reflux during absent basal LES

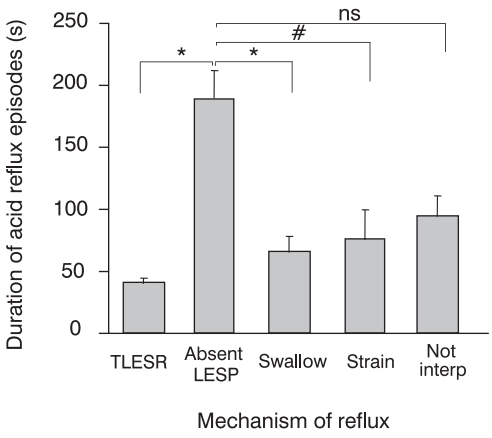

Figure 3
Duration of acid reflux episodes per motor mechanism during the 3-hour postprandial period of the 4-hour stationary study. *$P < 0.001$ and #$P < 0.02$ (ANOVA).

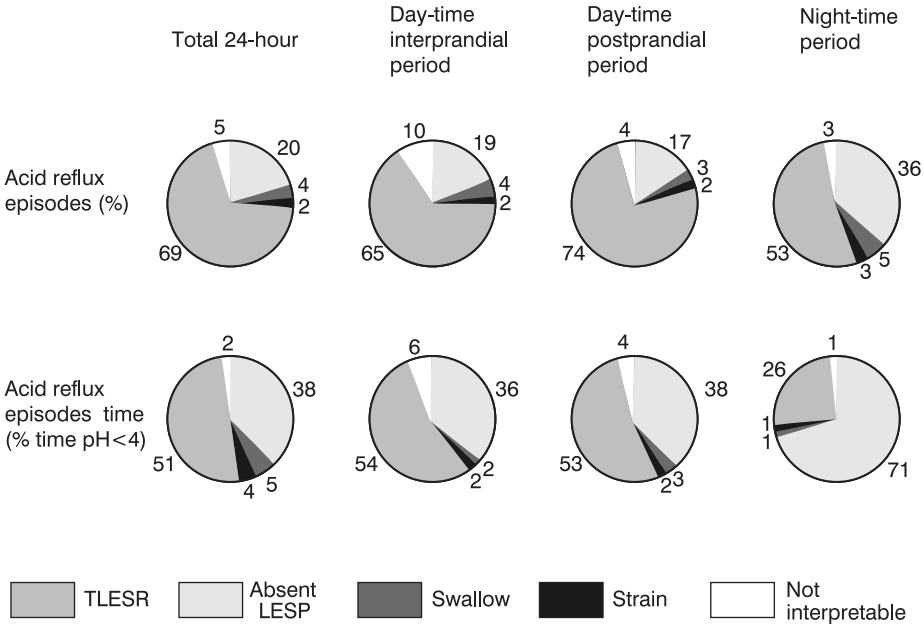

Figure 4

Contribution of the various motor mechanisms to the acid reflux frequency and the acid reflux exposure time during the total 24-hour, interprandial, postprandial, and night-time periods. TLESRs were responsible for the majority of reflux episodes in all periods. Note that for all but the night-time period, TLESRs also are the major contributor to the acid exposure time. At night, a low LES pressure predominates with respect to the esophageal acid exposure time.

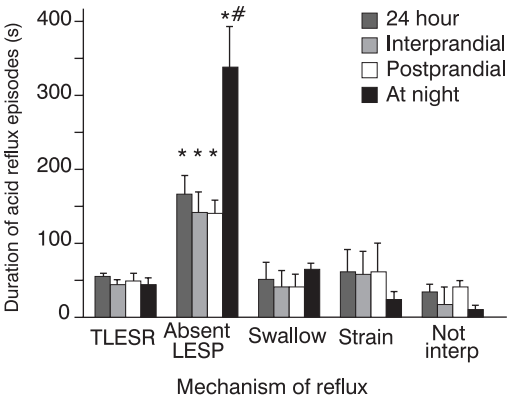

Figure 5

Duration of acid reflux episodes per motor mechanism during the 24-hour, interprandial, postprandial and night-time periods. *$P < 0.05$ *vs* swallow, strain, TLESR and not interpretable. #$P < 0.02$ *vs* the 24-hour, interprandial, and postprandial period (ANOVA).

pressure was significantly longer at night than either of the day-time periods or the total 24-hour period (Figure 5).

Consistent with our finding in the 4-hour stationary study, primary peristalsis was the most frequent clearing event (82%) during the 24-hour ambulatory study while secondary peristalsis (18%) occurred primarily after reflux during a TLESR (Table 4). During the total 24-hour period, most (88% ± 2 %) first clearing motor events were effective. For all periods, the time interval until the first clearing motor event after acid reflux that occurred during a TLESR was significantly shorter than when reflux was associated with absent basal LES pressure (Table 5). At night-time, the time interval for reflux associated with absent basal LES pressure was significantly longer than during either of the day-time or total 24-hour periods (Table 5). No differences were observed in the spectrum of reflux mechanisms and their contribution to acid exposure among patients with basal LES pressure < 5 mmHg at the start of the study (n=3) or with LA grade 0, or grade A oesophagitis.

Table 5
The time from onset of acid reflux of the first clearing motor event in the 24-hour ambulatory study.

	Nature of 1st clearing motor event			
	Total 24-hour	Day-time interprandial period	Day-time postprandial period	Night-time period
TLESR	26±4†	23±2‡	28±7†	33±13†
Absent LESP	71±17	64±19	51±11	180±81*
Swallow	24±9†	17±3‡	21±4‡	19±3‡
Strain	21±7†	25±7	33±1	28±13‡
Not interpretable	28±8†	23±7	34±10	27±4‡

†$P < 0.01$ *vs* absent LESP; ‡$P < 0.05$ *vs* absent LESP and *$P < 0.05$ *vs* total 24-hour, day-time interprandial and postprandial period. 1° p = primary peristalsis.
2° *p* = secondary peristalsis.

Discussion

Although TLESR has been identified as the most frequent physiological mechanism underlying gastroesophageal reflux [20], data on the esophageal acid reflux exposure time following a TLESR are limited. The major finding of this study was that acid reflux following a TLESR is frequent but acid exposure is significantly shorter compared with reflux during a period of absent basal LES pressure, the second most frequent mechanism of reflux in GERD patients without hiatal hernia. Despite this finding, TLESRs remain, apart from the night time period, the major contributor to not only the number of reflux episodes but also to the esophageal acid exposure time in GERD. During the night, however, whilst TLESRs remain the most frequent cause of acid reflux, reflux during absent basal LES pressure accounts for the majority of the esophageal acid exposure time.

In this investigation, the mix of motor events underlying esophageal acid reflux corroborates earlier reports on healthy subjects [2] and patients with GERD without hiatal hernia. [6,19] Hiatal hernia patients regularly exhibit a significant amount of reflux related to swallowing, straining and absent basal LES pressure, whereas in non-hernia patients the majority of reflux events is associated with TLESRs. [6] Heterogeneity of motor mechanisms among patients reduces the predictive value of the relationship between these events and the acid reflux exposure time for an individual patient with GERD. To circumvent this potential limitation patients with hiatal hernia were excluded. Additionally, in order to prevent bias by patients with a disproportionately large number of reflux events, data have been analysed and presented on a per-patient basis.

There has been considerable interest in the pharmacological control of TLESRs as a new target for treating reflux disease. [21-23] Recent interest has focused on aminobutric acid type B ($GABA_B$) receptor agonist baclofen that acts on both central and peripheral [24-26] receptors on vagal afferents, which are hypothesized to mediate triggering of TLESRs. Postprandial studies in healthy subjects [27] and patients with GERD [15,16] have shown reduction of the number of reflux events up to 50% and in the numbers of TLESRs of up to 60% whereas the effect on the acid exposure time was less [15] or even non-significant [16,27]. Although a drug acting exclusively on TLESRs would, according to our data, have a smaller effect on acid exposure vs. reflux incidence, these short (3-hour) studies were not designed to reliably assess effects on acid exposure. In contrast, recent 12-hour [28] and 24-hour [29] ambulatory pH monitoring studies found an equally large

effect on both the number of reflux events and the acid exposure time. In addition, Koek et al. [30] showed that baclofen had a more powerful effect at night-time when the contribution of TLESRs to acid exposure is relatively minor (Figure 4). This suggests that the effect of baclofen on basal LES pressure, as recently reported [31], may have a significant impact on acid exposure. From the above we may conclude that the present study provides a sound physiological foundation on which to develop therapy for reflux disease based on the pharmacological inhibition of TLESRs.

Although patients in the present study had relatively mild disease, this group is highly representative as patients with LA grade 0-B oesophagitis form the majority (>80%) of patients with GERD. [32] No differences in the spectrum of reflux mechanisms or their contribution to acid exposure were found among GERD patients with LA grade 0, grade A and grade B oesophagitis. Patients with more severe GERD, i.e. with LA grade C or D oesophagitis, exhibit a less TLESR-predominant spectrum of reflux mechanisms. [3,6] It is possible, therefore, that non-TLESR induced reflux might contribute an even larger proportion of acid exposure time in this group.

A key question raised by our study is why acid exposure following reflux during a period of absent basal LES pressure is more prolonged than that after reflux that occurs by other motor mechanisms including TLESR. To address this important issue, an analysis of timing of the first clearing motor event for each reflux event was performed. Our data show clearly that the time from the onset of reflux until the first clearing motor event was markedly longer for reflux associated with absent basal LES pressure than for reflux that occurred by other mechanisms. The reasons for this are unclear, however, it is possible that the characteristics of reflux, e.g. volume, are different and are less likely to trigger either primary peristalsis or secondary peristalsis. Whatever the explanation, these findings explain, at least partly, the prolonged acid exposure following reflux during absent basal LES pressure.

In the current study, acid exposure that occurred as a result of absent basal LES pressure during the night lasted significantly longer than that which occurred during the interprandial and postprandial periods. Two physiological mechanisms may account for this difference. First, in the current study, we found the time to the first motor clearing event for acid reflux events during absent basal LES pressure to be prolonged during the night-time period compared with either of the day-time periods. The reason for this is unclear. As has been shown previously [1,33,34], primary peristalsis was the most prevalent

clearing activity following gastroesophageal reflux. The rate of swallowing is reduced at night but this should apply equally to TLESR and non-TLESR associated reflux. Second, it has been reported that GERD patients have impaired acid clearance, particularly when recumbent [35], because of defective triggering of secondary peristalsis. [36] In keeping with these observations, the present study showed that the occurrence of secondary peristalsis following TLESR induced reflux events during the night-time was associated with relatively short reflux events

In summary, esophageal acid exposure associated with acid gastroesophageal reflux following TLESR is shorter-lasting compared with acid reflux following absent basal LES pressure. Nonetheless, apart from the night time period, TLESRs remain the major contributor to not only the number of reflux episodes but also to the esophageal acid exposure time. At night, TLESRs are the most frequent cause of acid reflux episodes but the majority of acid reflux exposure time is associated with absent basal LES pressure.

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7

Impaired bolus transit across the esophagogastric junction in postfundoplication dysphagia

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Abstract

This study assessed the effect of fundoplication on liquid and solid bolus transit across the esophagogastric junction (EGJ) in relation to EGJ dynamics and dysphagia. Twelve patients with gastroesophageal reflux disease (GERD) were studied before and after fundoplication. Concurrent high-resolution EGJ manometry and fluoroscopy were performed whilst swallowing liquid barium and a solid bolus. The EGJ transit time, EGJ opening duration, transit efficacy and EGJ relaxation were measured. During the test symptoms of dysphagia were scored using a visual analog scale. The minimal opening aperture at fluoroscopy was located at the manometric EGJ in all subjects. Fundoplication markedly reduced the EGJ opening diameter from 1.0 ± 0.1 cm to 0.6 ± 0.1 cm ($P < 0.01$) and rendered deglutative EGJ relaxation incomplete. After fundoplication, a higher intrabolus pressure was found ($P < 0.05$) associated with a reduced axial bolus length ($P < 0.001$). The EGJ transit time increased from 6.9 ± 0.9 s to 9.8 ± 1.0 s for liquids ($P < 0.01$) and from 2.8 ± 0.5 s to 5.8 ± 0.8 s ($P < 0.01$) for solids after fundoplication. No correlation between EGJ transit and dysphagia scores was observed before fundoplication. In contrast, EGJ transit time significantly correlated with dysphagia scores both during liquid ($r=0.84$; $P < 0.01$) and solid ($r=0.69$; $P < 0.05$) bolus transit following fundoplication.
In conclusion, fundoplication patients exhibit a restricted hiatal opening and an incomplete deglutative EGJ relaxation. To facilitate EGJ transit despite these altered EGJ dynamics a higher intrabolus pressure is created by augmented bolus compression. Fundoplication increases EGJ transit time, the degree of which is associated with post-operative dysphagia.

Introduction

Laparoscopic Nissen fundoplication is increasingly advocated as a surgical remedy for gastroesophageal reflux disease (GERD), and its efficacy for the long-term control of acid reflux has been reported to be as high as 90%. [3,17] Despite this success, dysphagia is a common side effect, reported in between 10-90%. [19, 23-25] At present, the principal underlying mechanical correlates of postoperative dysphagia are incompletely understood. Hypothesized involved mechanisms include incomplete deglutative esophagogastric junction (EGJ) relaxation, reduced axial motion at the EGJ and an increased esophagogastric transit time, particularly across the EGJ. [13,27,30]

Whilst esophageal bolus transit exclusively depends on the efficacy of esophageal peristalsis [12], bolus transit across the EGJ is a more complex process. In health and non-hernia patients, basal EGJ pressure is mainly attributable to the intrinsic lower esophageal sphincter (LES) pressure and extrinsic compression by the crural diaphragm, which are anatomically superimposed, hence, act in concert. [4,21] With deglutition, the esophageal body shortens, a phrenic ampulla is formed [14,16,26] and the intrinsic LES relaxes with partial inhibition of the crural diaphragm. [22] Intrabolus pressure builds up at the time of arrival of the peristaltic wave at the distal esophagus and facilitates flow across the EGJ when it overcomes the EGJ relaxation pressure, at the time of crural diaphragmatic relaxation (e.g. expiration). [15,28] EGJ bolus transit efficacy is a function of both the luminal diameter at the EGJ, the pressure difference across the EGJ and the physical properties of the luminal content. With fundoplication, the anatomy and mechanics of the EGJ are substantially altered. It is known that fundoplication impairs deglutative EGJ relaxation [11,27] and restricts hiatal opening. [13] Hence, EGJ transit characteristics are likely to be affected by fundoplication. However, the effect of fundoplication on the EGJ transit characteristics and postfundoplication dysphagia has not yet been prospectively examined. Therefore, the aims of this investigation were to determine the effect of a successful laparoscopic fundoplication on 1) the efficacy of EGJ transit for both liquids and solids, 2) the EGJ opening mechanics, and 3) the relation between EGJ transit and symptoms of dysphagia in patients studied both before and after laparoscopic fundoplication.

Patients and methods

Patients

Twelve consecutive patients (8 men, 4 women; median age 45.5 (29-60) years old) with chronic GERD established by symptom evaluation, upper GI endoscopy and 24-hour pH monitoring were included in the trial. GERD was defined by the presence of ≥ Los Angeles A esophagitis on recent endoscopy (9 of 12) and/or abnormal 24-hour ambulatory pH monitoring using a cutoff value of 6% total time with pH < 4 (11 of 12) with a proven association between reflux and symptoms (symptom association probability index (SAP) > 95%) (8 of 12). [32] On endoscopy, five patients had a small (< 3 cm) reducing hiatal hernia, four patients had a non-reducing (≥ 3 cm) hiatal hernia and three patients had no hiatal hernia. All patients suffered from refractory symptoms of GERD despite at least 40 mg of omeprazole daily and none were taking any medication known to affect esophageal motility. At three months after fundoplication, upper GI endoscopy and 24-hour pH monitoring were repeated. After fundoplication, no pathologic pH and no esophagitis or hiatal hernia was observed in any patient. One patient needing reoperation because of persistent reflux and herniation of the wrap above the diaphragm was excluded from the study. The medical ethics committee of the University Medical Center Utrecht approved the study and written informed consent was obtained from all participants.

Laparoscopic fundoplication

Laparoscopic fundoplication was performed using a technique described previously. [2] In short, the proximal fundus was mobilised by coagulating and dividing the gastrocolic and gastrosplenic omentum, including division of the short gastric vessels. The right crus was approximated and a floppy 360° fundoplication of 3.0-3.5 cm was constructed. Three non-resorbable stitches were used to secure the fundic wrap. The fundic wrap and diaphragm were identified with one and two hemoclips (<1cm apart) respectively to be visible on future X-rays. The clip identifying the fundic wrap was placed in the angle of His before constructing the fundic wrap, hence, it was located in the wrap after fundoplication.

Manometry assembly and recording technique

Each subject was studied with a high-resolution manometry system capable of displaying conventional line-plots as well as topographic contour plots. [6] A water perfused 16-channel silicone manometric assembly (DentSleeve Pty, Ltd, Wayville, South Australia) was used for pressure measurement. The assembly

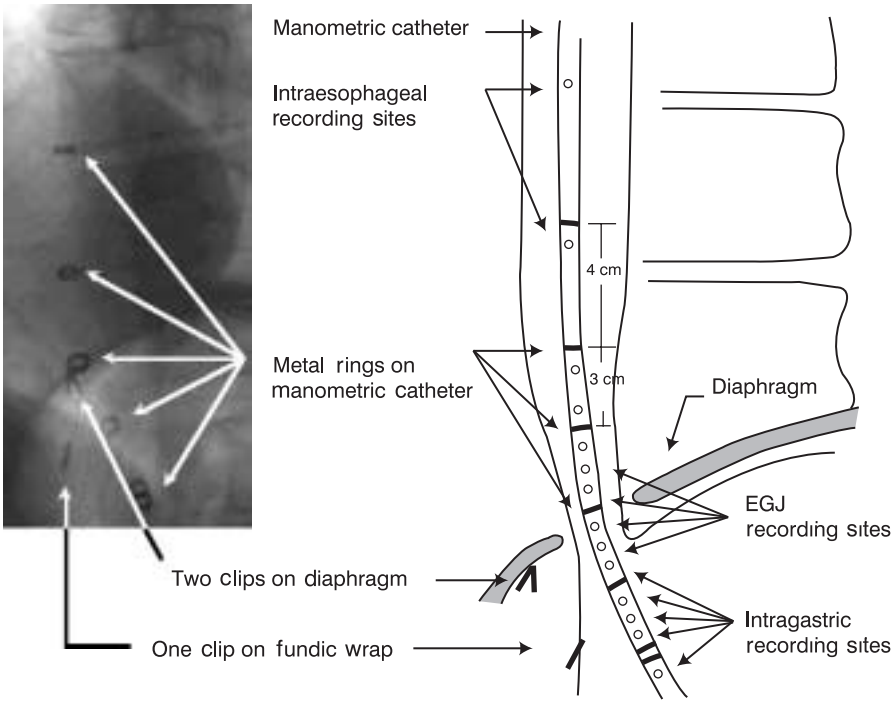

Figure 1
Manometry assembly used in experimental protocols. Recording sites were located in the pharynx, the esophagus, and an array of 11 recording sites (1 cm apart) straddled the distal esophagus, the EGJ and the proximal stomach. The intragastric recording site was 2 cm distal to the most distal side hole of the array. Two metal rings, visible on videofluorscopy images were affixed 2 cm proximal to the intragastric recording site. Five more rings were positioned at 3, 6, 9, 12 and 16 cm proximal from this double ring to reference video images to the manometry signal. Note the clips positioned on the fundic wrap (one) and the diaphragm (two).

(OD 4.2 mm, ID 0.4 mm) incorporated two pharyngeal side holes, two separate esophageal side holes (proximal and mid), and an array of eleven closely spaced (1-cm intervals) side-holes to assess pressure changes at the level of the distal esophagus, the EGJ and the gastric fundus (Figure 1). Each catheter lumen was perfused with degassed water at a rate of 0.15 mL/min using a pneumohydraulic perfusion pump (Arndorfer Medical Specialities, Greendale, Wisconsin, USA) and pressures were recorded with external pressure transducers (DPT-100, Medisize, Hillegom, The Netherlands). Seven metal

rings visible on X-ray were attached to the manometric assembly. Two rings, seperated 0.5 cm from each other, were positioned 2 cm proximal to the intragastric recording site. Five more rings were positioned at 3, 6, 9, 12 and 16 cm proximal from this double ring (Figure 1). Pressure data were digitised at a sampling frequency of 25 Hz and processed using Trace 1.2v software (G Hebbard) installed on a personal computer containing a data acquistion card (PCI-6023E National Instruments Corporation, Austin, Texas, USA). An image acquistion card (PCI-1411, National Instruments Corporation, Austin, Texas, USA) linked to a videofluoroscope (Easy Diagnost, Philips Medical Systems, Best, The Netherlands) enabled concurrent videofluoroscopy and manometry recording. Every second video frame was recorded and synchronised with the pressure data.

Symptom assessment

Dysphagia was defined as an unpleasant sensation of food remaining in the esophagus shortly after food intake. During the test, symptoms of dysphagia were scored using a visual analog scale from 0 (no difficulty swallowing) to 10 (unable to swallow) for each bolus.

EGJ transit studies

After an 8-hour fast, the manometry assembly was passed transnasally and then positioned so that from the array of 11 side-holes recording sites, 5 were positioned in the distal esophagus. With the catheter in this position 3-5 side-hole recording sites were within the esophagogastric high pressure zone and at least one side-hole was in the stomach. Subjects remained in the upright position during the study. After participants were placed behind the videofluoroscope, five 10-mL vol of liquid barium sulfate 1g/mL suspension (E-Z-EM Canada Inc., Montreal, Canada) were given and videofluoroscopy and manometry were recorded simultaneously as the bolus traversed the distal esophageal lumen and crossed the EGJ into the stomach. If the bolus did not clear within 20 s of the first swallow, subjects were asked to swallow again. If bolus or bolus residue remained after two swallows, 10-mL of water was given with subsequent swallow until complete clearance was achieved. Next, a radio-opaque solid bolus (1 cm3) was placed in subject's mouth. These boluses were made from 100 mL liquid barium mixed with 20 g of gelatin (Dr. Oetker GmbH, A-9500, Villach, Austria) and 200 mL water. The subject was asked to swallow the bolus without chewing together with 10-mL water and the swallowing

sequence detailed above for liquid barium was repeated for the solid bolus. After the two swallowing sequences were completed, the manometric catheter was removed and the two sequences were repeated.

Data analysis

Videofluoroscopy. Analysis of the videofluoroscopic recordings was accomplished with reference to the manometric data. Digital videofluoroscopic and manometric sequences were analyzed using Trace 1.2v analysis software. Data were corrected for fluoroscopic magnification using the known 4-cm distance between the most proximal adjacent metal rings affixed to the manometry catheter. Data collected on each swallow were (1) the esophageal transit time, defined as the interval between swallow onset and the time the bolus reached the upper margin of the EGJ; (2) the EGJ transit time, defined as the interval between the time the bolus reached the EGJ to the time when all of the bolus had traversed the EGJ into the stomach. EGJ transit time consisted of (3) the time from bolus arrival at the EGJ until the start of EGJ transit and (4) the time from start transit until the the bolus had completely cleared the esophagus, referred to as EGJ opening duration. The maximal diameter of the (5) phrenic ampulla and (6) the EGJ during bolus transit were measured as the distance between opposing walls. (7) The axial bolus length was defined as the smallest distance from the point of luminal closure at the top of the bolus till the most caudal part of the bolus at the level of the EGJ before EGJ transit.

Pressure recordings. The interpretation of esophageal body and EGJ motility was performed following methods described previously [1,8], using a combination of conventional manometric measurements and topographic contour plot assessment wherein concentric contour rings indicate increasing pressure amplitude. For visual simplicity, pressure levels were coloured according to a legend (Figure 2). To analyze the amplitudes and velocity of esophageal peristaltic contractions, the esophageal body was divided into upper, mid and lower segments. Intrathoracic esophageal peristaltic pressures were referenced to end expiratory pressures calculated automatically. The maximum pressure within each esophageal segment was calculated as the peristaltic amplitude for that segment. Velocity was calculated from the spatiotemporal plot of pressures. EGJ was defined as the high pressure zone separating the abdominal ($P > 0$ mmHg) from the thoracic cavity ($P < 0$ mmHg). The EGJ length was defined as the interval between the first and last contour line bordering the EGJ (Figure 2 and 3), averaging values around respiratory variation. All EGJ pres-

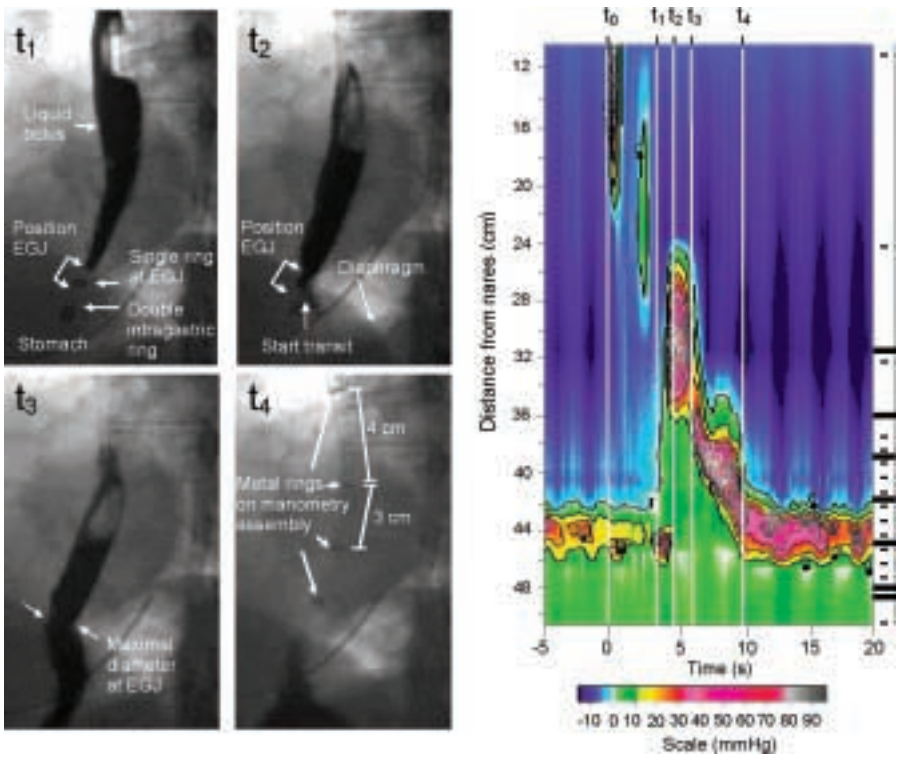

Figure 2

Fluoroscopic and manometric data on emptying across the EGJ in a representative GERD patient before fundoplication. Fluoroscopic tracings at left depict anatomic configuration at the time of bolus arrival at the EGJ (t_1), the start of bolus transit across the EGJ (t_2), at EGJ bolus transit (t_3) and at the completion of EGJ transit (t_4). Similarly, at right the corresponding timing of these images are indicated on topographic color plot by labeled vertical lines. Note that bolus arrival at the EGJ (t_1) corresponds with the appearance of intrabolus pressure and that EGJ transit starts directly after the diaphragmatic pinch due to inspiration (t_2) .

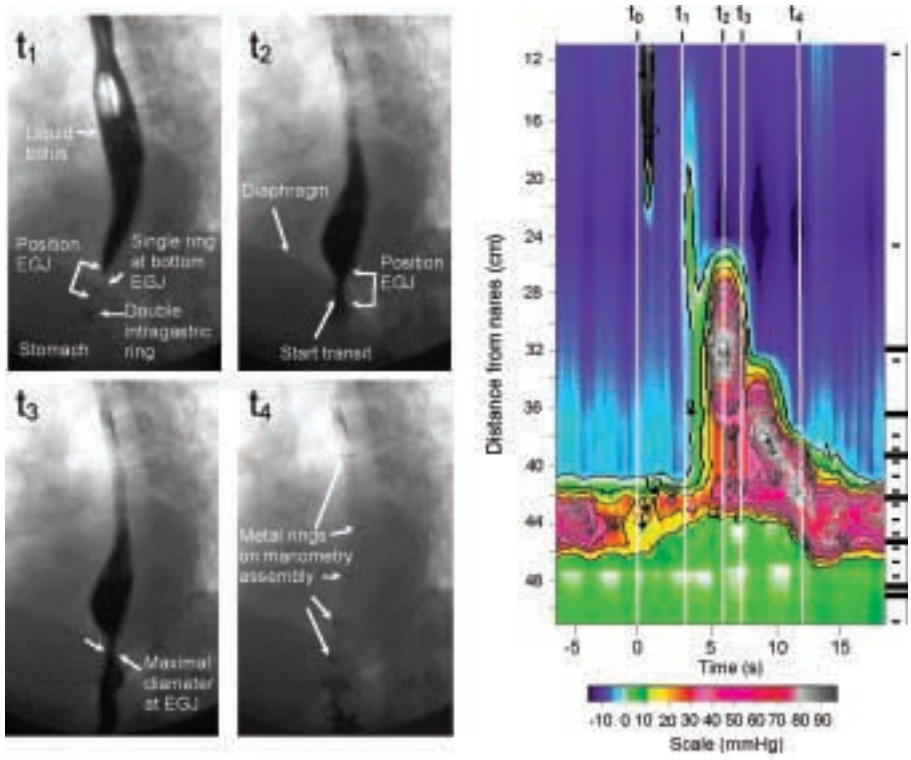

Figure 3

Fluoroscopic and manometric data on emptying across the EGJ in a representative postfundoplication patient presented as in Figure 2. Note that EGJ relaxation is incomplete (arrows), the intrabolus pressure is increased and that a narrowed and elongated outflow tract is associated with a reduced axial bolus length compared with Figure 2 (see Table 1&3 for summary data) measured after fundoplication.

sure data were referenced to intragastric pressure, calculated as the mean end expiratory pressures recorded by the intragastric sideholes. Basal EGJ pressure was calculated as the average maximal end-expiratory pressure at the EGJ over the 5 s preceding a swallow. The nadir EGJ pressure was defined as the 10th centile of the data generated using a 'virtual sleeve' positioned across the EGJ from the start of relaxation to the reconstitution of the lower esophageal sphincter. Ampullary intrabolus pressure was defined as the mean pressure of all maximal pressure data for each time point within the triangular region representing the elevated pressure preceding peristalsis.

Statistical analysis

Data were summarized as mean (SEM). Averaged data were compared using a paired Student *t* test. Pearson's correlation test was used to determine correlations. For all statistical tests the level of significance was < 0.05.

Results

Manometric variables of EGJ function.

Manometric data for patients before and after fundoplication are shown in Table 1. Fundoplication significantly increased EGJ length ($P < 0.01$). Neither basal EGJ resting pressure nor EGJ relaxation duration were affected by fundoplication. In contrast, the ampullary intrabolus pressure and the nadir EGJ relaxation

Table 1
Manometric variables of EGJ function.

	Before fundoplication	After fundoplication
EGJ length (mm)	26.8 ± 1.6	36.6 ± 1.7†
Basal EGJ pressure (mm Hg)	13.5 ± 3.7	19.6 ± 3.2
EGJ relaxation duration (s)	5.8 ± 0.4	5.9 ± 0.4
Nadir EGJ pressure (mm Hg)	2.7 ± 0.8	12.3 ± 3.3*
Intrabolus pressure (mm Hg)	4.4 ± 0.6	9.0 ± 1.6*

*$P < 0.05$ and †$P < 0.01$ *vs* patients before fundoplication.

Table 2
Esophageal and EGJ transit characteristics.

	Before fundoplication	After fundoplication
Liquid		
Esophageal transit time (s)	3.1 ± 0.4	2.6 ± 0.2
EGJ transit time (s)	6.9 ± 0.9	9.8 ± 1.0*
Incomplete esophageal emptying (%)	18.3 ± 6.7	20.0 ± 7.4
Solid		
Esophageal transit time (s)	14.2 ± 2.2	17.1 ± 2.8
EGJ transit time (s)	2.8 ± 0.5	5.8 ± 0.8*
Incomplete esophageal emptying (%)	21.7 ± 6.7	28.3 ± 8.3

*$P < 0.01$ *vs* patients before fundoplication.

pressure were both significantly increased by fundoplication (Table 1). Intragastric pressures among subject groups were similar; 2.5 ± 0.6 and 2.7 ± 0.6 mmHg for patients before and after fundoplication, respectively. Amplitudes and velocity of esophageal peristalsis were not affected by fundoplication. Comparing liquid with solid bolus transit, no manometric differences except from a higher peristaltic amplitude in the mid- ($P < 0.05$) and distal esophagus ($P < 0.05$) when swallowing solids, were observed after operation.

Esophageal and EGJ transit dynamics of both liquids and solids.

After operation, a satisfactory anatomical position of the fundic wrap was observed in all patients. Esophageal transit across the EGJ exhibited distinct characteristics before and after fundoplication. Figure 2 depicts a typical example of a concurrent manometric and fluoroscopic recording in a GERD patient before fundoplication. The traced fluoroscopic images in Figure 2 illustrate the position and anatomical configuration of the manometrically localized EGJ, at arrival of the liquid bolus at EGJ (t_1), at the time of the start of EGJ transit (t_2), at the time the EGJ was maximally distended (t_3) and at EGJ closure (t_4). It is evident from Figure 2 that the intrabolus pressures starts to built up directly after bolus arrival at the EGJ (t_1). It is also apparent that EGJ bolus transit starts at expiration when EGJ relaxation is complete (t_2) and the intrabolus pressure overcomes the EGJ relaxation pressure. Both the EGJ and the narrowest passage for entry into the stomach are located at the level of the diaphragmatic

hiatus. Figure 3 depicts an example swallow from the same patient after fundoplication. Except for an increased EGJ nadir relaxation pressure, fundoplication also increased EGJ length and diminished the opening diameter across the EGJ resulting in a narrowed, elongated outflow tract, depicted in Figure 3. As a consequence, a reduced axial bolus length with unaffected ampullary diameter (Table 3) and elevated intrabolus pressure were seen after fundoplication, evident when comparing Figure 2 and 3.

Associated with the altered EGJ dimensions transit time across the EGJ was prolonged after operation for both liquids and solids, whereas esophageal transit time was not affected (Table 2). Prolonged EGJ transit for liquids was exclusively attributable to the increase of the time from bolus arrival at the EGJ to the start of EGJ transit which increased from 2.3 ± 0.5 s before to 5.6 ± 0.9 s ($P < 0.01$) after operation as the time the bolus was actually traversing the EGJ, the EGJ opening duration, was not affected ($P > 0.05$) (Table 3). EGJ transit characteristics were unaffected by removal of the manometry assembly in all patients.

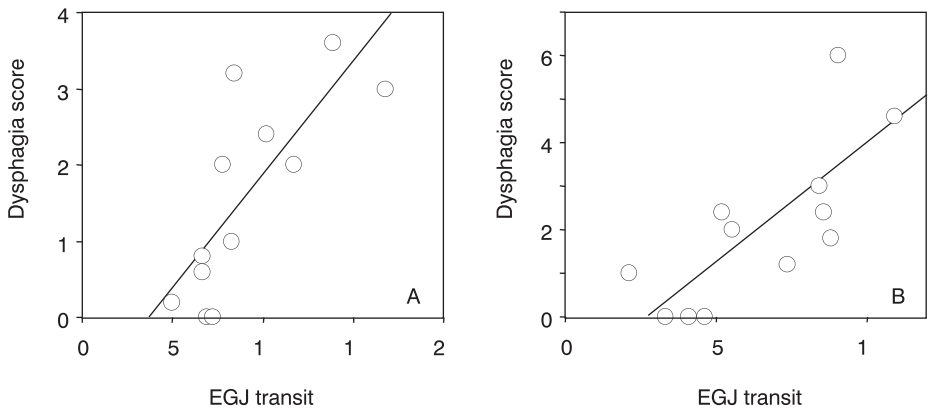

Figure 4

Correlation between dysphagia assessment scores and EGJ transit time for postfundoplication patients for liquid (A); r = 0.84, $P < 0.01$ and solid (B); r = 0.69; $P < 0.05$) bolus consistencies.

Table 3
Ampullary diameter and opening dynamics at the EGJ.

	Before fundoplication	After fundoplication
Axial bolus length (cm)	15.9 ± 0.7	10.4 ± 0.8*
Maximal ampullary diameter (cm)	2.3 ± 0.2	2.6 ± 0.2
EGJ opening duration (s)	5.1 ± 0.5	5.0 ± 0.6
Maximal hiatal diameter (cm)	1.0 ± 0.1	0.6 ± 0.1†

*$P < 0.001$ and †$P < 0.01$ *vs* patients before fundoplication

Relationship between EGJ transit time, EGJ pressure and symptoms of dysphagia.

Pre-operatively, mean dysphagia scores varied from 0 to 2.4 and from 0 to 4.3 for liquids and solids respectively. Post-operatively, dysphagia ranged from 0 to 3.7 and from 0 to 6.2 for liquids and solids repectively. Solids did induce significantly higher dysphagia scores than liquids before ($P < 0.05$) and after operation ($P < 0.05$). Although no significant relation between the EGJ transit time and the dysphagia score was present before fundoplication, a significant relation was observed for both liquids ($r = 0.84$; $P < 0.01$) and solids ($r = 0.69$; $P < 0.05$) after operation (Figure 4). In contrast, dysphagia scores did not relate to the intrabolus pressure or nadir EGJ relaxation pressure either before or after fundoplication.

Discussion

Although impaired bolus transit across the EGJ has been identified as an important physiological parameter underlying postoperative dysphagia [30], data on EGJ transit efficacy and characteristics after laparoscopic fundoplication are limited. The major findings of this study are that patients who have undergone a successful fundoplication exhibited an elongated EGJ with a restricted hiatal diameter which presumably resulted in an increased outflow resistance. To overcome this physiological barrier, a higher intrabolus pressure is created by

an augmented compression of the liquid bolus, evident from the reduced axial bolus length measured before EGJ transit. As a consequence, EGJ transit time for both liquids and solids increase with fundoplication, the degree of which is associated with post-fundoplication dysphagia. These findings suggest that the differences in EGJ transit efficacy account for the dysphagia symptoms reported after fundoplication.

In this prospective study, a markedly increased EGJ transit time for both liquids and solids is observed after fundoplication. This observation corroborates an earlier report comparing EGJ transit between fundoplication patients and healthy controls that also reported an affected EGJ transit efficacy with fundoplication. [30] A question raised by these data is why EGJ transit is impaired by fundoplication. Theoretically, EGJ transit depends on several mechanical parameters including viscosity of the bolus, the pressure gradient across the EGJ (intrabolus pressure – intragastric pressure) and the resistance to flow across the EGJ. A finding confirmed in the present study is the reduction of the hiatal diameter during liquid transit after fundoplication (Table 3). [14] This suggests that the resistance to flow across the EGJ, being inversely proportional to the fourth power of the hiatal diameter, increases after fundoplication. To generate flow across the EGJ, a pressure gradient in the direction of flow is required, according to Poiseuille's law. Therefore, as reported by Mathew and coworkers [20], and also found in the present study to be due to increased resistance, EGJ transit after fundoplication is associated with an elevated intrabolus pressure. This pressure, built up during the time between arrival of the front of the bolus at the EGJ and the actual opening of the EGJ (Figure 2 and 3), is required to physically open the EGJ during swallow induced LES relaxation. [18,28] Apparently, this elevated intrabolus pressure is generated by an augmented compression of the liquid bolus as the peristaltic wave approaches the EGJ. This is illustrated by the increased time from bolus arrival at the EGJ until the start of EGJ transit and the shorter axial bolus length with unaffected ampullary diameter found after fundoplication (Table 3).

The present study used a topographic high-resolution manometry color display and in fact three-dimensional analysis technique for assessing pre- and postoperative EGJ function. This technique has yielded new insights into the physiology of peristalsis [5-7] and it accurately detects EGJ function and incomplete EGJ relaxation. [29] In the present study, an array of 11 closely spaced (1-cm intervals) recording sites that sample simultaneously from the distal esophagus, the EGJ, and the gastric fundus, provide a complete and more detailed representation of EGJ function than a sleeve. (Figure 2 and 3) Representation as a topographic plot displays the spatiotemporal

characteristics of the pressure wave much more accurately than the fragmented picture that arises from displaying separate line plots. This color display depicts the time course of pressure at any particular level and the axial profile along the EGJ simultaneously. However, as the number of recording sites along the esophageal body is limited and separation of recording sites larger than 2 cm is known to distort the axial representation of data 9, the axial picture at the level of the proximal and mid esophagus is less representative.

An important intent in this study was to define the relationship between EGJ transit efficacy and dyphagia. In this study, we have shown that postoperative dysphagia scores do not relate to manometric parameters but are related to the transit time of both liquid and solid boluses across the EGJ instead. Interestingly, no such relationship existed before fundoplication. Apparently, other factors contribute to dysphagia in patients with GERD, such as esophageal hypersensitivity to distention due to mucosal inflammation 10 or a lowered sensory treshold to bolus distention. [31] Furthermore, incomplete esophageal emptying upon peristalsis might be another contributing parameter. This occurs if the muscle of the distal esophageal ampulla fails to generate the required increment of tone needed for EGJ transit which leads to retrograde flow. [13] Kahrilas et al. [14] have shown that incomplete esophageal emptying occurs equally frequently in GERD patients with hiatal hernia and fundoplication patients, consistent with findings of the present study (Table 3). Thus, although no unequivocal reason for pre-operative dysphagia has been found, post-operative dysphagia is likely due to the functional EGJ obstruction.

Although the present data reveal significantly increased total EGJ transit times after fundoplication, the time the EGJ was opened during liquid bolus transit, defined as the EGJ opening duration, appears unaffected (Table 3). Theoretically, with an observed EGJ diameter reduction from 1.0 to 0.6 cm by fundoplication, the flow velocity across the EGJ must almost double, as did the intrabolus pressure, which is the driving force. Thus, as a consequence of the enhanced flow velocity, the increased EGJ transit time after operation is solely attributable to the increased time from bolus arrival at the EGJ to the start of EGJ transit

In summary, the total EGJ transit time for both liquids and solids is markedly prolonged by laparoscopic fundoplication, the degree of which relates to post-operative dysphagia. The reduced EGJ transit efficacy is due to the increased outflow resistance evident from the narrowed and elongated hiatal passage likely due to a reduced EGJ compliance limiting EGJ opening.

To overcome this increased outflow resistance a higher intrabolus pressure is generated, built up over the time between arrival of the front of the bolus at the EGJ and the actual opening of the EGJ.

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8

Role of transsphincteric pressure and proximal gastric volume in acid reflux studied in GERD patients before and following fundoplication

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Abstract

This study was conducted to explore the effect of fundoplication on the esophago-gastric junction (EGJ) pressure profile and the role of the proximal gastric volume in determining acid reflux during TLESRs. Twenty GERD patients were studied before and after fundoplication along with 20 healthy controls. High resolution manometry and pH recording was performed for 1hr before and 2hr following meal ingestion (500 ml/ 300kcal). 3D ultrasonographic images of the stomach were acquired before and every 15 minutes after meal ingestion. From the 3D ultrasonographic images proximal gastric volumes were computed. Postprandial proximal to total gastric volume distribution ratios were significantly larger in GERD patients before fundoplication (0.57 ± 0.01; $P < 0.05$) and smaller following fundoplication (0.37 ± 0.01; $P < 0.001$) compared with controls (0.46 ± 0.01). The %TLESRs associated with acid reflux did not relate to proximal gastric volume in any subject group. The axial EGJ pressure profile was different for TLESRs with and without reflux in GERD patients ($P < 0.001$) as well as in healthy controls ($P < 0.01$). The pressure difference across the EGJ (∆EGJp) was significantly greater for TLESRs with acid reflux compared to TLESRs without acid reflux in both GERD patients (6.8 ± 0.6 vs 3.9 ± 0.4 mmHg; $P < 0.01$) and controls (5.0 ± 0.5 vs 3.0 ± 0.5 mmHg; $P < 0.05$). After fundoplication, ∆EGJp during TLESRs was 3.2 ± 0.9 mmHg, comparable to the ∆EGJp during TLESRs not associated with acid reflux in the other subject groups. Although the volume of the proximal stomach plays a key role in eliciting TLESRs, it is not related to the incidence of acid reflux during TLESRs. The axial EGJ pressure gradient plays a crucial role in the occurrence of acid reflux during a TLESR.

Introduction

Gastroesophageal reflux disease (GERD) is characterized by an increased frequency of acid reflux. [1-3] In both controls and patients with GERD, the majority of reflux events are associated with transient lower esophageal sphincter relaxations (TLESRs). [4-8] In GERD, TLESRs occur as frequently as in healthy controls but are more likely to be associated with acid reflux. [8-10] After fundoplication, both the number and percentage of TLESRs associated with acid reflux are markedly reduced. [11,12]

TLESR, a vagally mediated reflex, is triggered by gastric distension, especially distension in the area of the gastric cardia. [13] Animal data indicate that both tension and stretch mechanoreceptors are present in the stomach. [14-17] In recent studies, isovolumetric and/or isobaric barostat studies have clearly shown that proximal gastric volume, via stretch receptors, plays a pivotal role in triggering TLESRs. [18,19] In GERD, augmented and/or prolonged fundic accommodation has been repeatedly reported and fundoplication reduces meal-induced adaptive fundus relaxation. [20-23] Despite this the exact relationship between gastric volume, TLESRs and the frequency of acid reflux remains unclear. As the barostat technique, which has been considered to be the gold standard to assess gastric volume, is known to interfere with gastric accomodation [24] and emptying [25], we combined non-invasive 3D ultrasonography with concurrent manometry/pH-metry to examine why only some TLESRs are accompanied with acid reflux during physiological postprandial conditions. We hypothesized that the pressure profile across the esophagogastric junction (EGJ) during a TLESR with acid reflux, would be different from the profile during TLESRs without acid reflux. Therefore, the aim of this study was to explore the role of the proximal stomach and the EGJ pressure profile in determining acid reflux during TLESRs and to examine the effect of fundoplication on these parameters.

Patients and methods

Subjects

Twenty GERD patients (12 men, 8 women; median age 50.0 (29-69) years old) were studied, along with 20 normal subjects (10 men, 10 women; median age 28.0 (18-53) years old). Patients were studied on two occasions, before and three months after laparoscopic Nissen fundoplication. The presence of GERD was established by symptom evaluation, upper GI endoscopy and 24-hour pH monitoring and defined by the presence of ≥ Los Angeles A esophagitis on recent endoscopy (18 of 20) and/or abnormal 24-hour ambulatory pH monitoring using a cutoff value of 6.0% total time with pH < 4 and/or a proven association between reflux and symptoms (symptom association probability index (SAP) > 95%) (20 of 20). [26] Fourteen GERD patients (70%) had endoscopic evidence of an hiatal hernia. All GERD patients had refractory symptoms despite at least 40 mg of omeprazole daily. At three months after fundoplication, symptom evaluation, upper GI endoscopy and 24-hour pH monitoring were repeated. Administration of proton pump inhibitors and/or antacids was discontinued for at least 7 days prior to the study. The protocol was approved by the Medical Ethics Committee of the University Medical Center Utrecht, and written informed consent was obtained from all participants.

Laparoscopic fundoplication

Laparoscopic fundoplication was performed using a technique described previously. [27] In short, the proximal fundus was mobilised by coagulating and dividing the gastrocolic and gastrosplenic omentum, including division of the short gastric vessels. The right crus was approximated and a floppy 360° fundoplication of 3.0-3.5 cm was constructed. Three non-resorbable stitches were used to secure the fundic wrap. The fundic wrap and diaphragm were identified with one and two hemoclips (<1cm apart) respectively to be visible on future X-rays. The clip identifying the fundic wrap was placed in the angle of His before constructing the fundic wrap and was therfore located in the wrap after fundoplication.

Manometry, pH-metry and 3D-ultrasonography system

Esophageal manometry was performed using a 16-lumen assembly (OD 4.2 mm, ID 0.4 mm) that incorporated an array of eleven closely spaced (1-cm intervals) side holes to monitor distal esophageal, EGJ and proximal stomach pressures. Side holes 4, 8, 13, and 15 cm above the EGJ array recorded

esophageal body and pharyngeal pressures. One side hole 2 cm below the EGJ array recorded intragastric pressure. Each catheter lumen was perfused with degassed water at a rate of 0.15 mL/min using a pneumohydraulic perfusion pump (Arndorfer Medical Specialities, Greendale, Wisconsin, USA) and pressures were recorded with external pressure transducers (DPT-100, Medisize, Hillegom, The Netherlands). Pressure data were digitised at a sampling frequency of 25 Hz and processed using Trace 1.2v software (G Hebbard) installed on a computer and using a data acquistion card (PCI-6023E National Instruments Corporation, Austin, Texas, USA). Esophageal pH was measured with a glass electrode (model LOT 440, Ingold A.G., Urdorf, Switzerland) positioned 5 cm above the proximal margin of the EGJ. Manometry and pH data were stored in a digital data logger set at a sampling frequency of 12,5 Hz and processed using Trace 1.2v which is capable of displaying conventional line-plots as well as topographic contour plots. [28]

The 3D imaging system consisted of a commercially available ultrasound (US) scanner (Esaote-Pie Medical, Maastricht, the Netherlands) with a 3.5 MHz curved US probe and a tracking system (Esaote-Pie Medical, Maastricht, the Netherlands). The tracking system consisted of a transmitter generating a spatially varying magnetic field and a small receiver, attached to the US probe, containing 3 orthogonal coils to sense the magnetic field strength. [21] Using the 3D imaging system, the US probe with attached sensor was used to localise the left lateral and superior margins of the stomach and the pylorus. The depth of scanning was adjusted enabling an US scan of the stomach, superior mesenteric vein, aorta, left liver lobe and diaphragm or top of the gastric fundus. A standardised US scanning pattern was used, starting at the left lateral subcostal margin and then moving distally to the pylorus with the US probe in a vertical position. During the scan all participants suspended their breathing in inspiration. For each ultrasound scan approximately 300 – 400 2D ultrasound images were stored with a scan typically taking 15 – 20s to complete. The outer profile of the muscularis propria was outlined, and the area was calculated automatically using the built-in calliper and calculation program of the US scanner.

Manometry, pH-metry and 3D-ultrasonography recordings

Following an overnight fast, participants were seated comfortably in an upright position. The manometry assembly was passed transnasally after calibration and referencing of the catheter to atmospheric pressure at the level of the esophagus. Next, the assembly was positioned so that the array of 11 side hole

recording sites was straddling the EGJ with three to four recording sites located in the distal esophageal body, four to six recording sites within the esophagogastric high pressure zone, and at least two sites measuring intragastric pressure. Then, the pH catheter was inserted and positioned 5 cm above the upper margin of the EGJ. Subjects were allowed to accommodate to the presence of the catheter for 15 minutes. Next, ten 5-mL boluses of water were given. This was followed by a 1-h baseline and a 2-h postprandial recording. The test meal consisted of 200 mL of a lactose- and fiber- free milk drink, containing 3.3 g protein, 12.0 g carbohydrate, and 4.3 g fat, 300 kcal (Nutridrink, Nutricia, Zoetermeer, The Netherlands) mixed with 300 mL H_2O. The meal was ingested over 3 minutes and the end of this period was defined as time zero. The time during ingestion was excluded from analysis of reflux and pressure events. Ultrasonographic data were acquired while fasting and at 5, 15, 30, 45, 60, 75, 90, 105 and 120 minutes following meal ingestion. Occurrence of antral contractions was observed by 2D ultrasound before meal ingestion to evaluate for phase III of the gastric MMC (regular contractions with a frequency of 3/min). If a phase III pattern was observed, meal ingestion was postponed until phase I returned.

Data analysis

Pressure recordings; Esophageal body and EGJ motility were evaluated using a combination of conventional high resolution manometric measurements and topographic contour plot assessment wherein concentric contour rings indicate increasing pressure amplitude. [29,30] For visual simplicity, pressure levels were also coloured according to a legend (Figure 5). The EGJ was defined as the high pressure zone separating the abdominal from the thoracic cavity. Concurrent manometric and pH recordings were analyzed to characterize TLESRs, esophageal common cavities (CC's) and acid reflux events. TLESRs were defined according to published criteria. [31] A CC was defined as an abrupt increase in intraesophageal pressure to intragastric pressure in at least two distal esophageal recording sites. [32] For post-fundoplication patients, TLESRs were scored if the nadir EGJ pressure during EGJ relaxation was equal to or less than the residual relaxation pressure determined during repeated water swallows. [11] All EGJ pressure data were referenced to intragastric pressure, calculated as the mean end expiratory pressures recorded by the intragastric sideholes. The pressure profile across the EGJ during TLESRs was determined as follows:

1 Firstly, the upper and lower borders of the EGJ were identified. These were defined as the interval between the first and last contour line bordering the EGJ. Contours lines were displayed at 2 mmHg intervals between -15 and 80 mmHg, followed by 5 and 10 mmHg contours as values increased. Recording points between these contours were defined as being within the EGJ.
2 Secondly, end-expiratory nadir EGJ pressure was determined. This was defined as the 10th centile of the data generated using a 'virtual sleeve' positioned across the EGJ from the start of relaxation to the reconstitution of the lower esophageal sphincter.
3 Finally the EGJ pressure profile was measured. In order to account for differences in pressure profile related to timing of respiration, measurements were made at a consistent point in the respiratory cycle. This point was selected to be the end of the expiration (transition to inspiration) immediately prior to the onset of a reflux event (defined as an acid reflux event or a CC, see below) if present, or, if no acid reflux event or CC was present, at the end of the first expiration during the TLESR. Once this time point was identified, the EGJ pressure profile was constructed by taking averaged pressures referenced to atmospheric pressure over a 2 s interval, (1 s before and 1 s after the timepoint), from all recording sites from 2 cm below the caudal border to 2 cm above the cranial border of the EGJ.

Averaged pressure profiles for TLESRs with and without acid reflux per subject were constructed as well as an average profile for each group (Figure 6 and 7). From these pressure profiles, the pressure difference across the EGJ (ΔEGJp) during a TLESR was calculated as the mean gastric pressure minus the mean thoracic pressure. To evaluate the relative position of the diaphragm within the EGJ, the respiratory inversion point (RIP), defined as the location of the respiration associated inversion of pressure peaks within the EGJ, was determined. [33], RIP was referenced to the most caudal sidehole within the EGJ.
pH recordings; An acid reflux event was defined as a period with pH $<$ 4 following a drop of at least 1 pH-unit with a rate of fall $\geq$ 0.5 pH units/s for a minimum duration of 3 s or, if esophageal pH was already below 4, a further drop in pH of at least 1 pH unit sustained for at least 3 seconds. The end of an acid reflux event was defined by the return of esophageal pH to at least 80% of baseline for at least 5 s. The duration of each reflux event was defined as time with pH $<$ 4 per reflux event.

3D Ultrasonographic imaging; For gastric volume estimation, software with rendering and volume estimation capability was used (Invivo, Medcom, Darmstadt, Germany). The 300-400 2D sagital US frames were processed to construct 3D images. In the sagital US scanplanes of the inner layer of the stomach wall, corresponding to the interface between the outer profile of the gastric wall mucosa and the liquid meal, were outlined in an average of 20-30 scans. The computer then generated gastric contours in the intermediate frames using a triangulation technique. A 3D reconstructed image was created from this data, and the volume of the proximal 10 cm of the stomach (cranial to a plane perpendicular to the longitudinal axis of the stomach as determined form the 3D image) was measured. The investigator was blinded to the order of the tracings in time and to the origin of the tracing (patient or healthy subject). To address the problem of air bubbles in the fundus, the visible amount of air was estimated according to Tefera et al. [21] (0: no visible air; 1: small amounts; 2: moderate amounts; and 3: great amounts of air, disturbing the quality of the ultrasound, hence, necessitating exclusion from the study).

Statistical analysis

Data were summarized as mean (SEM). Normality was tested using the Kolmogorov-Smirnov test. Averaged data for GERD patients before and after fundoplication were compared using a paired Student *t*-test. Averaged 3D volume and EGJ pressure profile data were compared between controls, GERD patients and fundoplication patients using repeated measures analysis of variance (ANOVA). Pearson's correlation test was used to determine correlations. For all statistical tests the level of significance was set at < 0.05.

Results

Technical aspectes of 3D-ultrasonography

A total of two GERD patients (both grade 1), three healthy controls (one grade 2; two grade 1) and five fundoplication patients (one, grade 3; four, grade 2) had visible intragastric air pockets. None of the GERD patients or healthy controls but three of the Nissen fundoplication patients were excluded from analysis of proximal gastric volume, one due to large air pockets (grade 3) in the gastric fundus and two due to poor stomach visualization.

Table 1
Postprandial gastric volume distribution ratios in healthy subjects and GERD patients before and after fundoplication.

	Proximal / Total Gastric Volume Ratio 1st hour PP	Proximal / Total Gastric Volume Ratio 2nd hour PP
Control subjects	0.46 ± 0.008	0.52 ± 0.010
GERD patients	0.57 ± 0.010*†	0.52 ± 0.015
Fundoplication patients	0.37 ± 0.012‡	0.46 ± 0.022

Values are means ± SEM. *$P < 0.05$ *vs* controls; †$P < 0.001$ *vs* fundoplication; ‡$P < 0.001$ *vs* GERD patients and controls. PP = postprandially

Gastric volumes after a liquid nutrient

Fasting total gastric volume was similar among the three subject groups: 35 ± 3 mL in the controls, 34 ± 3 mL before, and 27 ± 3 mL after fundoplication. After the liquid meal, total gastric volumes were significantly smaller following fundoplication compared to before fundoplication ($P < 0.001$) and to controls ($P < 0.001$). Total gastric volumes did not differ between patients with GERD

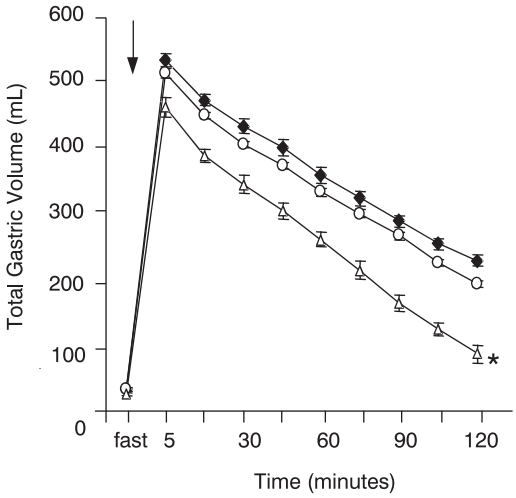

Figure 1
Gastric volumes before and after ingestion of a liquid nutrient in healthy subjects (n=20; o), GERD patients before (n=20; ♦), and after fundoplication (n=20; Δ). Arrow indicates start of meal ingestion. *$P < 0.001$ patients after *vs* before fundoplication and controls.

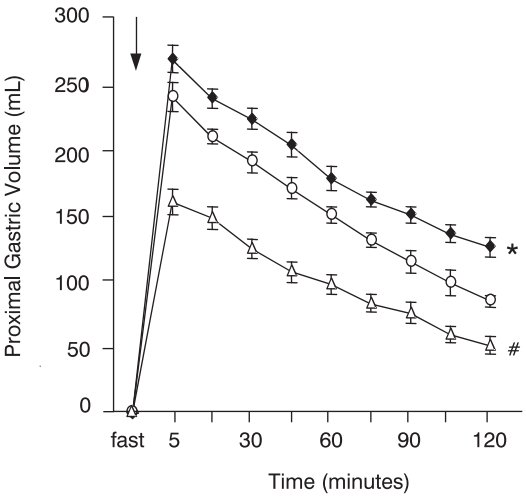

Figure 2
Proximal gastric volume measurements in healthy subjects (o), GERD patients before (♦), and after fundoplication (Δ). Arrow indicates start of meal ingestion. *P < 0.001 GERD patients *vs* controls and # P< 0.001 fundoplication patients *vs* controls.

before fundoplication and controls (P > 0.05) (Figure 1). Assessment of proximal gastric volume showed a similar pattern, with fundoplication significantly reducing proximal intragastric volume (P < 0.001), however GERD patients prior to fundoplication also exhibited larger proximal gastric volumes compared with controls (P < 0.001) (Figure 2).

To account for these differences in total gastric volume, ratios were used to assess postprandial volume changes. During the first hour after the meal, proximal to total gastric volume distribution ratios, were significantly larger before (P < 0.05) and smaller after fundoplication (P < 0.001) compared with healthy controls (Table 1).

Pattern of TLESR and acid reflux

The rate at which TLESRs occurred before and after meal ingestion for each subject group is illustrated in Figure 3. Normal subjects and GERD patients before fundoplication exhibited similar rates of TLESRs during all three periods whereas after operation, the rate of TLESR was markedly reduced. The postprandial increase in the rate of TLESR did not differ between GERD patients before fundoplication and controls. After fundoplication, however, the TLESR rate increase was significantly reduced (1.2 ± 0.4/h) compared to both GERD patients before fundoplication (3.3 ± 0.6/h; P < 0.01) as well as to controls (2.9

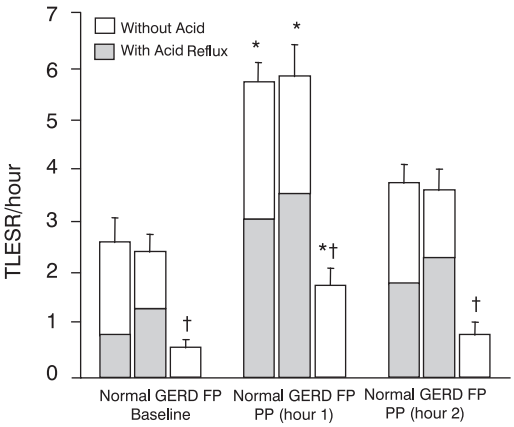

Figure 3
The rate at which TLESRs occurred and the precentage of TLESRs associated with acid reflux during baseline recording and after meal ingeston among subject groups. *$P < 0.01$ baseline *vs*. distension. †$P < 0.001$ fundoplication (FP) *vs*. normal controls and GERD patients before fundoplication.

± 0.5/h; $P < 0.01$). The percentage of TLESRs associated with acid reflux did not differ between controls and GERD patients before fundoplication for any period whereas after fundoplication, no TLESR was associated with acid reflux (Figure 3; $P < 0.001$).

Effect of fundic volume on TLESRs and acid reflux

A significant correlation was found between the rate of TLESRs and proximal stomach volume both during the first and second postprandial hour for both GERD patients before fundoplication (r = 0.71; $P < 0.01$ and r = 0.51; $P < 0.05$ resp.) and controls (r = 0.78; $P < 0.01$ and r = 0.48; $P < 0.01$ resp.) (Figure 4), whereas no such relationship was found after fundoplication. In contrast, the

Table 2
Pre- and postprandial pH-metric parameters.

	Acid Reflux Events / hour Acid			Reflux Duration (s) / event		
	Baseline	1st hour PP	2nd hour PP	Baseline	1st hour PP	2nd hour PP
Control subjects	2.2±0.6	3.7±0.8	3.0±0.7	44±17	34±9	46±15
GERD patients	2.0±0.7	6.8±1.2†	3.2±0.8	41±8	98±26†	63±20
Fundoplication patients	0.1±0.1*	0.2±0.2*	-	12±2*	34±19	-

Values are means ± SEM. *$P < 0.05$ *vs* GERD patients before operation and controls; †$P < 0.05$ *vs* controls and GERD patients after fundoplication; PP = postprandially

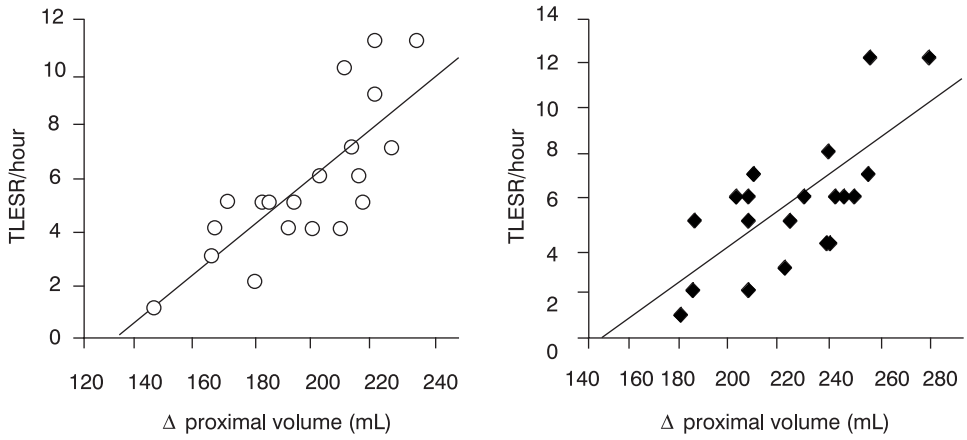

Figure 4
Relation between meal-induced volume increase of the proximal stomach and the number of TLESRs both in 20 controls (o; r = 0.78; $P < 0.01$) and 20 GERD patients before fundoplication (♦; r = 0.71; $P < 0.01$).

%TLESRs associated with acid reflux did not relate to either total or proximal gastric volume in either controls or GERD patients. Acid reflux frequency and duration after meal ingestion was higher in GERD patients before fundoplication compared to both other groups (Table 2) but, neither reflux frequency nor duration correlated with total or proximal stomach volume in any patient group. The percentage of TLESRs with acid reflux associated with a CC was similar amongst controls and GERD patients (96 and 95%, respectively) and significantly lower for TLESRs not associated with detectable acid reflux (78%; $P <$

Table 3
Nadir pressure during swallowing and during TLESRs with (+) and without (-) acid reflux in normal subjects, and GERD patients before and after fundoplication.

	Nadir EGJ pressure (mmHg) during swallows	TLESR nadir pressure (mmHg)	
		TLESRs +	TLESRs -
Control subjects	2.4±0.3	1.4±0.4	1.3±0.4
GERD patients	2.1±0.4	1.2±0.3	1.0±0.4
Fundoplication patients	5.3±0.5*	-	4.7±0.6*

*$P < 0.05$ *vs*. normal subjects and GERD patients before fundoplication.

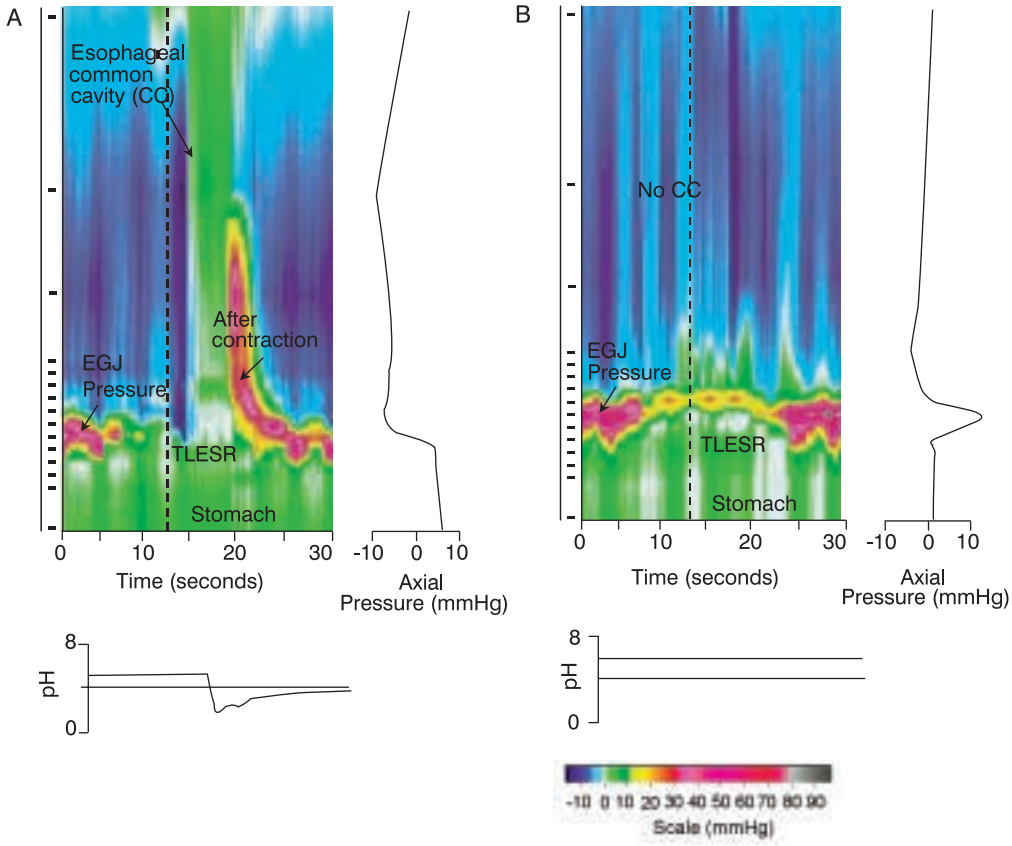

Figure 5

Topographic manometry and pH tracing illustrating an example of a TLESR recorded in a GERD patient before (A) and after fundoplication (B). Position of the catheter with its lumina is presented at left from the manometric color display. The vertical dashed line represents the time the axial pressure is presented. Note that in A, the EGJ relaxation is complete and accompanied by both a pH drop and a common cavity, whereas in B, neither condition is achieved. Only the caudel part of the EGJ does completely relax after operation which results in a cranially located EGJ pressure barrier.

0.05 and 73% $P < 0.05$, repectively). After operation, only 63% of TLESRs, none of which were associated with acid reflux, also corresponded in time with a CC ($P < 0.01$).

Nature of TLESRs with and without acid reflux.

Evident from Table 3, no differences in TLESR nadir pressure were found comparing TLESRs with and without acid reflux within each subject group. In health, the axial ΔEGJ pressure profile was different for TLESRs with and without acid reflux ($P < 0.01$; Figure 6) as well as in GERD patients ($P < 0.001$; Figure 7a).

Table 4

Pressure gradient across the EGJ (ΔEGJp) during swallowing and TLESRs with (+) and without (-) acid reflux in normal subjects, and GERD patients before and after fundoplication.

	ΔEGJp (mmHg) during swallows	ΔEGJp (mmHg) during TLESRs	
		TLESRs +	TLESRs -
Control subjects	2.8±0.7	5.0±0.5*	3.0±0.5
GERD patients	3.7±0.4	6.8±0.6†	3.9±0.4
Fundoplication patients	3.1±0.8	-	3.2±0.9

*$P < 0.05$ and †$P < 0.01$ *vs*. ΔEGJp during TLESRs without acid reflux and ΔEGJp during swallowing.

The pressure gradient across the EGJ (ΔEGJp = gastric pressure - thoracic pressure) was significantly greater during TLESRs accompanied by acid reflux compared to TLESRs not accompanied by acid reflux both in controls ($P < 0.01$) and GERD patients before operation ($P < 0.001$) (Table 4). Delta EGJp for

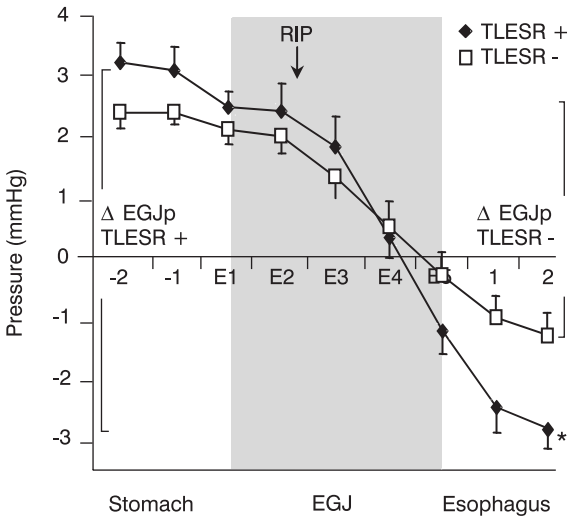

Figure 6

Pressure profile across the EGJ during TLESRs accompanied with (♦, TLESR +) and without acid (□, TLESR -) reflux. Minus 2 and -1 represent the two intragastric sideholes, E1-E5 represent five sideholes at the EGJ, and 1, 2 represent two distal esophageal sideholes. The grey area represents the level of the EGJ. *$P < 0.01$

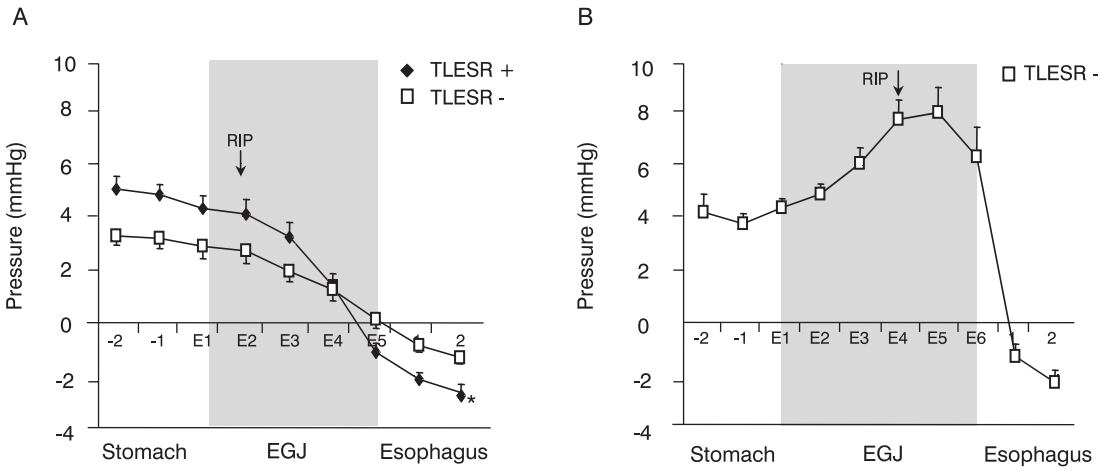

Figure 7
Pressure profile across the EGJ during TLESRs with (♦) and without acid (□) reflux in GERD patients before (A) and after laparoscopic Nissen fundoplication (B) presented as in Figure 6. *$P < 0.001$

TLESRs without acid reflux was similar to ΔEGJ during swallowing whilst ΔEGJp for TLESRs accompanied by acid reflux was markedly higher both in controls and in GERD patients before fundoplication (Table 4). Fundoplication rendered EGJ relaxation incomplete (Figure 5) and considerably altered the EGJ pressure profile (Figure 7b). After fundoplication, ΔEGJp was 3.2±0.9 mmHg, comparable to the ΔEGJp during TLESRs not associated with acid reflux in the other subject groups. Furthermore, the RIP was located at a similar position within the EGJ for controls and GERD patients. However, after operation, the RIP was positioned significantly more cranially ($P < 0.0001$) (Figure 7).

Discussion

This study is the first to directly examine the relation between fundic volume, TLESRs, and acid reflux in patients with GERD before and after fundoplication. In order to identify the impact of the pressure profile preceding acid reflux during a TLESR, high-resolution manometry was used to assess the pressure

profile across the esophagogastric junction (EGJ) just prior to the occurrence of acid reflux. The major findings of this study are that

1 Even though volume changes in the proximal stomach play a key role in eliciting TLESRs, fundic volume alone does not explain for the excess acid gastroesophageal reflux in patients with GERD.
2 After fundoplication, TLESRs may be elicited by mechanisms other than fundic distension.
3 The axial pressure profile across the EGJ plays a pivotal role in the determining gastroesophageal acid reflux during TLESR.
4 Fundoplication considerably alters the axial EGJ pressure profile with an over-all increase in EGJ pressure, thereby preventing acid reflux during a TLESR.

In this study, we confirmed, utilizing 3D ultrasonographic (US) imaging, that meal-induced fundic volume was larger in GERD patients than in controls. [20, 21] This is likely to be attributable to increased meal-induced adaptive relaxation in GERD patients, as demonstrated by recent barostat studies. [20,22] In addition to an abnormal gastric accommodation response, GERD patients had, as expected, more frequent and longer-lasting reflux events (Table 2). Whilst the latter might be due to ineffective clearance [34] or larger volumes of refluxate, it is hypothesized that the volume of the fundus may contribute to the frequency of reflux. [20] TLESRs are the most frequent motor event underlying gastroesophageal reflux. Although the receptive field for eliciting TLESRs is not completely clear, stretch receptors in the gastric cardiac region responding to gastric wall elongation, are commonly implicated. [35,36] Our data show that fundic volume is related to the rate of TLESRs, however, no such relation was present for the %TLESRs with acid reflux. It is therefore likely that other mechanisms such as pressure across the EGJ, or differences in resistance due to EGJ opening diameter and/or EGJ compliance [37] determine the timing, frequency and volume of reflux.

TLESRs are frequently associated with acid reflux. [38,39] It is still unclear why some TLESRs are associated with acid reflux whereas others are not. We hypothesize that the EGJ pressure profile, especially the pressure gradient across the EGJ (EGJ pressure), plays a key role in facilitating acid reflux. Flow through a tube is linearly related to the pressure gradient as the major driving force. We show that the pressure profile across the EGJ is different for TLESRs accompanied with acid reflux as opposed to TLESRs not accompanied with acid reflux (Figure 6 and 7). Evident from Table 4, the pressure gradient across

the EGJ (ΔEGJp) is higher in TLESRs with acid reflux than during TLESRs without acid reflux in GERD patients and controls. Interestingly, ΔEGJp during swallow induced EGJ relaxation is similar to ΔEGJp during TLESRs without acid reflux whilst ΔEGJp during TLESRs accompanied with acid reflux is higher. The reason why ΔEGJp is higher in the latter has not been further examined. ΔEGJp is a function of intra-gastric and intra-thoracic pressure. Inspiration decreases intra-thoracic pressure and increases intra-abdominal pressure, hence, increases ΔEGJp. In addition, physical activity increases intra-abdominal pressure. Normally, the pinchcock-like crural diaphragm pressure variations are related to the depth of inspiration as well as to other physical activity, i.e. coughing, vasalva maneuver. [40] However, during a TLESR, the activity of the crural diaphragm is inhibited, hence, facilitating gastroesophageal reflux. [41] Thus, the mean pressure gradient over the 2 sec at the transition from ex to inspiration might be higher in TLESRs associated with an acid reflux and/or CC event, due to respiratory variation. Therefore, it is reasonable to assume that slight differences in the depth of in- and expiration contribute to ΔEGJp. From the above we may conclude that the EGJ pressure profile, especially ΔEGJ, is an important physiological parameter in gastroesophageal reflux.

Although a reduction of the TLESR rate after fundoplication, was again confirmed [11,12], we found a continuing significant meal-induced augmentation in TLESR rate. This is in contrast to previous data [12,42], reporting no significant TLESR increase after gastric distension following fundoplication. In previous studies, however, air infusion or a barostat bag was used instead of a meal for mechanical distension to elicit TLESRs after fundoplication. [12,42] With fundoplication, the gastric cardia is within the fundic wrap, presumably with a reduced ability to stretch.[43] In addition, Zerbib et al. [44] demonstrated that a meal directly instilled into the duodenum also elicits TLESRs, suggesting the involvement of nutrient-induced hormonal factors, especially CCK. This observation is in concordance with our observation that proximal gastric volume did not correlate to the rate of TLESRs after fundoplication. Probably, other factors, including hormonal facters, are more important in TLESR eliciation after fundoplication. The EGJ pressure profile during a TLESR was substantially altered by fundoplication (Figure 7). From this profile we conclude that ΔEGJ must be ≥ 4 mmHg (maximal EGJ pressure - intragastric pressure) to accomplish flow towards the esophagus. In theory, the positive abdominal to thoracical pressure gradient facilitates flow towards the intrathoracic esophagus (i.e. gastroesophageal reflux), mechanically prevented by the EGJ high-pressure zone,

except during EGJ relaxation. After fundoplication, it is evident that whilst the caudal part of the EGJ reaches a nadir pressure ≤ 2 mmHg, hence completely relaxes, pressure in the more cranial part remains high (Figure 5). Although the data reported reveal that the axial EGJ pressure changes following fundoplication, it does not identify the components of the EGJ responsible for this increased pressure. We selected the respiratory inverstion point (RIP), i.e. the diaphragm, to represent the transition from the thoracic to the abdominal compartment. In theory, the RIP can be confused with the pressure inversion point (PIP), the latter being caused by sliding of a high-pressure zone along pressure sensors. [45] However, by using high resolution manometry and spatiotemporal analysis, this distiction became obvious. Whilst PIP's may be located at the caudal or cranial EGJ margin, the RIP is typically located within the EGJ. Consistent with elongation of the subdiaphragmatic component of EGJ pressure, reported by Kahrilas et al. [46], we showed a more cranially located RIP after fundoplication. This is likely to be caused by surgical repositioning of the EGJ intra-abdominally, and suggests that the diaphragm might play an important role in the anti-reflux efficacy of fundoplication.

In summary, we have examined the relationship between physiological postprandial fundic volume, TLESRs, acid reflux and the pressure profile across the relaxed EGJ before and after fundoplication using a combination of 3D ultrasonography, topographic manometry, and pH-metry. Although fundic volume plays an imporant role in eliciting TLESRs, it does not determine the occurrence of acid reflux during TLESRs. After fundoplication, TLESR elicitation may be due to mechanisms other than proximal gastric distension. The axial EGJ pressure profile and the pressure gradient across the EGJ during a TLESR play a key role in the occurrence and the prevention of acid gastroesophageal reflux.

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9

Effects of partial (Belsey Mark IV) and complete (Nissen) fundoplication on proximal gastric function and esophagogastric junction dynamics

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Abstract

This study aimed to assess the effects of Belsey Mark IV 270 degrees (partial) and Nissen 360 degrees (complete) fundoplication on proximal stomach function, transient lower esophageal sphincter relaxation (TLESR) elicitation and the esophago-gastric junction (EGJ) pressure profile during TLESR to further elucidate the mechanism of action of fundoplication. Ten patients after partial and ten patients after complete fundoplication were studied. High resolution EGJ manometry and pH recording were performed for 1h at baseline and 2hr following meal ingestion (500 ml/ 300kcal). 3D ultrasonographic images of the stomach were acquired every 15 minutes after meal ingestion. From the 3D ultrasonographic images proximal gastric volumes were computed. Postprandial proximal to complete gastric volume distribution ratios were larger in patients after partial (0.42 ± 0.028) than after complete fundoplication (0.37 ± 0.035; $P < 0.05$). Partial fundoplication resulted in a higher postprandial rate of TLESR (1.7 ± 0.3/h) than complete fundoplication (0.8 ± 0.2/h; $P < 0.05$). The pressure gradient across the EGJ during TLESR was markedly different among both subject groups. Patients after partial fundoplication exhibit a larger meal-induced increase in proximal stomach volume, a higher TLESR rate, and a minimally affected axial EGJ pressure profile compared to patients after complete fundoplication.

Introduction

Laparoscopic Nissen fundoplication has been increasingly advocated as a surgical remedy for gastroesophageal reflux disease (GERD). Its efficacy for the long-term control of acid reflux is reported to be as high as 90%. [1,2] In patients with impaired esophageal peristalsis and in patients with after Nissen dysphagia or gas bloat, partial fundoplication according to Belsey Mark IV or Toupet, has been proposed as an alternative. [3,4] Whilst both techniques are equally effective in controlling acid reflux, partial fundoplication seems to be less frequently associated with dyphagia or gas bloat. [3-5] The principal underlying mechanism of action of antireflux surgery is not fully understood. Possible mechanisms include increased esophagogastric junction pressure (EGJ), incomplete EGJ relaxation, and a reduced rate of transient lower esophageal sphincter (TLESR) [6-8] In a recent study, it has been reported that fundoplication renders EGJ relaxation incomplete. [8] The effect on the pressure profile across the EGJ, however, has not yet been evaluated. Although recent studies have established that TLESR elicitation is attenuated and reduced in number per 24 hours in patients after complete fundoplication, reports to date on the effect of partial fundoplication on TLESR are limited. [9] TLESRs are a vagally mediated reflex elicited by distension and/or accommodation of the proximal stomach, especially the area of the gastric cardia. Following Nissen fundoplication, a 360 degrees fundic wrap surrounds this area possibly limiting such distension. However, with a Belsey Mark IV procedure no such wrap is created but instead the proximal stomach is plicated against the distal esophagus over 270 degrees instead. [10] Therefore, it is reasonable to hypothesize that the anatomic alterations after a Belsey Mark IV procedure may have less impact on the threshold for eliciting TLESRs. Although in recent studies it has been established that meal-induced adaptive gastric relaxation is impaired with Nissen fundoplication, [11,12] the effect of Belsey Mark IV antireflux sugery on fundus physiology, TLESR or the pressure profile of the EGJ is unknown. The aims of this study were to compare the effect of a 360 degrees fundoplication, with a 270 degrees wrap on 1) fundic volume, using a noninvasive real-time 3D ultrasound technique, 2) the relationship between fundic volume and TLESR elicitation after a liquid nutrient and 3) on the EGJ pressure profile during TLESRs.

Patients and methods

Subjects

Ten patients after partial fundoplication (6 men, 4 women; median age 56.5 (34-70) years old) and ten patients after laparoscopic Nissen fundoplication (6 men, 4 women; median age 50.0 (29-69) years old) were studied. Partial fundoplication was performed as a reoperation for a slipped Nissen or a combination of slipping and telescoping. Laparoscopic Nissen was perfomed in case of refractory gastroesophageal reflux disease (GERD). Data were compared with data obtained from 20 healthy subjects (10 men, 10 women; median age 28.0 (18-53) years old). All patients were at least 3 months after surgery at the time of the study, were free of heartburn, had no significant dysphagia, and were using no antisecretory drugs. The protocol was approved by the medical ethics committee of the University Medical Center Utrecht, and written informed consent was obtained from all participants.

Surgical procedures

Belsey Mark IV antireflux operation. The Belsey Mark IV procedure was performed using a technique described previously. [10] In short, access was gained through a left-sided thoracotomy in the 6th intercostal space. The esophagus up to the aortic arch and gastric cardia are mobilized. The fibro-fatty tissue ("fat pad") in front of the cardia was removed and two rows of three mattress sutures, encompassing approximately 270° of the esophagus, are created. After tying the first row, the partial fundoplication was gently pushed back into the abdomen. Then the second row of sutures was tied. Finally, the previously inserted sutures through the right crus are tied to create the posterior buttress.

Nissen fundoplication. Nissen fundoplication was performed laparoscopically using a technique described previously. [13] In short, the proximal fundus was mobilized by coagulating and dividing the gastrocolic and gastrosplenic omentum, including division of the short gastric vessels. The right crus was approximated and a floppy 360° fundoplication of 3.0-3.5 cm was constructed. Three non-resorbable stitches were used to secure the fundic wrap.

Experimental protocol

After an overnight fast, the silicone manometry catheter was passed transnasally after calibration and referenced to atmospheric pressure in a vertical position at the level of the esophagus. Next, the catheter was positioned so that the array of 11 side hole recording sites straddled the EGJ with three to four side hole recording sites located in the distal esophagus, four to six side hole

recording sites within the EGJ, and at least two side holes measuring gastric pressure. Then, the pH catheter was inserted and positioned at 5 cm above the upper margin of the EGJ. During the test participants were seated in an upright position. Subjects were allowed to accommodate to the presence of the catheter for 15 minutes, after which ten 5-mL vol of water were given. This was followed by a 1-h baseline recording period and a 2-h period after meal ingestion. The meal (500 mL) consisted of a 200 mL lactose- and fiber-free milk drink, containing 3.3 g proteins, 12.0 g carbohydrates, and 4.3 g fat, 300 kcal (Nutridrink, Nutricia, Zoetermeer, The Netherlands) mixed with 300 mL H_2O. The test meal was ingested within 3 minutes during phase I of the gastric MMC (confirmed on 2D ultrasound) and the end of the ingestion period was defined as time zero. Ultrasonographic data were acquired while fasting and at 5, 15, 30, 45, 60, 75, 90, 105 and 120 minutes after meal ingestion.

Esophageal manometry and pH-metry. Esophageal manometry was performed using a 16-lumen assembly (OD 4.2 mm, ID 0.4 mm) that incorporated an array of eleven side holes spaced at 1-cm intervals to assess distal esophageal, EGJ and proximal stomach pressures. Four side holes at levels 4, 8, 13, and 15 cm above the EGJ array recorded esophageal body and intrapharyngeal pressures. One side hole at level 2 cm below the EGJ array recorded intragastric pressure. Each catheter lumen was perfused with degassed water at a rate of 0.15 mL/min using a pneumohydraulic perfusion pump (Arndorfer Medical Specialities, Greendale, Wisconsin, USA) and pressures were recorded with external pressure transducers (DPT-100, Medisize, Hillegom, The Netherlands). Pressure data were digitised at a sampling frequency of 25 Hz and processed using Trace 1.2v software (G Hebbard) installed on a personal computer containing a data acquistion card (PCI-6023E National Instruments Corporation, Austin, Texas, USA). Esophageal pH was measured with a glass electrode (model LOT 440, Ingold A.G., Urdorf, Switzerland) positioned at 5 cm above the proximal margin of the EGJ. Manometry and pH data were stored in a digital data logger set at a sampling frequency of 12,5 Hz and processed using Trace 1.2v capable of displaying conventional line-plots as well as topographic contour plots. [14]

3D ultrasonographic assessment of gastric volumes. The 3D imaging system consisted of a commercially available ultrasound (US) scanner (Esaote-Pie Medical, Maastricht, the Netherlands) with a 3.5 MHz curved US probe and a tracking system (Esaote-Pie Medical, Maastricht, the Netherlands). The tracking system consisted of a transmitter generating a spatially varying magnetic field

and a small receiver, attached to the US probe, containing 3 orthogonal coils to sense the magnetic field strength. [15] Using the 3D imaging system, the US probe with attached sensor was used to localise the left lateral and superior margins of the stomach and the pylorus. The depth of scanning was adjusted enabling a US scan of the stomach, superior mesenteric vein, aorta, left liver lobe and diaphragm on top of the gastric fundus. A standardised US scanning pattern was used, starting at the left lateral subcostal margin and then moving distally to the pylorus having the US probe in a vertical position. During the scan all participants suspended their breathing in inspiration. For each scan approximately 300 – 400 2D sagital images were stored with a scan typically lasting 15 – 20 s. The outer profile of the muscularis propria was outlined, and the area was calculated automatically using the built-in calliper and calculation program of the US scanner.

Data analysis

Pressure recordings. A combination of high resolution manometry and topographic contour plot assessment wherein concentric rings indicate increasing pressure amplitude was used to study esophageal and EGJ motility. [16,17] For visual simplicity, pressure levels were also coloured according to a legend. The EGJ was defined as the high pressure zone separating the abdominal ($P > 0$ mmHg) from the thoracic cavity ($P < 0$ mmHg). Nadir EGJ pressure was defined as the 10th centile of the data generated using a 'virtual sleeve' positioned across the EGJ from the start of relaxation to the reconstitution of the lower esophageal sphincter. Concurrent manometric and pH recordings were analyzed to characterize TLESRs, esophageal common cavities (CC's) and acid reflux. TLESRs were defined according to the criteria published previously. [18] A CC was defined as an abrupt increase in intraesophageal pressure to intragastric pressure in at least two distal esophageal recording sites. [19] For the fundoplication patients, TLESRs were scored if the nadir EGJ pressure during EGJ relaxation was equal to or less than the residual relaxation pressure determined during repeated water swallows. [6] EGJ relaxation was defined as complete if nadir EGJ pressure was ≤ 2 mmHg. The pressure profile across the EGJ during TLESRs was determined as follows:

1 Firstly, the upper and lower borders of the EGJ were identified. These were defined as the interval between the first and last contour line bordering the EGJ. Contours lines were displayed at 2 mmHg intervals between -15 and 80 mmHg, followed by 5 and 10 mmHg contours as values increased.

Recording points between these contours were defined as being within the EGJ.

2 Secondly, end-expiratory nadir EGJ pressure was determined. This was defined as the 10th centile of the data generated using a 'virtual sleeve' positioned across the EGJ from the start of relaxation to the reconstitution of the lower esophageal sphincter.

3 Finally the EGJ pressure profile was measured. In order to account for differences in pressure profile related to timing of respiration, measurements were made at a consistent point in the respiratory cycle. This point was selected to be the end of the expiration (transition to inspiration) immediately prior to the onset of a reflux event (defined as an acid reflux event or a CC, see below) if present, or, if no acid reflux event or CC waspresent, at the end of the first expiration during the TLESR. Once this timepoint was identified, the EGJ pressure profile was constructed by taking averaged pressures referenced to atmospheric pressure over a 2 s interval , (1 s before and 1 s after the timepoint), from all recording sites from 2 cm below the caudal border to 2 cm above the cranial border of the EGJ.

Averaged pressure profiles for TLESRs with and without acid reflux per subject were constructed as well as an average profile for each group (Figure 6). From these pressure profiles, the pressure gradient across the EGJ (ΔEGJp) during a TLESR was calculated as the mean gastric pressure minus the mean thoracic pressure. After Nissen fundoplication, in all patients six sideholes were present within the EGJ as opposed to five sideholes in the other subject groups. Data from the 3rd and 4th sidehole within the EGJ for Nissen patients were averaged enabling statistical comparison. Pressures during this part of the analysis were all referenced to atmospheric pressure. To assess the pressure gradient across the EGJ (ΔEGJp) during a TLESR the mean gastric pressure minus the mean thoracic pressure for TLESRs was calculated per subject.

pH recordings. An acid reflux episode was defined as a period with pH < 4 after a drop of at least 1 pH-unit with a velocity ≥ 0.5 pH units/s for a minimum duration of 3 s or, if esophageal pH was already below 4, a further drop in pH of at least 1 pH unit sustained for at least 3 seconds. The end of an acid reflux episode was defined by the return of esophageal pH to at least 80% of baseline for at least 5 s. The duration of each reflux event was defined as time with pH < 4 per reflux episode.

3D Ultrasonographic imaging. For gastric volume estimation we used software enabling rendering and volume estimation (Invivo, Medcom, Darmstadt, Germany). The 2D sagital US frames (300-400 per recording) were processed to construct 3D images. In the sagital US scanplanes the inner layer of the stomach wall, corresponding to the interface between the outer profile of the gastric wall mucosa and the liquid nutrition, was outlined in an average of 20-30 planes. The computer using a triangulation technique generated gastric contours in the intermediate frames. Then a 3D reconstructed image and volume of the stomach was obtained. From this 3D reconstruction, the proximal part was separated by a dividing plane 10 cm below the diaphragm perpendicular to the longitudinal axis of the stomach. The investigator was blinded to the order of the tracings in time and to the origin of the tracing (patient or healthy subject). From previous 3D US studies performed in healthy subjects, a normal range of complete and proximal gastric volume data was derived, displayed in Figure 1 and 2. To address the problem of air bubbles in the fundus, the visible amount of air was estimated according to Tefera et al. [15] (0: no visible air; 1: small amounts; 2: moderate amounts; and 3: great amounts of air, disturbing the quality of the ultrasound, hence, necessitating exclusion from the study).

Statistical analysis

Data were summarized as mean (SEM). Normality was tested using Kolmogorov-Smirnov test. Averaged data were compared using a Student *t* test and Bonferroni's correction was applied when comparing the rate of TLESRs between patients after patial and complete fundoplication at fasting and during the 1st and 2nd postprandial hour. At consecutive time points averaged 3D volume data were compared among patients after complete and partial fundoplication using repeated measures analysis of variance (ANOVA). Likewise, pressures profiles were compared using repeated measures analysis of variance (ANOVA). Pearson's correlation test was used to determine correlations. For all statistical tests the level of significance was < 0.05.

Results

Technical aspectes of 3D ultrasonography

Three patients after complete fundoplication (one, grade 3; two, grade 2) and 2 patients after partial fundoplication (two, grade 2) had visible intragastric air pockets. None of patients after partial but two of the patients after complete fundoplication were excluded, one due to large air pockets (grade 3) in the gastric fundus and one due to poor stomach visualization.

Complete and proximal gastric volumes after a liquid meal

Fasting gastric volume was similar among subject groups: 25 ± 3 mL after complete and 32 ± 6 mL after partial fundoplication. After a liquid meal, 3D total gastric volumes were signficantly greater in patients after partial than after complete fundoplication ($P < 0.05$). The 3D total gastric volumes after partial fundoplication were within the normal range (Figure 1). Although meal-induced proximal gastric volume was greater after partial than after complete fundoplication ($P < 0.05$), both were reduced if compared with the normal range (Figure 2). Evident from Table 1, proximal to total gastric volume distribution ratios showed the same pattern.

Relation between proximal gastric volume, TLESRs and acid reflux

The pre- and postprandial rate of TLESRs is illustrated in Figure 3. At baseline, partial and complete fundoplication patients exhibited a similar TLESR rate, markedly lower than controls ($P < 0.05$). Following the meal, the rate of TLESRs increased in both groups. Meal-induced TLESR rate increase was significantly

Table 1
Postprandial gastric volume distribution ratios in patients after partial and complete fundoplication

	Proximal / Total Gastric Volume Ratio 1st hour PP	Proximal / Total Gastric Volume Ratio 2nd hour PP
Partial fundoplication	0.42 ± 0.028*	0.45 ± 0.039
Complete fundoplication	0.37 ± 0.035	0.46 ± 0.059
Control subjects	0.48 ± 0.019	0.53 ± 0.021

Values are means ± SEM. In grey reference values for 20 normal controls are provided.
*$P < 0.05$ *vs* complete fundoplication

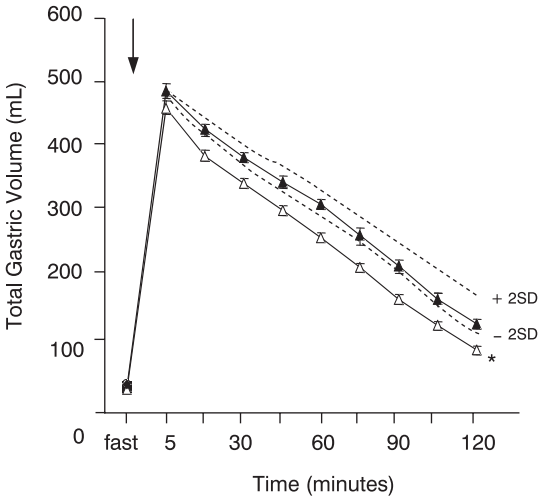

Figure 1
Gastric volumes before and after ingestion of a liquid nutrient in patients after partial (n=10; ▲) and after complete (n=10; △) fundoplication. The dashed lines represent the range (mean ± 2SD) found in 20 normal controls. Arrow indicates start of meal ingestion.
**P* < 0.05 *vs*. partial fundoplication patients.

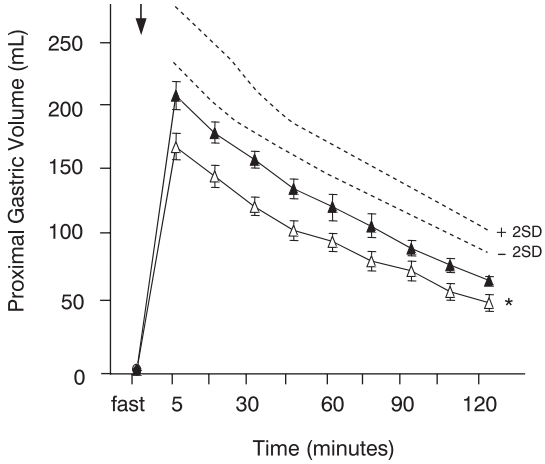

Figure 2
Proximal gastric volume measurements in patients after partial (▲) and after complete (△) fundoplication. The dashed lines represent the range (mean ± 2SD) found in 20 normal controls. Arrow indicates start of meal ingestion.
**P* < 0.05 *vs*. partial fundoplication patients.

higher for patients after a partial (1.7 ± 0.3/h) than after a complete fundoplication (0.8 ± 0.2/h; $P < 0.05$). Both patients after partial and complete fundoplication exhibited a lower absolute number of TLESRs and percentage of TLESRs associated with acid reflux, compared to the normal range (Figure 3). Similarly, acid reflux frequency (Table 2) and total esophageal acid exposure was reduced to a similar extent by both 270 degrees and 360 degrees antireflux operations.

Whilst a strong relationship was found between the increase in proximal stomach volume and the TLESR rate in patients after partial fundoplication (r=0.79; $P < 0.01$) (Figure 4), during the first hour after meal ingestion, no such relationship

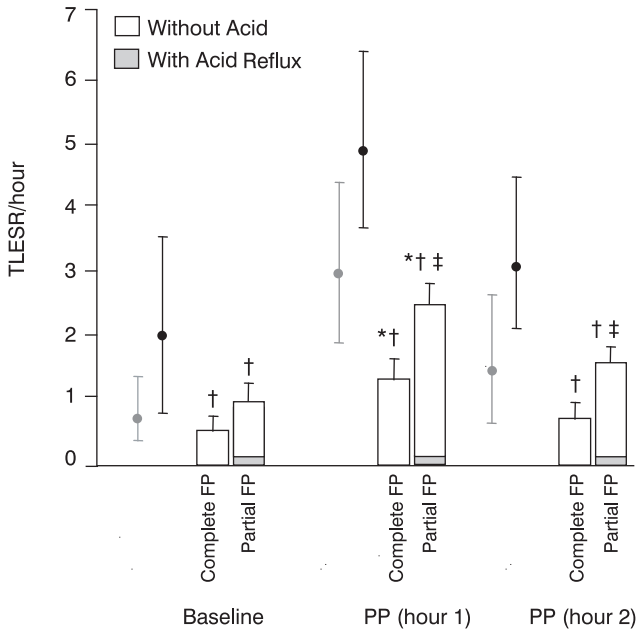

Figure 3

The rate at which TLESRs occurred and the precentage of TLESRs associated with acid reflux during baseline recording and after a meal among patients after either partial and complete fundoplication. The vertical black and grey lines represent the ranges (mean ± 2SD) of the rate of TLESRs and the number of TLESRs associated with acid reflux respectively in 20 normal controls. *$P < 0.05$ baseline *vs* 1st hour postprandially. †$P < 0.01$ *vs* controls. ‡$P < 0.05$ *vs* patients after complete fundoplication.

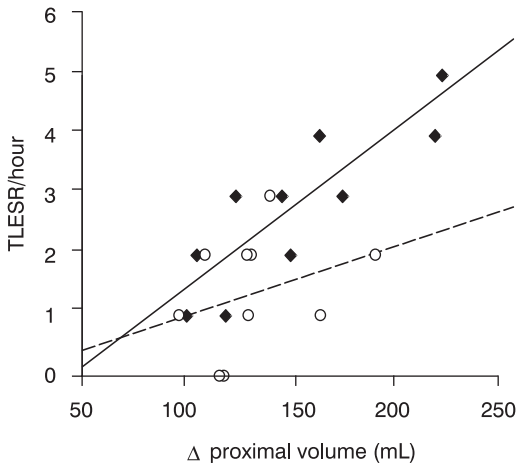

Figure 4

Relation between meal-induced volume increase of the proximal stomach and the number of TLESRs both in 10 patients after partial (♦; r = 0.79; $P < 0.01$) and 10 patients after complete (o; r = 0.33; $P > 0.05$) fundoplication.

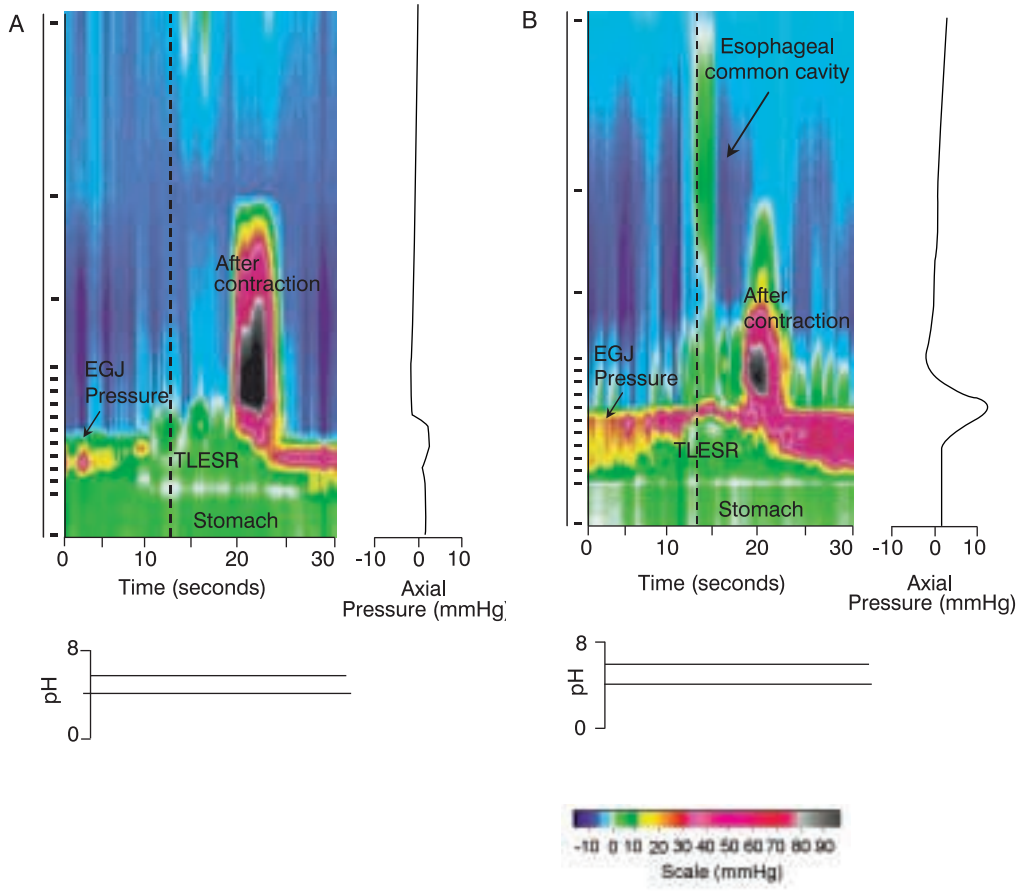

Figure 5

Topographic manometry and pH tracing illustrating an example of a TLESR recorded during baseline period in a patient after partial fundoplication (A) and in a patient after complete fundoplication (B). Position of the catheter with its lumina is presented at left from the manometric color display. The vertical dashed line represents the time the axial pressure is presented. Note that in A, the EGJ relaxation is complete, whereas in B, the cranial part of the EGJ does not complety relax. Both TLESRs were not accompanied by acid reflux.

Table 2
Pre- and postprandial pH-metric parameters.

	Acid Reflux Episodes / hour		
	Baseline	1st hour PP	2nd hour PP
Partial fundoplication	0.4 ± 0.3	0.3 ± 0.2*	0.2 ± 0.1*
Complete fundoplication	0.1 ± 0.1	0.3 ± 0.3*	-
Control subjects	2.0 ± 1.0	4.1 ± 1.2	3.2 ± 1.1

Values are means ± SEM. PP = postprandially. In grey reference values for 20 normal controls are provided. *$P < 0.05$ *vs* controls.

was present after a complete fundoplication. Neither reflux frequency nor the %TLESRs with acid reflux were related to the total gastric volume increase, proximal gastric volume increase or proximal to total gastric volume distribution ratio in any subject group.

EGJ pressure profile during TLESRs

Qualitative and quantitative differences were observed comparing pressure profiles during TLESRs in patients after partial or complete fundoplication. Note that the cranial part of the EGJ does completely relax after a partial

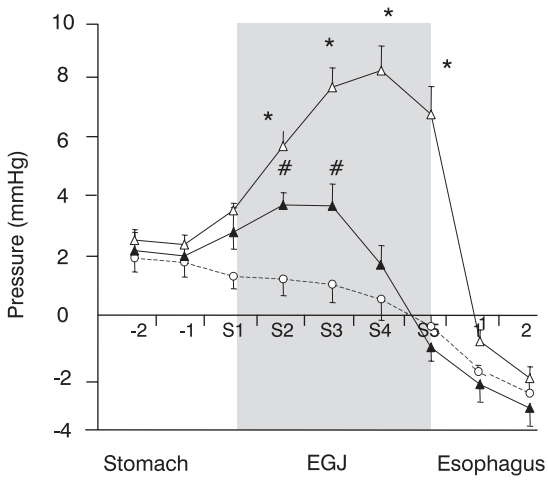

Figure 6
Pressure profile across the EGJ during TLESRs in patients after partial (▲) and after complete fundoplication (Δ). In grey (o) the reference values for 20 healthy volunteers are depicted. Minus 2 and -1 represent the two intragastric sideholes, E1-E5 represent five sideholes at the EGJ, and 1, 2 represent two distal esophageal sideholes. The grey area represents the level of the EGJ. *$P < 0.05$ *vs* partial fundoplication patients. #$P < 0.05$ *vs* controls.

Table 3
Nadir EGJ pressure and pressure gradient across the EGJ (ΔEGJp) during swallowing and during TLESRs in patients after partial and complete fundoplication.

	Nadir EGJ pressure (mmHg)		ΔEGJp (mmHg)	
	Swallows	TLESRs	Swallows	TLESRs
Partial fundoplication	2.3 ± 0.5	1.4 ± 0.4	2.8 ± 0.4	3.8 ± 0.7
Complete fundoplication	5.6 ± 0.7†	4.6 ± 0.8†	3.0 ± 0.7	3.2 ± 0.9
Control subjects	2.1 ± 0.4	1.2 ± 0.2	2.7 ± 0.6	4.1 ± 0.6

Values are means ± SEM. EGJ: esophagogastric junction. † $P < 0.05$ *vs* controls and patients after partial fundoplication.

fundoplication (Figure 5A) whilst after a 360 degrees fundoplication (Figure 5B) EGJ relaxation is incomplete. Evident from Table 3, nadir EGJ pressure both during swallow and TLESR induced EGJ relaxation was lower in patients after partial than after total fundoplication ($P < 0.05$). The axial EGJ pressure profile during a TLESR is illustrated in Figure 6. Note that complete fundoplication patients exhibit a pressure 'barrier' at the cranial side of the EGJ. This 'barrier' is less profound after partial fundoplication. The EGJ pressure gradient across the EGJ (ΔEGJp) during either swallow or TLESR induced EGJ relaxation is not different among subject groups (Table 3).

Discussion

In this study we have examined the differences between the effects of a complete and partial fundoplication on proximal stomach volume, EGJ pressure profile, TLESRs, and acid reflux. The major findings were that partial fundoplication leaves a higher postprandial rate of TLESRs than a complete wrap. Whilst most TLESRs after complete fundoplication were characterized by a higher residual pressure (incomplete relaxation), TLESRs after partial fundoplication were complete. TLESRs after complete fundoplication exhibited an axial EGJ pressure profile with an over-all increase in pressure, whereas this profile

was only minimally affected after a partial procedure. In addition, absolute and relative proximal gastric postprandial volumes were reduced to a greater extent after complete than after partial fundoplication. These data suggest that limited changes in axial EGJ pressure observed at EGJ relaxation, suffice to effectively reduce reflux during TLESR. This is in keeping with clinical studies assessing the efficacy of partial fundoplication. [20]

In the present study, a liquid meal was found to be an effective trigger for TLESRs in both subject groups. Whilst meal-induced TLESR rate increase was about three per hour for controls, the increase in TLESRs was markedly reduced by both antireflux procedures. This observation is in agreement with earlier reports on complete [6-8] and partial [9,21,22] fundoplication that also reported a reduced number of meal or distension induced TLESRs after fundoplication. However, after partial fundoplication we found the meal-induced TLESR rate to be twice as high as that after complete fundoplication. A question raised by these data is why more postprandial TLESRs are seen after a partial procedure. TLESRs are vagally mediated in response to gastric distension. Animal data indicate that the vagal afferent field for eliciting TLESRs is localized within the gastric cardiac region, and that both tension and stretch receptors are involved. [23-26] Meal-induced gastric accommodation is another vagally mediated reflex that results in adaptive relaxation of the proximal stomach. [27-30] The current study shows that, in patients after complete fundoplication, meal-induced proximal gastric volume increase is reduced to a greater extent than in patients after a partial fundic wrap (Figure 2). A reduced proximal gastric volume results in a diminshed cardiac cross-sectional area, which, in turn, results in decreased wall elongation, thereby reducing the activation of stretch (volume) receptors potentially responsible for eliciting TLESRs. A larger postprandial proximal gastric volume, hence, may explain for the higher postprandial TLESR rate found after partial fundoplication. Our data corroborate data recently provided by Penagini et al. [31], suggesting that volume changes, eliciting stretch receptors, play an important role in TLESR eliciation. The circular fixation of the top of gastric cardia around the distal esophagus may further reduce the ability for the fundus to stretch or elongate. After partial fundoplication, this receptive area is more or less in its normal anatomic position and still capable to accommodate to filling of the stomach by a meal. This might explain that TLESRs relate to fundic volume after partial and not after complete fundic wrap.

In the present study, proximal gastric accommodation to a meal was impaired both after partial and complete fundoplication which is in line with previous data [11,12,32]. However, we have found that proximal gastric volume was markedly more reduced after complete than after partial fundoplication (Figure 2). This finding is at variance with recent barostat data [32] demonstating a similar reduction of the gastric accommodation response after a meal in patients with partial and complete fundoplication. Methodological differences may account for the discrepancy. Firstly, in the present study 3D ultrasound (US) imaging was used to assess meal-induced gastric volume changes. This 3D US technique is based on imaging of the gastric wall, hence, measures gastric volume directly in the normal postprandial state. [33] This non-invasive technique allows assessment of the entire stomach and permits partitioning of the proximal stomach, unlike the invasive barostat method, which exclusively assesses the proximal stomach. The barsostat technique, might, erroneously suggest to measure fundic volume whereas due to distal displacement of the barostat bag [32] the bag is in the body of the stomach. Moreover, the barostat as such accellerates gastric emptying. [34] Secondly, in the current study a 270 degrees fundoplication has been studied, whereas Lindeboom et al. (32) assessed patients after a posterior hemi-fundoplication.

Another finding confirmed in the present study was of complete EGJ relaxation during TLESRs following partial fundoplication (Figure 5A) as opposed to incomplete relaxation after complete fundoplication (Figure 5B). Rydberg et al. [22], comparing complete (Nissen) with partial posterior (Toupet) fundoplication, also reported a markedly higher nadir EGJ pressures during TLESRs in the former. In the present study, the comparative figures during swallow induced EGJ relaxation were similar (Table 3). In addition to nadir EGJ pressure, we also recorded point pressure data at 1-cm intervals across the EGJ during TLESRs resulting in an axial EGJ pressure profile. It is evident that the over-all pressure at EGJ level during TLESRs was markedly higher in patients after a 360 degrees than after a 270 degrees fundoplication and that relaxation was incomplete after complete fundoplication (Figure 5). Whilst the caudal part of the EGJ reaches a nadir pressure $\leq$ 2 mmHg, and hence completely relaxes, pressure in the more cranial part remains elevated (Figure 5A and B). In contrast, after partial fundoplication (Belsey Mark IV), the only difference in axial EGJ profile compared to controls was a small pressure increase observed in the more caudal part of the EGJ (Figure 6). Furthermore, the pressure difference across the EGJ (ΔEGJp) during a TLESR, which is the driving force for

gastroesophageal reflux, was not different among subject groups (Table 3). Thus, ΔEGJp did not distinguish partial from complete fundoplication patients and controls. Both partial and complete fundoplication created a manometrical identifiable EGJ pressure barrier during TLESR thereby protecting the esophagus from the gastric content. Ideally, this compromised retrograde flow after operation does not come at the expense of the ability to vent gastric gas from the stomach. The observed axial EGJ pressure pattern during a TLESR provides a potential explanation for the higher frequency of upper abdominal symptoms related to increased amounts of gastro-intestinal gas after complete as compared to partial fundoplication. [22,35]

In summary, patients after partial fundoplication have a larger meal-induced increase in proximal stomach volume, a higher postprandial rate of TLESRs, and a similar pressure gradient across the EGJ during EGJ relaxation as compared to patients after complete fundoplication. The axial EGJ pressure profile after partial fundoplication shows a minimally increased pressure barrier during TLESR which might help to prevent acid reflux at TLESRs.

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Summary

The studies presented in this thesis have reported on the elicitation of transient lower esophageal sphincter relaxations (TLESRs) in health, gastroesophageal reflux disease (GERD) and postfundoplication. The relationship between the esophageal acid exposure time and the underlying manometric motor mechanisms, especially TLESRs, in non-hernia patients with GERD is examined. Also the effect of fundoplication on esophageal motility, bolus transit across the esophagogastric junction (EGJ) and intragastric distribution has been evaluated. The studies give new insights into the origin of postoperative dysphagia, odynophagia and dyspepsia. Furthermore, the role of the proximal stomach and the pressure gradient across the EGJ on acid reflux during TLESRs has been assessed with new technical modalities combining three dimensional (3D) ultrasonographic imaging, high-resolution topographic manometry and pH-metry.

Chapter 1 offers a general introduction describing the current knowledge on the role of the EGJ and gastric physiology in the genesis of reflux disease. Also the known effects of antireflux surgery (fundoplication) on esophageal acid exposure, EGJ motor function, specifically TLESR elicitation, and gastric accommodation are summarized. Furthermore, the incentives for and aims of the research presented in this thesis are outlined.

Chapter 2 compares the effect of graded fundic distension and meal-induced fundic relaxation on the rate of TLESRs in healthy human subjects. In the first part of the study, the effect of intra-fundic pressure increments applied by the barostat on EGJ function, especially the rate of TLESRs, was studied. In the second part of the study, the effect of a meal on fundic relaxation and TLESRs was observed. It was shown that the TLESR rate in healthy subjects is directly related to the degree of proximal gastric distension and that pressure-controlled distension is a more potent trigger of TLESRs than a meal. This observation can be explained by the fact that mechanical distension of the stomach leads to a higher wall tension, resulting in an additional stimulation of the in series 'tension' receptors triggering TLESRs.

In Chapter 3 an experimental technique using simultaneous EGJ manometry and distension by means of a barostat was used to obtain better insight into the effect of persistent mechanical distension applied in the proximal gastric area on TLESR elicitation and gastric accommodation after fundoplication. Also the efficacy of TLESRs in facilitating gastric venting after fundoplication was compared to normal controls and GERD patients. This study showed that fundopli-

cation patients exhibit a diminished rate of TLESRs both at rest and during isobaric gastric distension compared with normal controls and GERD patients. Second, TLESRs in fundoplication patients were characterized by a higher residual pressure and a lower efficacy of facilitating gastric venting than was seen in normal subjects or GERD patients. Finally, gastric accommodation, another vagally mediated reflex, was not impaired with fundoplication. These data indicate that that the vagal afferent field for triggering TLESRs was contained within a wider field than that for elicitation of gastric receptive relaxation and that only the first is affected by fundoplication.

In Chapter 4 it is assessed whether a successful Nissen fundoplication affects esophageal contractile activity on the long-term and, if so, whether altered esophageal motility is related with changes in EGJ dynamics and with postoperative symptoms of dysphagia and odynophagia. We showed that Nissen fundoplication results in a marked increase in peristaltic amplitude in the distal esophagus and that this amplitude is significantly related with the altered EGJ dynamics, especially basal EGJ pressure and nadir EGJ relaxation pressure. This amplitude appears not to increase any further after 3 months. Peristaltic amplitudes in the range of nutcracker esophagus (more than 180 mmHg) were observed in four of 34 patients and three of these reported odynophagia. These findings strongly suggest that the creation of a high-pressure zone at the level of the EGJ affects esophageal body motility and may, in a small proportion of patients, lead to the development of a nutcracker esophagus.

Chapter 5 reports on non-invasive 3D ultrasonographic imaging for the investigation of partial gastric volumes in relation to postoperative dyspeptic symptoms in patients after laparoscopic fundoplication. It was elucidated that patients with dyspeptic symptoms after fundoplication exhibit a markedly increased distal stomach volume after meal ingestion compared with either nondyspeptic fundoplication patients and healthy controls. Whilst meal-induced increase in proximal stomach volume was reduced in fundoplication patients compared with controls, no significant differences between dyspeptic and nondyspeptic fundoplication patients was found. Dyspeptic fundoplication patients had a higher postprandial score for fullness, nausea, and pain than nondyspeptic patients and controls. Interestingly, the increase in distal stomach volume was related to the postcibal epigastric fullness increase. These findings suggest that fundoplication affects proximal stomach accommodation leading to an augmented distal stomach volume, which is associated with the upper gastrointestinal fullness sensation.

In Chapter 6 the relationship between the esophageal acid exposure time, esophageal clearance and the underlying manometric motor mechanisms, especially TLESRs, is examined in non-hernia patients with GERD. Although TLESR has been identified as the most frequent physiological mechanism underlying gastroesophageal reflux, data on the esophageal acid reflux exposure time following a TLESR are lacking. The major finding of this study was that acid reflux following a TLESR is frequent but acid exposure is significantly shorter compared with reflux during a period of absent basal LES pressure, the second most frequent mechanism of reflux in non-hernia patients with GERD. Despite this finding, TLESRs remain, apart from the night time period, the major contributor to not only the number of reflux episodes but also to the esophageal acid exposure time in GERD. During the night, however, whilst TLESRs remain the most frequent cause of acid reflux, reflux during absent basal LES pressure accounts for the majority of the esophageal acid exposure time.

In Chapter 7 a combined high-resolution topographic manometry and videofluorsocopy protocol was used to prospectively assess the effect of a successful laparoscopic fundoplication on EGJ transit efficacy for both liquids and solids. Apart from EGJ transit, the EGJ opening dynamics were examined along with the relationship between transit across the EGJ and symptoms of dysphagia in patients studied before and 3 months after laparoscopic Nissen fundoplication. We showed that the total EGJ transit time for both liquids and solids is markedly prolonged by fundoplication, the degree of which relates to postoperative dysphagia. This reduced EGJ transit efficacy is due to the increased outflow resistance evident from the narrowed and elongated hiatal passage likely due to a reduced EGJ compliance limiting EGJ opening. To overcome this increased outflow resistance a higher intrabolus pressure is generated, built up over the time between arrival of the front of the bolus at the EGJ and the actual opening of the EGJ.

In Chapter 8 a prospective study performed in 20 patients with GERD before and 3 months after fundoplication is presented. This study was conducted to explore the effect of fundoplication on the esophagogastric junction (EGJ) pressure profile and the role of the proximal stomach in acid reflux during TLESRs. We utilized a combination of 3D ultrasonography, topographic manometry, and pH-metry. We showed that even though volume changes in the proximal stom-

ach play a key role in TLESR elicitation, fundic volume alone does not does not explain the excess gastroesophageal reflux in patients with GERD. In contrast, after fundoplication TLESRs may be elicited by mechanisms other than fundic distension. A very important novel finding is that the axial pressure profile across the EGJ plays a pivotal role in the genesis of gastroesophageal acid reflux during a TLESR. This axial EGJ pressure profile is considerably altered by fundoplication resulting in an over-all increase in EGJ pressure, preventing acid reflux during a TLESR.

In Chapter 9 the effect of a partial (Belsey Mark IV) and a complete (Nissen) fundoplication on proximal stomach function, TLESR elicitation and the EGJ pressure profile during a TLESR was evaluated. It was shown that, although both groups were lower than controls, Belsey Mark IV patients exhibited a higher postprandial rate of TLESRs than after Nissen fundoplication. Whilst most TLESRs after complete fundoplication were characterized by a higher residual pressure (incomplete relaxation), TLESRs after partial fundoplication were complete. In addition, TLESRs after complete fundoplication exhibited an axial EGJ pressure profile with an over-all increase in pressure, whereas this profile during TLESRs after partial operation was only minimally affected. In line with TLESR elicitation, absolute and relative proximal gastric postprandial volumes were reduced to a greater extent after a Nissen than after a Belsey Mark IV antireflux procedure. These findings suggest that, minimal changes in axial EGJ pressure observed at EGJ relaxation, may already lead to effective reflux control.

Interpretation and conclusions

In order to optimize antireflux strategies, the genesis of underlying motor mechanisms of gastroesophageal reflux and the physiological sequalae of antireflux surgery (fundoplication) need to be fully elucidated. The studies described in this thesis lead to the following conclusions:

1 The rate of TLESRs relates to the degree of proximal gastric distension. The biomechanical changes during gastric distension with a barostat are a more powerful trigger for TLESRs than the more physiologic meal-induced changes in fundic volume.

2 Laparoscopic fundoplication impairs TLESR elicitation and renders EGJ relaxation incomplete. However, gastric accommodation to mechanical distension is not impaired with fundoplication.

3 Within 3 months after fundoplication the amplitude of esophageal peristalsis increased substantially, leading to a “nutcracker esophagus” and odynophagia in a subgroup of patients. This phenomenon does not appear to progress with time.

4 Fundoplication patients exhibit an attenuated accommodation of the proximal stomach leading to an increased distension of the distal stomach. Augmented distal stomach distension was more pronounced in dyspeptic fundoplication patients and related with the increase in postprandial sensations of fullness.

5 Although esophageal acid exposure following a TLESR is shorter than reflux during absent basal LES pressure, TLESRs remain the major contributor to esophageal acid exposure during the day. At night, however, reflux during absence of basal LES pressure, is the major contributor to acid exposure.

6 Fundoplication patients have a restricted hiatal opening and an incomplete deglutative EGJ relaxation. Consequently, the EGJ transit time is prolonged, the degree of which is directly related to the degree of postoperative dysphagia.

7 Although the volume of the proximal stomach plays a key role in eliciting TLESRs, it does not contribute to the incidence of acid reflux during TLESRs. The axial EGJ pressure gradient plays a crucial role in the occurrence of acid reflux during a TLESR.

8 Patients after partial (Belsey Mark IV) fundoplication exhibit a larger meal-induced increase in proximal stomach volume and a higher TLESR rate than patients after a complete (Nissen) fundoplication. The over-all pressure profile across the EGJ was markedly higher after a complete fundoplication compared to partial fundoplication.

In conclusion

This thesis provides new insights into EGJ physiology, especially on the role of the proximal stomach in TLESR eliciation and on the role of the EGJ pressure gradient on gastroesophageal reflux during a TLESR. In addition, the effect of fundoplication on, esophageal and EGJ motility, intragastric distribution, and EGJ transit efficacy has been further elucidated. It is now apparent that altered intragastric distribution plays a pivotal role in the genesis of postfundoplication dyspepsia. Changes of fundic and EGJ anatomy with fundoplication lead to a different pressure profile across the EGJ thereby preventing esophageal acid reflux during a TLESR and limiting EGJ transit efficacy which as such relates to postoperative dysphagia.

Nederlandse samenvatting

De studies in dit proefschrift beschrijven het ontstaan van 'transient lower oesophageal sfincter relaxations' (TLOSRs) bij gezonde proefpersonen, patiënten met gastro-oesofageale refluxziekte (GORZ) en patiënten na antireflux chirurgie (fundoplicatie). De relatie tussen de blootstelling van het onderste deel van de slokdarm aan zure reflux en de mechanismen die hieraan ten grondslag liggen, in het bijzonder TLOSRs, worden bestudeerd bij patiënten met GORZ. Ook het effect van fundoplicatie op de motoriek van de slokdarm, de passage van een bolus door het sfinctercomplex en de intragastrische volume verdeling worden bestudeerd. De studies geven nieuwe inzichten in het ontstaan van dysfagie, odynofagie en dyspepsie. Eveneens worden de rol van de proximale maag en de drukgradiënt ter hoogte van het sfinctercomplex op het ontstaan van zure reflux tijdens TLOSRs onderzocht met behulp van 3D echografie, topografische manometrie en pH-metrie.

Hoofdstuk 1 vormt de algemene introductie. Hierin wordt de huidige kennis over de rol van het sfinctercomplex en de maag bij het ontstaan van GORZ beschreven. Ook het effect van antireflux chirurgie (fundoplicatie) op de blootstelling van de slokdarm aan zure reflux, op de motoriek van het sfinctercomplex en de accommodatie van de maag worden samengevat. Ook worden de doelstellingen van dit proefschrift gepresenteerd.

In hoofdstuk 2 wordt het effect van mechanische distensie en van de door maaltijd geïnduceerde relaxatie van de fundus op het ontstaan van TLOSRs bij gezonde vrijwilligers beschreven. In het eerste deel van de studie wordt het effect van een door de barostat geïnduceerde druktoename in de fundus op de functie van het sfinctercomplex bestudeerd. In het tweede deel van de studie wordt het effect van adaptieve relaxatie van de proximale maag op het aantal TLOSRs beschreven. Er wordt getoond dat het aantal TLOSRs bij gezonde vrijwilligers is gerelateerd aan de mate van distensie van de proximale maag en dat druk-gecontroleerde distensie een sterkere stimulus is voor TLOSRs dan een maaltijd. Deze bevindingen zijn te verklaren door het feit dat mechanische distensie van de maag leidt tot een hogere wandspanning. Dit resulteert in een extra stimulatie van de in serie geschakelde spanningsreceptoren.

In hoofdstuk 3 wordt gebruik gemaakt van een experimentele techniek waarin manometrie van het sfinctercomplex wordt gecombineerd met distensie van de proximale maag door de barostat. Hiermee wordt inzicht verkregen in het effect

van continue distensie van de proximale maag op het ontstaan van TLOSRs en de accommodatie van de maag na fundoplicatie. Ook de mogelijkheid van TLOSRs om lucht te laten ontsnappen uit de maag na fundoplicatie wordt vergeleken tussen gezonde vrijwilligers en patiënten met GORZ. Deze studie laat zien dat patiënten na fundoplicatie minder TLOSRs hebben in vergelijking met gezonde vrijwilligers en patiënten met GORZ, zowel in rust als tijdens isobare distensie. Ten tweede, TLOSRs na fundoplicatie hebben een hogere rustdruk in vergelijking met gezonde vrijwilligers en patiënten met GORZ en zijn derhalve minder geschikt om lucht te laten ontsnappen uit de maag. Tenslotte, accommodatie van de maag was niet aangedaan door fundoplicatie. Deze gegevens betekenen dat de vagale afferente receptoren voor het 'triggeren' van TLOSRs zich in een groter gebied bevinden dan de receptoren die receptieve relaxatie van de maag bewerkstelligen en dat alleen de eerste is aangetast door fundoplicatie.

In hoofdstuk 4 wordt onderzocht of een succesvolle Nissen fundoplicatie de contractiliteit van de slokdarm beïnvloedt, en indien dit zo is, of de veranderde motoriek is gerelateerd aan de veranderingen van de dynamiek van het sfinctercomplex en aan postoperatieve symptomen zoals dysfagie en odynofagie. Het blijkt dat het aanleggen van een Nissen fundoplicatie resulteert in een aanzienlijke toename van de amplitudo van peristaltische contracties in de distale slokdarm en dat deze amplitudo is gerelateerd aan de veranderingen van de dynamiek van het sfinctercomplex, in het bijzonder aan de sfincter rustdruk en restdruk tijdens relaxatie. De amplitudo blijkt na 3 maanden niet verder toe te nemen. Amplitudo's in de orde van grootte van een notenkraker slokdarm (groter dan 180 mmHg) werden gemeten in vier van de 34 patiënten en drie van hen hadden odynofagie. Deze bevindingen suggereren dat het aanleggen van een hoge drukzone ter hoogte van het sfinctercomplex de motoriek van de slokdarm beïnvloedt en dat dit in een klein deel van de patiënten kan leiden tot de ontwikkeling van een 'notenkraker slokdarm'.

Hoofdstuk 5 handelt over niet-invasieve 3D echografie, toegepast om deel-volumina van de maag te relateren aan postoperatieve dyspeptische symptomen in patiënten na laparoscopische fundoplicatie. Na een maaltijd vertonen patiënten met dyspeptische symptomen na fundoplicatie een groter distaal maagvolume dan patiënten na fundoplicatie zonder dyspeptische klachten en gezonde vrijwilligers. Hoewel maaltijd geïnduceerde toename van

het proximale maagvolume was verminderd bij patiënten na fundoplicatie in vergelijking met gezonde vrijwilligers, werden er geen signficante verschillen tussen dyspeptische en niet-dyspeptische patiënten na fundoplicatie gevonden. Patiënten met dyspepsie na fundoplicatie hadden meer klachten van een vol gevoel, misselijkheid en pijn in epigastrio dan niet-dyspeptische patiënten en gezonde vrijwilligers. Interessant is dat de toename van het distaal maagvolume was gecorreleerd aan de postprandiale toename van het vol gevoel. Deze bevindingen suggereren dat fundoplicatie de accommodatie van de proximale maag beïnvloedt en dat dit een toename van het distale maagvolume tot gevolg heeft. Deze toename blijkt te zijn gerelateerd aan de sensatie van een vol gevoel in epigastrio.

In hoofdstuk 6 wordt, bij patiënten met GORZ zonder hiatus hernia, de relatie ondezocht tussen de duur van blootstelling van de distale slokdarm aan zure reflux, en de onderliggende mechanismen. Ofschoon gastro-oesofageale zure reflux meestal wordt veroorzaakt door een TLOSR, zijn er geen gegevens die de relatie tussen de duur van blootstelling van de slokdarm aan zure reflux en het veroorzakend mechanisme tonen. De belangrijkste bevinding van deze studie is dat zure reflux ten gevolge van een TLOSR vaak optreedt. De duur van blootstelling van de slokdarm aan zure reflux is als gevolg van een TLOSR echter significant korter dan de duur van blootstelling die optreedt als gevolg van een lage sfincter druk, het tweede meest voorkomende mechanisme van gastro-oesofageale reflux bij deze groep patiënten. Ondanks deze bevinding blijft een TLOSR, behalve in de nachtelijke periode, het belangrijkste mechanisme voor zowel de frequentie als de duur van blootstelling van de slokdarm aan zure reflux bij patiënten met GORZ. Echter, gedurende de nacht treden TLOSRs frequent op, maar zorgt reflux ten gevolge van een lage sfincterdruk voor het overgrote deel van de blootstelling van de slokdarm aan zure reflux.

In hoofdstuk 7 wordt gebruik gemaakt van een protocol waarin topografische manometrie wordt gecombineerd met doorlichting met als doel de passage door het sfinctercomplex te bestuderen na een succesvolle laparoscopische fundoplicatie. Zowel voor als 3 maanden na fundoplicatie worden, behalve de sfincter passage, eveneens het openen van de sfincter, en de relatie tussen de passage en dysfagie bestudeerd. Het blijkt dat de sfincterpassagetijd aanmerkelijk is verlengd door fundoplicatie en dat de mate van verlenging correleert met de mate van dysfagie. De vertraging van de passage door het

sfinctercomplex wordt veroorzaakt door een grotere weerstand die ontstaat doordat de doorgang kleiner is en het traject is verlengd waarschijnlijk mede ten gevolg van een verminderde compliance waardoor het openen van de sfincter wordt belemmerd. Om deze grotere weerstand te overwinnen wordt een grotere intrabolusdruk gecreeërd. Deze druk wordt opgebouwd in het tijdinterval vanaf het moment dat de bolus ter hoogte van het sfinctercomplex arriveert tot aan het opengaan van de sfincter.

Hoofdstuk 8 betreft een prospectieve studie die is verricht bij 20 patiënten met GORZ voor en 3 maanden na fundoplicatie. Het doel is om het effect van een fundoplicatie op het drukprofiel ter hoogte van het onderste slokdarmsfincter-complex te onderzoeken. Eveneens wordt de rol van de proximale maag op zure reflux tijdens TLOSRs onderzocht. Er wordt gebruik gemaakt van 3D echografie, topografische manometrie en pH-metrie. Ondanks het feit dat volume veranderingen van de proximale maag een belangrijke rol spelen bij het ontstaan van TLOSRs, blijkt het volume van de fundus de hoge frequentie van reflux bij patiënten met refluxziekte niet te verklaren. Na operatie ontstaan TLOSRs door een ander mechanisme dan door distensie van de fundus. Een zeer relevante bevinding is dat het axiale drukprofiel ter hoogte van het sfincter-complex een belangrijke rol speelt bij het ontstaan van gastro-oesofageale reflux tijdens een TLOSR. Dit drukprofiel is ingrijpend veranderd door fundoplicatie en dit resulteert in een algehele druktoename ter hoogte van de sfincter tijdens een TLOSR. Dit voorkomt het ontstaan van zure reflux tijdens een TLOSR.

In hoofdstuk 9 wordt het effect van een partiële (Belsey Mark IV) en een complete (Nissen) fundoplicatie op de functie van de proximale maag, het ontstaan van TLOSRs en het drukprofiel ter hoogte van het sfinctercomplex tijdens een TLOSR bestudeerd. Patiënten na partiële en complete fundoplicatie tonen minder TLOSRs dan gezonde vrijwilligers. Patiënten na Belsey Mark IV operatie hebben een grotere postprandiale TLOSR frequentie dan patiënten na Nissen fundoplicatie. Terwijl de meeste TLOSRs na een complete fundoplicatie worden gekarakteriseerd door een hogere restdruk (incomplete relaxatie), is de relaxatie van TLOSRs na partiële fundoplicatie compleet. TLOSRs na een complete fundoplicatie vertonen een axiaal drukprofiel met een algehele druk-toename, terwijl dit profiel tijdens een TLOSR na een partiële fundoplicatie slechts minimaal is gewijzigd. Overeenkomstig het ontstaan van TLOSRs,

worden het absoluut en relatief volume van de proximale maag na een maaltijd in grotere mate gereduceerd na een Nissen dan na een Belsey Mark IV antirefluxoperatie. Deze bevindingen suggereren dat geringe veranderingen in het axiale drukprofiel ter hoogte van het sfinctercomplex tijdens relaxatie van de sfincter al voldoende zijn voor effectieve preventie van gastro-oesofageale reflux.

Interpretatie en conclusies

Om antirefluxbehandeling te optimalizeren, is het noodzakelijk om de mechanismen van reflux en de fysiologische gevolgen van een antirefluxoperatie (fundoplicatie) te kennen. De studies in dit proefschrift leiden tot de volgende conclusies:

1 Het aantal TLOSRs bij gezonde vrijwilligers is gerelateerd aan de mate van distensie van de proximale maag. De biomechanische veranderingen tijdens mechanische distensie van de maag door een barostat zijn een sterkere stimulus voor TLOSRs dan de meer fysiologische maaltijd geïnduceerde veranderingen in het volume van de fundus van de maag.

2 Laparoscopische fundoplicatie vermindert het aantal TLOSRs en zorgt ervoor dat de relaxatie van de onderste slokdarmsfincter incompleet wordt. Echter, adaptieve relaxatie van de maag tijdens mechanische distensie is niet verminderd na fundoplicatie.

3 Drie maanden na fundoplicatie neemt de amplitudo van de slokdarmperistaltiek aanzienlijk toe. Dit kan leiden tot een ‘notenkraker slokdarm’ en odynofagie bij een subgroep. Dit fenomeen blijkt niet progressief te zijn.

4 Patiënten na fundoplicatie vertonen een verminderde adaptieve relaxatie van de proximale maag. Het gevolg hiervan is een toename van het distale maagvolume. Deze toename is meer uitgesproken bij patiënten met dyspeptische klachten en is gerelateerd aan de toename van de postprandiale sensatie ‘vol gevoel’.

5 De duur van blootstelling van de slokdarm aan zure reflux na het optreden van een TLOSR is korter dan indien reflux optreedt als gevolg van een lage sfincter druk. Toch blijven TLOSRs de belangrijkste veroorzakers van zure reflux overdag. Echter, ‘s nachts wordt het grootste deel van de duur van blootstelling van de slokdarm aan zure reflux veroorzaakt door een lage sfincterdruk.

6 Patiënten na fundoplicatie kunnen de sfincter nog maar in beperkte mate openen en vertonen een incomplete relaxatie van de onderste slokdarmsfincter. Als gevolg hiervan is de sfincterpassagetijd verlengd en de mate van verlenging correleert met de ernst van de dysfagie na fundoplicatie.

7 Ofschoon het volume van de proximale maag een belangrijke rol speelt bij het ontstaan van TLOSRs, verklaart het de hoge incidentie van zure reflux bij patiënten met GORZ niet. De axiale druk ter hoogte van de sfincter speelt een cruciale rol bij het ontstaan van zure reflux tijdens een TLOSR.

8 Patiënten na partiële (Belsey Mark IV) fundoplicatie tonen een grotere maaltijd geïnduceerde toename van de proximale maag en een groter aantal TLOSRs dan patiënten na een complete (Nissen) fundoplicatie. De druk van het drukprofiel ter hoogte van het sfinctercomplex is aanzienlijk hoger na een complete fundoplicatie dan na een partiële fundoplicatie.

Concluderend

Dit proefschrift biedt nieuwe inzichten in de fysiologie van het onderste slokdarm-sfinctercomplex. Zowel de rol van de proximale maag op het ontstaan van TLOSRs als de rol van de drukgradiënt ter hoogte van het sfinctercomplex op het ontstaan van zure reflux tijdens een TLOSR is verduidelijkt. Ook het effect van fundoplicatie op de motoriek van de slokdarm, de motoriek van het sfinctercomplex, de intragastrische distributie en de sfincterpassage zijn verder in kaart gebracht. Het is nu duidelijk dat een veranderde intragastrische volumeverdeling een belangrijke rol speelt bij het ontstaan van dyspepsie na fundoplicatie en dat een vertraagde passage door het sfinctercomplex kan leiden tot dysfagie na operatie. Veranderingen in de anatomie van de proximale maag en het sfinctercomplex leiden tot een ander drukprofiel ter hoogte van de sfincter en dit voorkomt gastro-oesofageale reflux tijdens een TLOSR.

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Curriculum vitae auctoris

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Bob Scheffer is geboren op 11 februari 1974 in Heerlen. Na het behalen van het Gymnasium-diploma aan het St. Bernardinuscollege in Heerlen, studeerde hij van 1992 tot 1993 geneeskunde aan de Katholieke Universiteit van Leuven. Vanaf 1993 studeerde hij geneeskunde aan de Universiteit Utrecht. Na het laatste studiejaar deed hij onderzoek aan de Universidade de Sâo Paulo (U.S.P.) naar de NAD(P)H oxidoreductase activiteit in de artiewand onder begeleiding van Prof. F.R.M. Laurindo. Na het behalen van het doctoraal examen (december 1997) deed hij van februari tot juli 1998 full-time onderzoek naar het ontstaan van TLORs bij gezonde vrijwilligers onder begeleiding van Prof. Dr. L.M.A. Akkermans. Dit onderzoek werd voortgezet van augustus tot oktober 1998 aan de Northwestern University in Chicago onder begeleiding van Prof. P.J. Kahrilas. Tijdens de daarop volgende co-schappen genoot hij het co-schap gynaecologie en obstetrie in het Monash Medical Center in Melbourne. In november 2000 behaalde hij het artsexamen en vanaf februari 2001 werd hij aangesteld als arts-onderzoeker in het MMC te Amersfoort en het UMC te Utrecht onder begeleiding van Drs. J.R. Vermeijden, Prof. Dr. M. Samsom en Prof. Dr. H.G. Gooszen. Op 1 april 2004 is hij gestart met zijn vooropleiding interne geneeskunde in het St. Antonius ziekenhuis te Nieuwegein (opleider: Dr. H.C.M. Haanen). Vanaf 2007 zal hij zijn opleiding tot gastroenteroloog voortzetten in het UMC te Utrecht (opleider: Prof. Dr. M. Samsom).