Studies on gastroesophageal reflux disease

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Studies on gastroesophageal reflux disease

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(met een samenvatting in het Nederlands)

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Co-promotoren: Dr. A.J. Bredenoord
Dr. M.E. Numans

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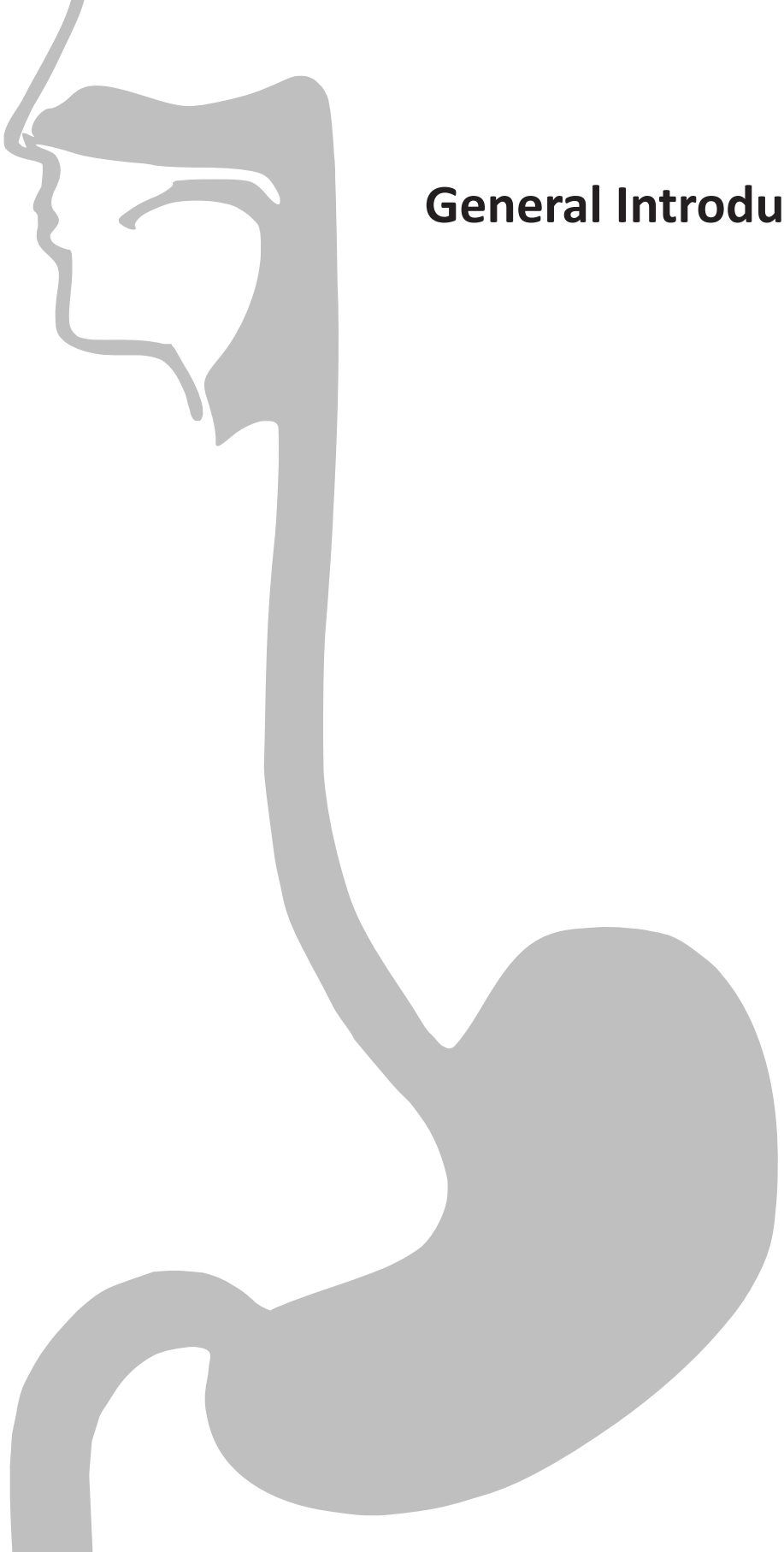


General Introduction

MC Aanen

Definition of gastroesophageal reflux disease

Gastroesophageal reflux is defined as the retrograde flow of gastric contents into the esophagus. On itself, reflux is a physiological phenomenon. However, reflux may become a disease (Gastroesophageal Reflux Disease or GERD) when it is responsible for the occurrence of symptoms sufficiently severe to impair quality of life and/or the development of esophageal mucosal lesions (1;2).

Epidemiology and demographics

GERD is a very common disease, especially in the Western world. At least 10-20% of the general population experience GERD symptoms on a weekly basis (3). Heartburn and regurgitation are typical symptoms of GERD. Atypical symptoms include epigastric pain, dysphagia, coughing, hoarseness, globus sensation, belching and chest pain (1;4). The presence of symptoms can lead to a severe reduction in quality of life to a level that can be compared to patients who have suffered an acute coronary event (5;6). Esophageal lesions are found in up to 15% of the general population, but most of these subjects are asymptomatic (7;8).

No significant association has been found between sex and GERD (3). However, GERD symptoms seem to occur more frequently in women and reflux-associated esophageal lesions, such as erosive esophagitis, Barrett's esophagus and esophageal carcinoma, are found more frequently in men (9). This observation is probably due to differences in consultation frequency between the sexes thereby affecting the healthcare-based morbidity registrations (9;10).

Excess in body mass index (BMI) has been confirmed in longitudinal studies to be associated with both gastroesophageal reflux symptoms and esophagitis (11;12). This could explain the high prevalence of GERD in Western countries (3). GERD is however also becoming more prevalent in Asia, a phenomenon which does not seems completely explained by an overall BMI increase (13;14). Lifestyle modifications which include dietary changes, smoking and postprandial recumbency could explain this phenomenon in these Asian countries (13;15). The standard treatment for GERD is the pharmacological inhibition of gastric acid secretion, in addition to lifestyle adjustments, if appropriate.

The most efficacious drugs are the so-called proton pump inhibitors. The use of a proton pump inhibitor has shown to rapidly improve the quality of life in the majority of patients (16). Secondly, adequate treatment of GERD prevents serious complications (17-19).

Pathophysiology

Gastroesophageal reflux is prevented by the anti-reflux barrier, consisting of an intrinsic and extrinsic sphincter, constituted by the lower esophageal sphincter (LES) and the crural part of the diaphragm respectively (20). Normally these sphincters overlap and act in concert in order reduce the occurrence of gastroesophageal reflux. Any alterations of these anatomic

structures, for example spatial separation that occurs in patients with a hiatal hernia, can cause an increase in gastroesophageal reflux events during episodes with an acute increase of intra-abdominal pressure, e.g. coughing. Reflux can also occur by means of transient lower esophageal sphincter relaxations (TLERS) (21). This brainstem-mediated reflex protects against dilatation of the stomach by enabling ingested air to be ventilated (22).

The pathophysiology underlying the perception of reflux symptoms is complex and incompletely understood. GERD should be considered a multi-factorial disease in which refluxate characteristics, reflux profile, the condition of the esophageal mucosa and visceral sensitivity, which when heightened referred to as esophageal hypersensitivity, all seem to play a role in the perception of GERD symptoms (23-25)

Diagnosing GERD

The multifactorial character of the disease makes GERD a difficult entity to diagnose. As GERD is defined as mucosal lesions and/or symptoms caused by reflux of gastric contents, these two abnormalities are searched for in the clinical work-up of patients suspected for GERD. The role of endoscopy in the process of diagnosing GERD is debatable as it is an expensive tool and the prevalence of endoscopic lesions in GERD patients is low and a negative endoscopy does not exclude GERD (26). However, if acid-induced lesions in the esophagus are found, this provides absolute proof of GERD and such a strong positive test result is often much more difficult to obtain with other GERD screening methods (27).

When upper endoscopy reveals no abnormalities it is essential to determine whether a causative relationship exists between gastroesophageal reflux episodes and reflux symptoms. This is performed with 24-hour reflux monitoring, in which the patient indicates the onset of each symptom that is perceived. In order to test whether symptoms and reflux episodes are related, symptom association analysis is performed. This can be done using several different indices (28).The most frequently used indices are the symptom association probability (SAP), the symptom index (SI) and the symptom sensitivity index (SSI) (29-31). The SI represents the percentage of the number of reflux events associated with symptoms and the SSI the percentage of the number of symptoms associated with reflux episodes. Both the SI and SSI have disadvantages: the former does not take the total number of reflux events into account while the latter does not include the total number of symptom episodes in the equation. The SAP however, does take both parameters into account as the index expresses the statistical relationship between the occurrence of symptoms and reflux episodes using the Fisher exact test. The disadvantage of the SAP is that it is complex and difficult to calculate manually (28). Measuring patients in an ambulatory setting is preferable as patients are investigated in their own environment thereby simulating a normal day routine as in which they normally experience their symptoms.

The most commonly used method to detect reflux as well as symptoms is with a 24-hour esophageal pH recording (32). However, the detection by pH recording is limited as only acid

reflux events are measured (33). Impedance monitoring can detect both oral and aboral bolus movement in the esophagus through multiple intraluminal electrodes that measure changes in resistance to alternating electrical current (34-36). Impedance measuring is very sensitive for detection of small volumes while it also distinguishes liquid and gaseous reflux. Combined impedance and pH monitoring provides information about the acidity as well as the liquid and gas components of reflux events (33).

The recording techniques described above are predominantly used in secondary care, as they are far too invasive, laborious and expensive for primary care practice. Furthermore, as the vast majority of patients reacts satisfactorily to a proton pump inhibitor, most patients with reflux symptoms are managed in primary care and remain there. Besides a patients' general reflux history, often the response to a short course of an acid suppressant, the so-called proton pump inhibitor (PPI) test, is used (37). A positive response, i.e. a reduction in symptoms, is used as evidence for the presence of GERD. The diagnostic test characteristics of the PPI test are however under discussion, the relationship between reflux events and symptoms cannot be established by this test and in case a diagnostic uncertainty arises, the options of the general practitioner are limited.

In this thesis several issues related to the methods for diagnosing GERD were addressed. Firstly, various ways of detecting reflux in esophageal pH and pressure recordings will be investigated. Subsequently, the reproducibility of pH recording-based reflux-symptom association analysis will be studied. Thirdly, the diagnostic value of some of the screening tests that are used in primary care practice will be investigated.

In addition, one study was conducted that aimed to assess the role of dietary sodium intake in the pathogenesis of GERD

The following questions will be addressed in this thesis:

1. The common cavity phenomenon, as observed manometrically, has been used in several studies as indicator of gastroesophageal reflux. In these studies a common cavity associated with a fall in pH was interpreted as liquid reflux while a common cavity without a pH change was considered to represent gaseous reflux. With the advent of esophageal impedance recording it has become possible to study common cavities and their relationship to all types of reflux events. The question to be addressed in this thesis is: how reliable is the manometric common cavity phenomenon as an indicator of gastroesophageal reflux events?

2. Esophageal pH recording has been in use for several decades and, after endoscopy, it is still the most frequently used tool for the detection of GERD. However, with the new gold standard of combined pH-impedance monitoring, the question should be posed whether pH recording alone can still be regarded as sufficiently reliable to diagnose GERD clinically.

3. Symptom association probability indices are important for diagnosing GERD. Clinically it is essential to know whether in repeated measurements under similar circumstances the same result will be obtained. Thus, it was felt that the reproducibility of the symptom association analysis indices required investigation.

4. More and more evidence is accumulating that GERD is a multi-factorial disease. Patients can be divided in 4 groups according to the presence or absence of pathological reflux and a positive or negative reflux-symptom association outcome. The symptomatic response to treatment with a PPI might differ between these 4 groups. We wished to address the question which groups benefit the most from PPI treatment.

5. The PPI test is often used in primary care and its diagnostic accuracy has been investigated in several studies. However, the diagnostic value of the PPI test was never assessed with the use of the SAP as reference test. The specific question that we wished to address was whether the PPI test has additional value when used in conjunction with a reflux history.

6. Most GERD patients are diagnosed and treated in primary care. However, general practitioners do not have easy access to reliable diagnostic tests for GERD. Therefore, a reflux-specific questionnaire might be useful, if it would increase diagnostic accuracy and reduce inter-observer variability. Additionally a suitable questionnaire could be used to quantify the therapeutic response. The Reflux Disease Questionnaire (RDQ) was designed especially for primary care practice. The question addressed in this thesis was whether the RDQ could be a useful diagnostic tool for the diagnosis of GERD in general practice.

7. In developing countries GERD is becoming more and more prevalent, which might be explained by lifestyle modifications. Several investigations, including epidemiological, twin and physiological studies, have suggested that an increased dietary salt intake is associated with GERD symptoms. In a double-blind, placebo-controlled, cross-over study we addressed the question whether a direct causal relationship exists between an increased salt intake and gastroesophageal reflux events.

REFERENCES

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

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

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

(4) Klauser AG, Schindlbeck NE, Muller-Lissner SA. Symptoms in gastro-oesophageal reflux disease. Lancet 1990; 335(8683):205-208.

(5) Irvine EJ. Quality of life assessment in gastro-oesophageal reflux disease. Gut 2004; 53 Suppl 4:35-39.

(6) Kulig M, Leodolter A, Vieth M, Schulte E, Jaspersen D, Labenz J et al. Quality of life in relation to symptoms in patients with gastro-oesophageal reflux disease-- an analysis based on the ProGERD initiative. Aliment Pharmacol Ther 2003; 18(8):767-776.

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

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

(9) van Kerkhoven LA, van Rijswijck SJ, van Rossum LG, Laheij RJ, Witteman EM, Tan AC et al. Open-access upper gastrointestinal endoscopy a decade after the introduction of proton pump inhibitors and helicobacter pylori eradication: a shift in endoscopic findings. Digestion 2007; 75(4):227-231.

(10) van der Linden MW, Westert GP, de Bakker DH, Schellevis FG. Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk. Klachten en aandoeningen in de bevolking en in de huisartspraktijk. Utrecht/Bilthoven: NIVEL/RIVM, 2004.

(11) Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. JAMA 2003; 290(1):66-72.

(12) Ruhl CE, Everhart JE. Overweight, but not high dietary fat intake, increases risk of gastroesophageal reflux disease hospitalization: the NHANES I Epidemiologic Followup Study. First National Health and Nutrition Examination Survey. Ann Epidemiol 1999; 9(7):424-435.

(13) Goh KL. Changing epidemiology of gastroesophageal reflux disease in the Asian-Pacific region: an overview. J Gastroenterol Hepatol 2004; 19 Suppl 3:S22-S25.

(14) Tee ES. Obesity in Asia: prevalence and issues in assessment methodologies. Asia Pac J Clin Nutr 2002; 11 Suppl 8:S694-S701.

(15) DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol 2005; 100(1):190-200.

(16) van Pinxteren B, Numans ME, Lau J, de Wit NJ, Hungin AP, Bonis PA. Short-term treatment of gastroesophageal reflux disease. J Gen Intern Med 2003; 18(9):755-763.

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

(18) Martinez S, Malagon I, Garewal H, Fass R. Non-erosive reflux disease (NERD) - is it really just a mild form of gastroesophageal reflux disease? Gastroenterology 2001; 120 (5 suppl):A424.

(19) Pace F, Bollani S, Molteni P, Bianchi PG. Natural history of gastro-oesophageal reflux disease without oesophagitis (NERD)--a reappraisal 10 years on. Dig Liver Dis 2004; 36(2):111-115.

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

(21) Bredenoord AJ, Weusten BL, Timmer R, Smout AJ. Air swallowing, belching, and reflux in patients with gastroesophageal reflux disease. Am J Gastroenterol 2006; 101(8):1721-1726.

(22) McNally E, Kelly E, Ingelflinger F. Mechanism of belching:effects of gastric distension with air. Gastroenterology 1964; 46:254-259.

(23) Barlow WJ, Orlando RC. The pathogenesis of heartburn in nonerosive reflux disease: a unifying hypothesis. Gastroenterology 2005; 128(3):771-778.

(24) Karamanolis G, Sifrim D. Developments in pathogenesis and diagnosis of gastroesophageal reflux disease. Curr Opin Gastroenterol 2007; 23(4):428-433.

(25) Boeckxstaens GE. Review article: the pathophysiology of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2007; 26(2):149-160.

(26) Vakil N. Endoscopy in GERD: Boondoggle, Diagnostic Test, or Risk Management Tool? Am J Gastroenterol 2008; 103(2):276-278.

(27) Pace F, Manes G, Conio M, Bianchi PG. Pretreatment endoscopy--pro & contra: endoscopy is needed before treatment in all patients with gastroesophageal reflux disease. Endoscopy 2006; 38(3):271-275.

(28) Bredenoord AJ, Weusten BL, Smout AJ. Symptom association analysis in ambulatory gastro-oesophageal reflux monitoring. Gut 2005; 54(12):1810-1817.

(29) Breumelhof R, Smout AJ. The symptom sensitivity index: a valuable additional parameter in 24-hour esophageal pH recording. Am J Gastroenterol 1991; 86(2):160-164.

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

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

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

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

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

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

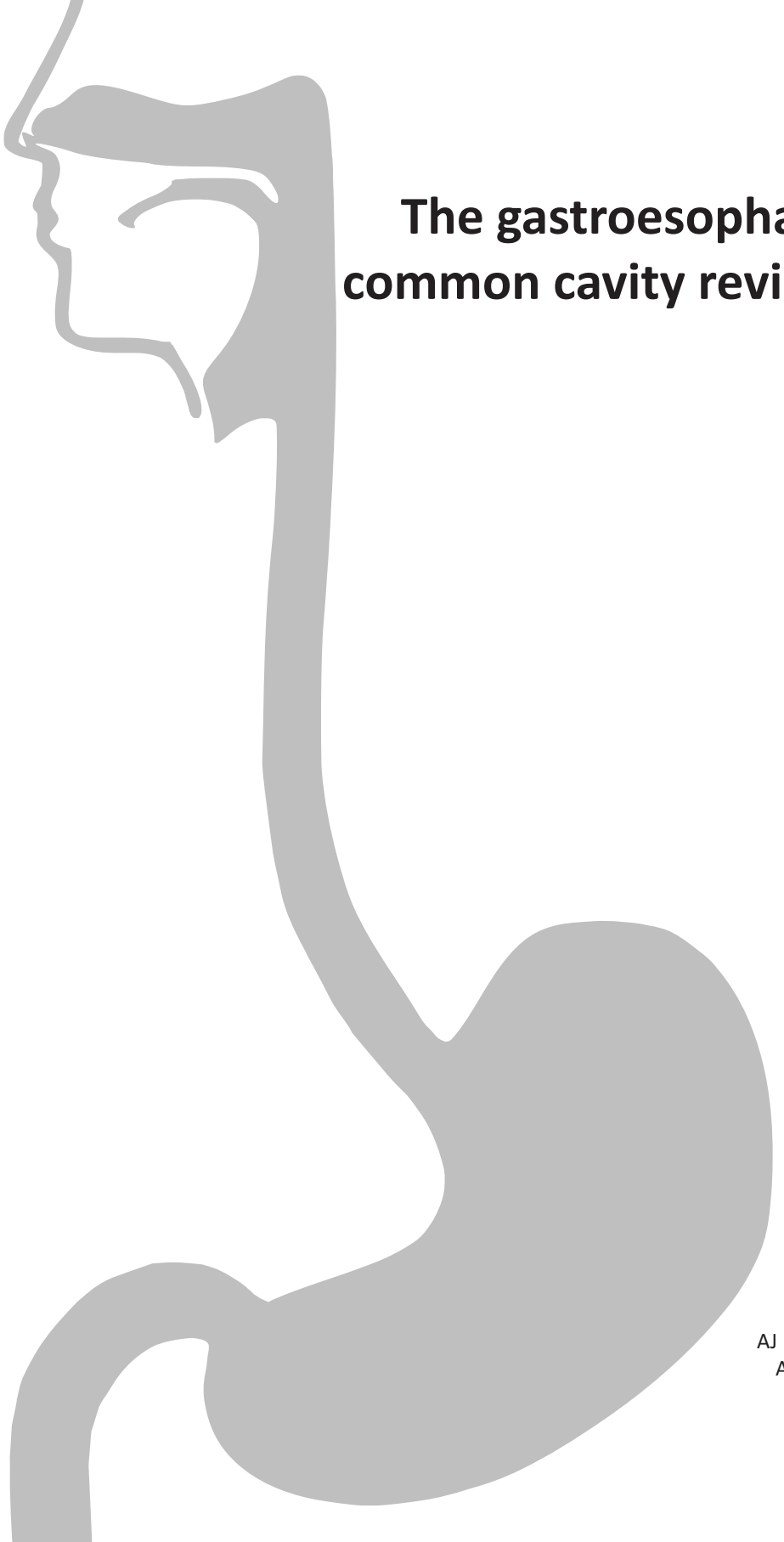
(36) Silny J, Knigge K, Fass J, Rau G, Matern S, Schumpelick V. Verification of the intraluminal multiple electrical impedance measurement for the recording of gastrointestinal motility. J Gastrointest mot 1993; 5:107-122.

(37) Numans ME, Lau J, de Wit NJ, Bonis PA. Short-term treatment with proton-pump inhibitors as a test for gastroesophageal reflux disease: a meta-analysis of diagnostic test characteristics. Ann Intern Med 2004; 140(7):518-527.

Chapter 1

*"And what is the greatest number? Number **one**."*
~ David Hume, Scottish Philosopher and Historian

Scandinavian Journal of Gastroenterology 2006



The gastroesophageal common cavity revisited

MC Aanen
AJ Bredenoord
AJPM Smout

ABSTRACT

Background

The manometric common cavity phenomenon has been used as indicator of gastro-esophageal reflux of liquid or gaseous substances.

Methods

Using combined pH and impedance recording as reference standard the value of a common cavity as indicator of gastroesophageal reflux was tested. Ten healthy male subjects underwent combined stationary pressure, pH and impedance recording for 4.5 h. After 1.15 h of recording, a reflux-eliciting meal was consumed. The chi-squared and Kolmogorov–Smirnov tests were used for the statistical analysis.

Results

A common cavity was found in 95 (43%) of the 223 reflux events detected by impedance, while seven common cavities were unrelated to a reflux episode. In 54% of the reflux events detected by impedance without a common cavity, a possible common cavity was obscured by either contractile activity or artefacts of various origin. The types of reflux associated with a common cavity (liquid 60%, mixed 31%, gas 9%) and without a common cavity (liquid 59%, mixed 29%, gas 12%) did not differ, nor did the acidity of the reflux episodes (with common cavity: acid 67%; without common cavity: acid 58%).

Conclusion

The common cavity is a specific but not a sensitive marker of gastroesophageal reflux. Furthermore, common cavities are not specific for a particular type of reflux.

INTRODUCTION

During relaxation of the lower esophageal sphincter (LES) a connection is formed between the esophagus in the thoracic cavity and the stomach in the abdominal cavity (1). This phenomenon can be observed manometrically as a simultaneous intra-esophageal pressure rise to gastric pressure level and this is referred to as the common cavity phenomenon (1-3). The first description of this phenomenon was reported by McNally et al. in 1964 (3).

They observed that when air escaped from an inflated stomach, equalization of gastric and esophageal pressures occurred. In many subsequent studies the common cavity phenomenon has been used to detect gaseous reflux or belching (3-11). However, others observed that reflux of liquid material was also able to create a common cavity, as most acidic reflux episodes were found to be associated with this phenomenon (1;2;12-15). As a consequence, common cavities associated with a fall in esophageal pH were interpreted as acidic liquid reflux and common cavities without pH change as gaseous reflux (11;12;15).

Recently, the use of intraluminal impedance monitoring has made clear that a low pH does not always imply the presence of liquid reflux while non-acid reflux can also contain liquids. As impedance monitoring can detect both gas and fluid transport in oral and aboral direction it is, in combination with pH recording, the most optimal method for assessing the type and acidity of reflux events (15). Therefore, the aim of this study was to test the value of reflux detection by means of common cavity analysis, using combined impedance and pH recording as reference.

METHODS

Patients

In this study, 10 healthy male volunteers [age 28 ± 3 years and body mass index (BMI) mean 22 ± 0.7 kg/m2] underwent combined stationary manometry, pH and impedance recording for 4.5 h. All volunteers were free of gastrointestinal symptoms and did not take any medication. Two days before recording all volunteers refrained from smoking and alcohol use. Informed written consent was obtained before the start of the study and the protocol was approved by the Medical Ethics Committee of the University Medical Center, Utrecht.

Study Protocol

After an overnight fast, a manometry catheter (described below) was inserted through the nose. After positioning of the manometry catheter, the impedance and the pH catheter were transnasally introduced and positioned according to the manometric pressure profile (see below). All subjects were in an upright position during the recording period and were asked to minimize movements. After 1 h and 15 min of continuous recording, a reflux-eliciting meal was consumed consisting of a hamburger (McDonald's Quarter Pounder), 20 g of fresh onions, 44 g of chips and 475 mL of orange juice (in total 967 kcal). The meal had to be finished within 15 min. A postprandial recording period of 3 h completed the protocol.

Manometry and pH monitoring

For manometry a water-perfused 10-channel silicone rubber assembly with inner diameter of 0.4 mm and outer diameter of 4 mm with a 6 cm long reversed-perfused sleeve sensor (DentSleeve International Ltd, Mississauga, ON, Canada) was used. The manometric catheter was positioned such that the sleeve sensor straddled the LES. Four pharyngeal side-holes (at 24, 26, 28 and 30 cm proximal to the upper border of the sleeve), three esophageal body side-holes (at 4, 9 and 14 cm proximal to the upper border of the sleeve) and a gastric side-hole (2 cm distal from the sleeve) were used to record pressures. The sleeve sensor, gastric and

esophageal side-holes were perfused at a rate of 0.2 mL/min with degassed water, using hydraulic flow restrictors (DentSleeve International Ltd).The pharyngeal side-holes were perfused with air at a rate of 0.8 mL/min. The side-hole that registered the pharyngeal contraction best was selected while the other pharyngeal side-holes were not perfused in order to prevent mechanically stimulated transient LES relaxations (TLESRs) (16).

Pressures were recorded with external pressure transducers (Abbott, Sligo, Ireland). Intraluminal pH monitoring was performed with a glass pH catheter (Ingold AG, Urdorf, Switzerland) that was positioned 5 cm above the manometrically defined upper border of the LES. The pH data were stored together with the manometric data in digital format in two 12-channel data loggers (MMS, Enschede, the Netherlands), using a sample frequency of 8 Hz. At the end of the study all data were transferred to the harddisc of the computer.

Impedance monitoring

For impedance monitoring a 7-channel impedance catheter (outer diameter 2.3 mm) was used (Aachen University of Technology, FEMU, Aachen, Germany). The seven recording segments formed by pairs of ring electrodes at 2-cm intervals were located at 0–2, 2–4, 4–6, 8–10, 10–12, 14–16 and 17–19 cm above the upper border of the manometrically located LES. Impedance signals were stored in a digital system (Aachen University of Technology) using a sampling frequency of 50 Hz (17).

Data analysis

The period of meal consumption was excluded from the analysis. Comparisons were made between impedance- and pH-detected reflux episodes coinciding with a manometric common cavity and those without a manometric common cavity. In the impedance signals, reflux episodes were identified and classified as either liquid, mixed or gaseous reflux based on previously described criteria (15). Furthermore, using the pH tracings, the reflux events were classified as either acidic (pH <4) or weakly acidic (pH 4–7), weakly alkaline (pH >7) or superimposed reflux (15).

A common cavity was defined as a rise in esophageal body pressure to gastric pressure that occurred within 1 s and that was maintained for at least 0.5 s in at least two of the three esophageal body pressure tracings (see Figure 1) (11;13). To determine why some common cavities are seen only in distal and others only in proximal pressure tracings, the proximal and distal visible common cavities were compared. A proximal common cavity was defined as a pressure rise that was seen in all esophageal pressure channels or in the two most proximal esophageal channels. A distal common cavity was defined as one in which the pressure rise was visible in the distal two pressure channels.

Artefacts caused by body movement, coughing or straining were defined as a simultaneous pressure increase or decrease in all tracings. The liquid volume clearance time was defined as the time interval between a drop of ≥50% of baseline impedance and the return to a value above this point. Acidic clearance time was defined as the time when the pH was below 4 during a reflux episode. The duration of a common cavity was measured from maximum distal esophageal pressure rise until drop of pressure or until a secondary peristaltic wave.

Statistics

The chi-squared and Kolmogorov–Smirnov tests were used to determine statistical differences between variables. Differences were considered statistically significant when $p < 0.05$. The data are presented as median (interquartile range).

RESULTS

All 10 healthy volunteers completed the protocol and a total of 223 reflux episodes were detected with combined impedance-pH monitoring. In the manometry recordings 102 common cavity events were found. Ninety-five of the 223 reflux episodes identified on impedance-pH monitoring (43%) were accompanied by a common cavity. In 54% of the 128 reflux events without a common cavity the events were obscured by the co-occurrence of swallow-induced peristalsis, non-swallow-induced peristalsis or artefacts. The 46% remaining reflux events without a common cavity the pressure signal was well interpretable but these events did not meet the criteria for a common cavity. The seven common cavity events that were not detected by combined impedance-pH monitoring were not analyzed further.

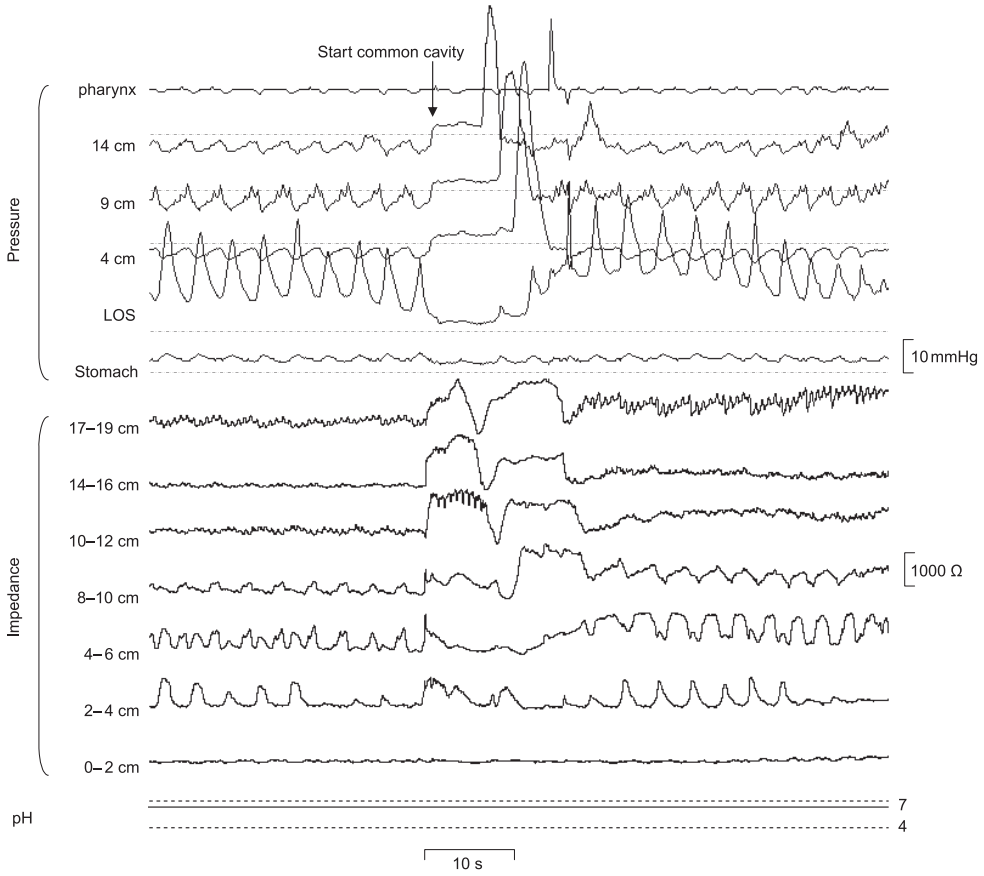


Figure 1. An example of a common cavity phenomenon characterized by a sudden and sustained rise in esophageal pressure to gastric pressure in all three esophageal pressure channels. In this example the common cavity phenomenon is associated with a transient lower esophageal sphincter relaxation and gas reflux, as indicated by a sudden rise in impedance that propagates to the most proximal impedance channel.

Sixty-four percent (61 of 95) of all reflux episodes with a common cavity was associated with a pH drop below 4. Three of the nine gas reflux episodes identified by a common cavity coincided with a pH drop below 4 and 17 of the 57 liquid reflux events were weakly acidic. The type and acidity of the reflux episodes detected by a common cavity did not differ from those detected by impedance monitoring (see Figure 2a). Most common cavity reflux episodes coincided with acidic liquid reflux ($p < 0.01$, see Figure 2b). Weakly alkaline and superimposed reflux events were rare [both 1.8% (4 of 223)] and occurred during both reflux with and without a common cavity phenomenon.

The proximal extent of gaseous and liquid reflux events with and without a common cavity was similar as were the nadir pH, acid and volume clearance times see Table 1). Most (85% = 81 of 95) common cavities were visible in the proximal esophageal pressure tracing. The proximal extent of liquid and gaseous reflux events was not significantly different for proximal or distal common cavities (see Figure 3). Comparable acid [proximal 16 (7–49), distal 29 (6–76)] and volume clearance time [proximal 16.0 (12.0–22.0), distal 18.5 (14.5–24.8)] were found for proximal and distal common cavities. The median duration of a common cavity was 6 s (4–8). The duration of proximal [6.0 (4.0–8.0)] and distal common cavities [6.0 (4.0–9.5)] were similar.

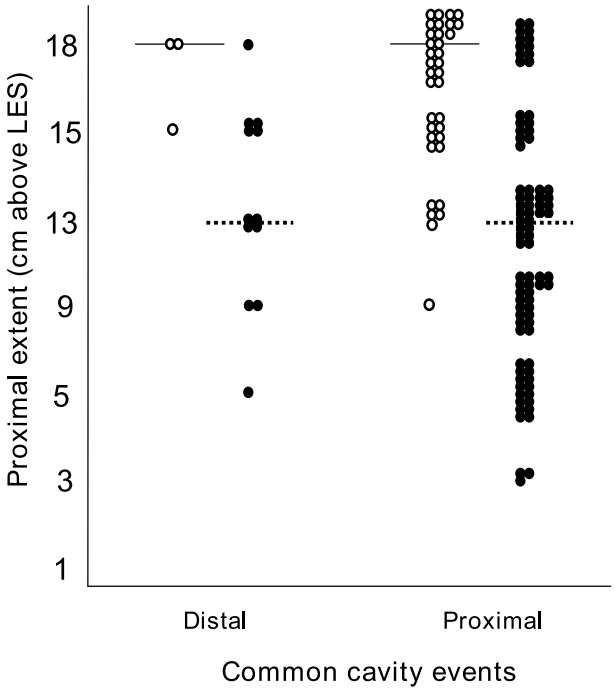


Figure 3. The proximal extent of gas (grey dots) and liquid (black dots) reflux events did not differ between proximal and distal common cavities. The horizontal lines represent the group median.

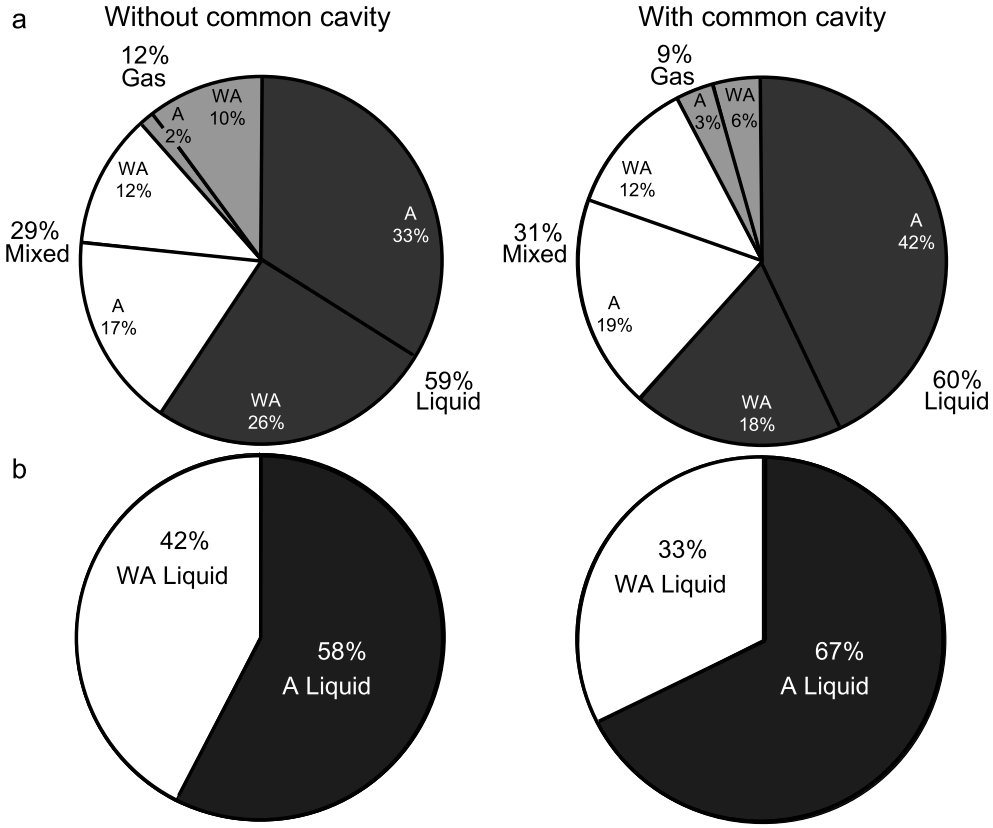


Figure 2. Distribution of subtypes of reflux episodes, classified according to physical [(**a**) liquid, gas and mixed; (**b**) liquid containing] and chemical [acid (A), weakly acidic (WA)]characteristics of the refluxate, with and without associated common cavity.

	Without common cavity		With common cavity	
	n	**Median (25–75th)**	**n**	**Median (25–75th)**
Gas extent (cm)	52	18 (18–18)	38	18 (18–15)
Liquid extent (cm)	113	9 (5–15)	86	13 (9–15)
Volume clearance (s)	113	15 (11–22)	86	16 (13–22.3)
pH begin	113	6.0 (5.4–6.7)	86	6.2 (5.8–6.6)
pH nadir	68	2.7 (1.9–3.2)	69	2.7 (2.0–3.7)
Acid clearance (s)	65	13 (6–124)	59	16 (6–56)

Table 1. Characteristics of reflux events with and without a manometric common cavity

DISCUSSION

Since the 1960s, the manometric common cavity phenomenon has been regarded as indicative of the presence of gastroesophageal reflux, but its true value as a reflux indicator could not be assessed, due to the absence of a gold standard. Nowadays combined intraluminal impedance and pH recording is considered the most optimal way to study reflux and this technique was therefore used as reference standard to determine the value of the manometric common cavity phenomenon as a gastroesophageal reflux indicator (15).

We found that common cavities represented 43% of all reflux episodes detected with the combination impedance and pH, indicating a low sensitivity. Nevertheless, a high specificity was found as most common cavity phenomena (93%) coincided with reflux events observed by combined impedance-pH recordings. Half of the reflux episodes without a common cavity phenomenon did not meet the criteria. Interpretation of the manometric tracings of the other half of the reflux events without a common cavity was complicated by pressure increasing events (swallow-induced peristalsis, secondary peristalsis, spontaneous contractions or artefacts). This finding underlines the advantage of reflux detection by impedance monitoring. Impedance tracings are less affected by events that increase intra-esophageal pressure.

Previous studies have confirmed the fact that manometry performs less well than impedance and pH monitoring (18;19). However, in these studies only 23– 31% of the reflux events detected with pH and impedance were missed with the common cavity phenomenon compared with the 57% found in this study. The discordance with our study could be due to the fact that in both studies the volunteers were in recumbent position during the recording. In a recumbent position, gravity prolongs the presence of refluxate in the esophagus. Manometrically, this results in a higher proportion of reflux episodes coinciding with a common cavity pressure pattern (20). Furthermore, the study by Shay and Richter (18) included gastroesophageal reflux disease (GERD) patients who presumably could have greater refluxate volumes than healthy volunteers, facilitating the occurrence of a common cavity (18;20;21).

As it is not possible to detect gaseous reflux with pH monitoring, common cavities have been used as indicator for this type of reflux (3-11). We, however, found in our study that common cavities can be caused by pure liquid, pure gaseous and mixed gas–liquid reflux, and thus do not exclusively result from gaseous reflux. Most common cavities were associated with acidic liquid reflux, which is the most common reflux type in healthy volunteers (22). It seems that the reflux episodes visible as a common cavity reflect all reflux types that can be found with impedance monitoring. Furthermore, our findings disprove the assumption that a common cavity associated with a pH drop represents liquid reflux. Thirty-three percent of the gaseous reflux events presenting as a common cavity had a pH below 4 while 30% of the liquid reflux episodes with a common cavity phenomenon was weakly acidic. Gaseous reflux without identifiable liquid component but with a pH drop below 4 has been described before as “acid vapour” (21).

For the detection of reflux both impedance monitoring and manometry are depended on the volume of the refluxate, in contrast to pH recording. It has been shown that impedance can detect volumes as small as 1 mL, while probably more volume is required to raise the intra-esophageal pressure to intra-gastric level (23). The exact quantity needed is unknown and whether or not this reflux volume leads to a distension of the esophagus remains to be investigated (19;24;25). We, however, did not find any difference between the volume clearance time for the episodes with and without a common cavity, or did the volume clearance time differ between reflux episodes with proximal or distal common cavities, indirectly suggesting that the volume of reflux episodes with and without common cavities may have been similar.

Furthermore, no differences were found between the proximal extent of liquid or gaseous reflux between reflux events with and without a common cavity which suggest that these reflux characteristics are of no influence on the presence of a common cavity phenomenon. In addition, the visibility of a common cavity phenomenon was not depended on the proximal extent of the refluxate or on the duration of a common cavity.

In this study, a manometric common cavity phenomenon was considered to represent equalization of gastric and esophageal pressure during opening of the LES and to be associated with flux of gas, liquid or both from the stomach to the esophagus (2). However, in a recent pH impedance and ultrasound combined study it was suggested that a common cavity wave was not due to movement of gastric contents into esophagus but the effect of esophageal longitudinal muscle contractions (19). These conclusions were based on the observation that the time of onset of reflux as detected by impedance was not consistently associated with common cavity pressure wave. We believe, however that the authors may have used a too short time interval (0.1 s) to be able to link a common cavity pressure rise with reflux entry in the esophagus. The potential error that results from the use of three separate catheters for recording three different physical entities (pH, pressure and impedance) with their different velocities, presumably sampled at different frequencies (unmentioned for both pH and manometry may have been bigger than the selected time interval. The authors' conclusion that a simultaneous manometric common cavity pressure rise is unlikely to be due to retrograde traveling gastroesophageal reflux as seen with impedance may therefore be incorrect.

In conclusion, the manometric common cavity phenomenon represents a specific but insensitive indicator of gastroesophageal reflux. Common cavities frequently coincide with acid liquid reflux events and they are thus not exclusively representative for gaseous reflux.

REFERENCES

(1) Butterfield DG, Struthers JE, Jr., Showalter JP. A test of gastroesophageal sphincter competence. The common cavity test. Am J Dig Dis 1972; 17(5):415-421.

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

(3) McNally E, Kelly E, Ingelflinger F. Mechanism of belching:effects of gastric distension with air. Gastroenterology 1964; 46:254-259.

(4) Holloway RH, Wyman JB, Dent J. Failure of transient lower oesophageal sphincter relaxation in response to gastric distension in patients with achalasia: evidence for neural mediation of transient lower oesophageal sphincter relaxations. Gut 1989; 30(6):762-767.

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

(6) Lang IM, Medda BK, Shaker R. Mechanisms of reflexes induced by esophageal distension. Am J Physiol Gastrointest Liver Physiol 2001; 281(5):G1246-G1263.

(7) Shaker R, Ren J, Kern M, Dodds WJ, Hogan WJ, Li Q. Mechanisms of airway protection and upper esophageal sphincter opening during belching. Am J Physiol 1992; 262(4 Pt 1):G621-G628.

(8) Straathof JW, Ringers J, Lamers CB, Masclee AA. Provocation of transient lower esophageal sphincter relaxations by gastric distension with air. Am J Gastroenterol 2001; 96(8):2317-2323.

(9) Tew S, Ackroyd R, Jamieson GG, Holloway RH. Belching and bloating: facts and fantasy after antireflux surgery. Br J Surg 2000; 87(4):477-481.

(10) Wyman JB, Dent J, Heddle R, Dodds WJ, Toouli J, Lewis I. Belching: a clue to understanding of pathological gastroesophageal reflux? Gastroenterology 1984; 86:1303.

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

(12) Barham CP, Gotley DC, Mills A, Alderson D. Precipitating causes of acid reflux episodes in ambulant patients with gastro-oesophageal reflux disease. Gut 1995; 36(4):505-510.

(13) Martin CJ, Patrikios J, Dent J. Abolition of gas reflux and transient lower esophageal sphincter relaxation by vagal blockade in the dog. Gastroenterology 1986; 91(4):890-896.

(14) Patrikios J, Martin CJ, Dent J. Relationship of transient lower esophageal sphincter relaxation to postprandial gastroesophageal reflux and belching in dogs. Gastroenterology 1986; 90(3):545-551.

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

(16) Trifan A, Shaker R, Ren J, Mittal RK, Saeian K, Dua K et al. Inhibition of resting lower esophageal sphincter pressure by pharyngeal water stimulation in humans. Gastroenterology 1995; 108(2):441-446.

(17) Bredenoord AJ, Weusten BL, Timmer R, Smout AJ. Minimum sample frequency for multichannel intraluminal impedance measurement of the oesophagus. Neurogastroenterol Motil 2004; 16(6):713-719.

(18) Shay S, Richter J. Direct comparison of impedance, manometry, and pH Probe in detecting reflux before and after a meal. Dig Dis Sci 2005; 50(9):1584-1590.

(19) Tipnis NA, Liu J, Puckett JL, Mittal RK. Common Cavity Pressure during Gastro-Esophageal Reflux: Reassessment Using Simultaneous Pressure, Impedance and Ultrasound Imaging. Am J Physiol Gastrointest Liver Physiol 2006; 290(6):G1146-G1156.

(20) Shay SS, Bomeli S, Richter J. Multichannel intraluminal impedance accurately detects fasting, recumbent reflux events and their clearing. Am J Physiol Gastrointest Liver Physiol 2002; 283(2):G376-G383.

(21) Bredenoord AJ, Weusten BL, Curvers WL, Timmer R, Smout AJ. Determinants of perception of heartburn and regurgitation. Gut 2006; 55(3):313-8.

(22) Shay S, Tutuian R, Sifrim D, Vela M, Wise J, Balaji N et al. Twenty-four hour ambulatory simultaneous impedance and pH monitoring: a multicenter report of normal values from 60 healthy volunteers. Am J Gastroenterol 2004; 99(6):1037-1043.

(23) Srinivasan R, Vela MF, Katz PO, Tutuian R, Castell JA, Castell DO. Esophageal function testing using multichannel intraluminal impedance. Am J Physiol Gastrointest Liver Physiol 2001; 280(3):G457-G462.

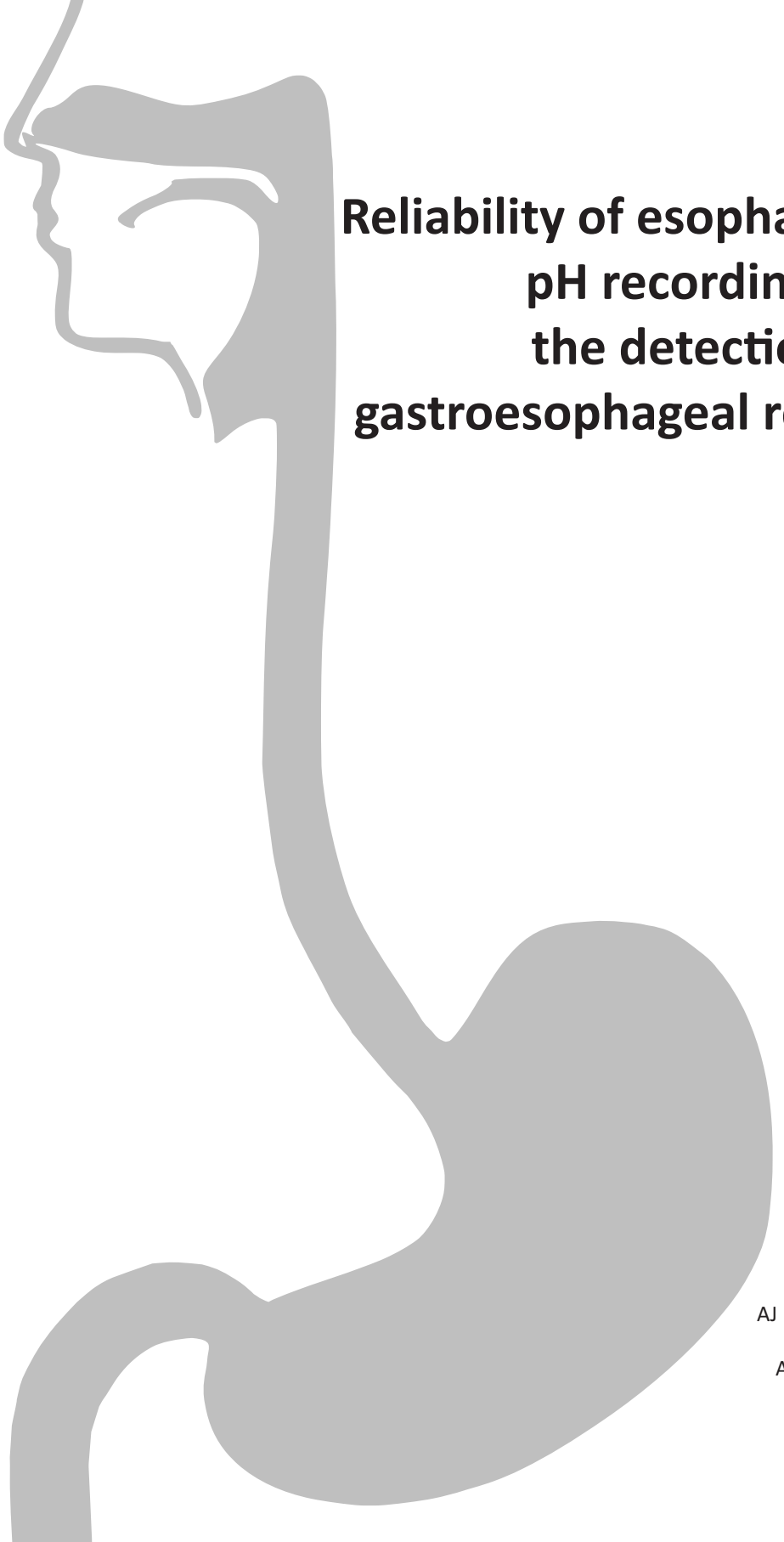
(24) Tipnis N, Mittal Y, Liu J. Gastroesophaegal reflux induced distension of esophagus. Comparison between symptomatic and asymptomatic reflux episodes. Gastroenterology 2004; 126:A-111.

(25) Tipnis N, Mittal Y, Liu J. Reflux through an untrasonographic eye. Measuring esophageal distension during spontaneous gastroesophageal reflux episodes. Gastroenterology 2004; 126:A-320.

Chapter 2

*"Oh how fine it is to know a thing or **two**!"*
~ Moliere, French Playwright

Submitted



Reliability of esophageal pH recording for the detection of gastroesophageal reflux

MC Aanen
AJ Bredenoord
M Samsom
AJPM Smout

ABSTRACT

Background

Despite the new gold standard esophageal impedance, esophageal pH monitoring is still used frequently for detection of gastroesophageal reflux (GER). Besides pH drops from above to below pH4 also drops of ≥1 are used as marker for GER. In this study the accuracy of pH drops for detection of GER was investigated, using impedance monitoring as gold standard.

Methods

Nineteen GERD patients (9 males, 55±11yrs) underwent combined 24-h pH-impedance recording off acid-suppressive therapy. All pH drops ≥0.5pH units, with a duration 4s, reaching the nadir pH within 5s after the onset were included. Reflux events detected with impedance monitoring were taken as reference.

Results

In total 2221 pH drops were found; 47% were acid (nadir pH<4), 47% were weakly acidic (nadir pH between pH 7-4) and 5% were superimposed (pH drop starting below pH 4). The sensitivity of acid, weakly acidic and superimposed pH drops ≥1 was 91%, 28%, 24% respectively and the % of false-positive reflux episodes was 20%, 56% and 54%. Acid reflux with a cut-off ≥0.5 and ≤3.3 had a moderate-to-good sensitivity (94%-70%) and low false-positive percentages (23%-13%). In contrast, weakly acidic and superimposed reflux showed for all cut-off values a greater false-positive than true-positive percentage.

Conclusion

Compared to impedance monitoring, detection of reflux with pH monitoring is clearly inferior. When pH drops ≥1 irrespective of nadir pH are used as an indicator of reflux episodes the number of reflux episodes is overestimated drops from above to below 4 with cut-offs between ≥0.5 and ≤3.3 are most indicative for true reflux episodes.

INTRODUCTION

Despite the overall recognition of impedance monitoring as new gold standard, esophageal pH-monitoring is still the most frequently used tool for detection of gastroesophageal reflux (1;2). Its persistent popularity is based on the relatively low cost involved, the resistance to replace still functional equipment and the ease of analyzing the tracings (3). Analyzing 24-hour impedance tracings is often performed manually as automatic analysis with dedicated software programs is still suboptimal (3;4).

With pH monitoring reflux events are detected as a rapid drop in pH, reflecting an intra-esophageal increase in acidity. Traditionally, a pH threshold of 4 is used and only episodes with a pH drop from above to below pH 4 are classified as reflux episodes. However, a pH fall with a magnitude >1 pH unit but not necessarily reaching a nadir of pH <4 could also indicate gastro-esophageal reflux (5;6). Thus, theoretically, besides detection of acid reflux episodes pH monitoring also allows detection of superimposed reflux (pH drops starting below pH 4) and weakly acidic reflux (nadir pH between 4 and 7). The validity of this concept can be investigated with impedance monitoring as the gold standard for reflux detection (1).

Hence, in this study we wished to investigate the accuracy of pH drops in detecting acid, weakly acidic and superimposed reflux.

METHODS

Patients

Nineteen patients with GERD (9 male, age 55 ±11 years) were included. Informed written consent was obtained before the start of the study and the protocol was approved by the Medical Ethics Committee of the University Medical Center, Utrecht.

Combined 24-h pH-impedance monitoring

All subjects underwent combined 24-hour esophageal pH-impedance recording. Prior to the 24-hour pH-impedance recording the position of the lower esophageal sphincter (LES) was identified manometrically using a 10-channel silicone rubber catheter with a sleeve sensor (DentSleeve International Ltd, Mississauga, Ontario, Canada) which was perfused at a rate of 0.2 mL/min with degassed water, using hydraulic flow restrictors (DentSleeve International Ltd, Mississauga, Ontario, Canada). The pressures were recorded with external pressure transducers (Abbott, Sligo, Ireland). After removal of the manometric catheter, a glass pH catheter with in-built reference electrode (Ingold, Urdorf, Switzerland) was placed transnasally 5 cm above the LES. The pH catheter was attached to a digital datalogger (MMS, Enschede, the Netherlands) which used a sampling frequency of 2 Hz and calibrated with 3.2 and 7.4 pH buffer solutions. For impedance monitoring a 7-channel impedance catheter (outer diameter 2.3 mm) was used (Aachen University of Technology, FEMU, Aachen, Germany). The 7 impedance recording segments consisted of pairs of ring electrodes at 2-cm intervals which were located at 0–2, 2–4, 4–6, 8–10, 10–12, 14–16, and 17–19 cm above the upper border of the manometrically located LES. Impedance signals were stored in a digital system (Aachen University of Technology, FEMU, Aachen, Germany) using a sampling frequency of 50 Hz (7).

Patients were instructed to restrict their intake to 3 meals and 4 beverages at standardized times during the 24 hours. Meals and drinks had to be consumed within 30 and 15 minutes, respectively. Patients were encouraged to maintain their normal daily activities during the 24-hour pH study.

Data analysis

The periods of meal and beverage consumption were excluded from the analysis. The impedance and pH tracings were analyzed separately, with the investigator blinded for the recording made with the other technique.

In the pH recordings all pH drops of at least 0.5 pH units that had a minimum duration of 4 seconds and reached the nadir pH within 5 seconds after the onset of the pH drop were identified. A minimum time interval of 15 seconds between each pH drop was used for repetitive events, in case pH drops occurred within 15 seconds the pH drop with the largest amplitude was considered for analysis.

In the impedance recordings gas and liquid (including pure liquid plus mixed liquid events) episodes were detected and the proximal extent of these episodes was determined according to the Porto consensus criteria (5). Subsequently, all pH drops ≥0.5 pH units were compared to events detected with impedance monitoring. When a pH drop was not associated with a reflux event as detected by impedance monitoring, the impedance tracing was analyzed for signs of a swallow, i.e. antegrade bolus movement.

Liquid volume clearance times were determined for each liquid-containing reflux episode and defined as the time interval between a drop of 50% of baseline impedance and the return to a value above this point.

Statistics

The pH-detected reflux episodes that were also detected by impedance were considered to be true-positive while pH drops not detected by impedance were regarded as false-positive. Reflux episodes detected by impedance only were regarded as false-negatives, as were pH drops that were detected with impedance but fell below the pH drops cut-off point. Sensitivity was calculated by dividing the number of true-positives by the sum of true-positives plus false-negatives. The false-positive ratio was calculated by dividing the number of false-positives by the sum of false-positives plus false-negatives.

In normally distributed data differences were determined with a Student t-test and otherwise with a Wilcoxon test. All data are shown in means and 95% confidence intervals (CI).

	% detected TP (TP/TP+FN)	% missed FN/ (FN+TP)
All pH drops		
Drops ≥ 0.5	76	24
Drops ≥ 1.0	63	37
Drops ≥ 1.5	53	47
pH drops from pH≥4 to pH<4		
Drops ≥ 0.5	94	6
Drops ≥ 1.0	91	9
Drops ≥ 1.5	85	15
pH drops with nadir pH between 4 and 7		
Drops ≥ 0.5	50	50
Drops ≥ 1.0	28	72
Drops ≥ 1.5	14	86
pH drops starting at pH<4		
Drops ≥ 0.5	51	51
Drops ≥ 1.0	24	76
Drops ≥ 1.5	10	90

Table 1. Reliability of pH drops shown for each pH drop according to reflux type.

RESULTS

The 19 patients who underwent a 24-h pH recording (mean duration: 21h 35min) had a total time with pH below 4 of 7.7 % (CI 5.8-9.6), of which 8.7% occurred in the upright position (CI 6.4-10.9) and 6.2% in the supine position (CI 3.7-8.7).

In total, 2221 pH drops ≥0.5 pH units were found, 47% of which had a nadir pH below 4 (suggestive of acid reflux), 47% had a drop with nadir pH 7-4 (suggestive of weakly acidic reflux), and in 5% a drop occurred when pH was already below 4 (suggestive of superimposed reflux). Overall, only 51% of the pH drops ≥0.5 were also recognized as a reflux event in the impedance recordings. Per subject an average number of 63 (46-80) pH drops were also detected with impedance and 54 (34-74) pH drops were not detected with impedance. Drops pH suggestive of acid reflux were more often confirmed by impedance recording than pH drops suggestive of weakly acidic and/or superimposed reflux (figure 1).

Acid reflux with a pH drop ≥0.5 and ≤3.3 had a true-positive percentage ranging from 94% and the false-positive percentage ranged from 23%. However pH drops larger than 3.3, the true-positive ratio dropped below 50% en eventually when pH drops were larger than 5 the percentages of true-positive equaled the false-positive percentage. Weakly acidic and superimposed reflux showed a greater false-positive than true-positive percentage for all cut-off values.

In table 1 the proportion of reflux episodes that was detected (sensitivity) and the percentage of reflux episodes that was missed by using different cut-off values for pH drops is shown. With increasing cut-off values the proportion of reflux episodes that was detected decreased, in favour of a decrease in proportion of false-positives.

Of the pH drops ≥0.5 without any evidence of a reflux event on impedance monitoring, 48% coincided with a swallow. In 61%, 44% and 40% of the acid, weakly acidic and superimposed pH drops ≥0.5 respectively and in 65%, 58% and 59% of the acid, weakly acidic and superimposed pH drops ≥1 respectively an impedance-detected swallow was present.

Of the 1585 reflux events detected with impedance monitoring, 76% were associated with a pH drop ≥0.5 pH. Of the remaining 26% of the reflux episodes that were not accompanied by a drop in pH drop a stable pH above 4 was found in 88% and in a stable pH below 4 in 12%. Reflux events detected with impedance monitoring that were accompanied by a pH drop ≥0.5 on the pH recording were most frequently liquid while an impedance-detected reflux event without a pH drop ≥0.5 was either liquid or gas (see figure 2).

The proximal extent of gaseous and liquid reflux did not differ between the reflux events that did and did not coincided with a pH drop.

Reflux episodes with a pH drop ≥0.5 pH unit and a nadir pH below 4 had a longer volume clearance time (acid reflux 19.4 (16.8-22.0)) compared to weakly acidic reflux events (14.0 (10.9-17.2), superimposed reflux events (15.5 (10.3-20.7)) and reflux events without a pH drop (9.7 (6.9-12.5), $p<0.01$).

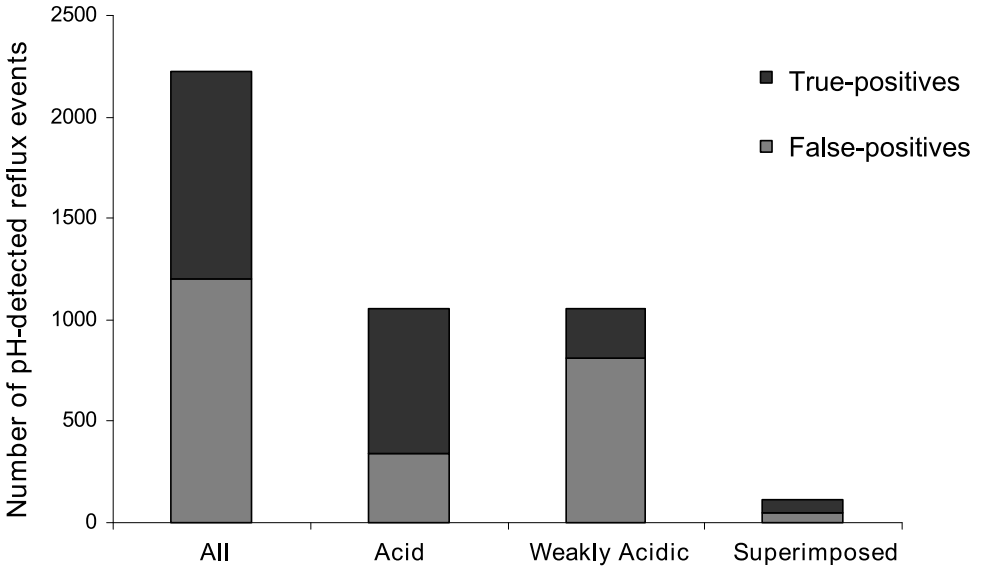


Figure 1. The number of acid, weakly acidic and superimposed pH drops divided according to those detected by impedance (true-positive) and those not detected by impedance recording (false-positive)

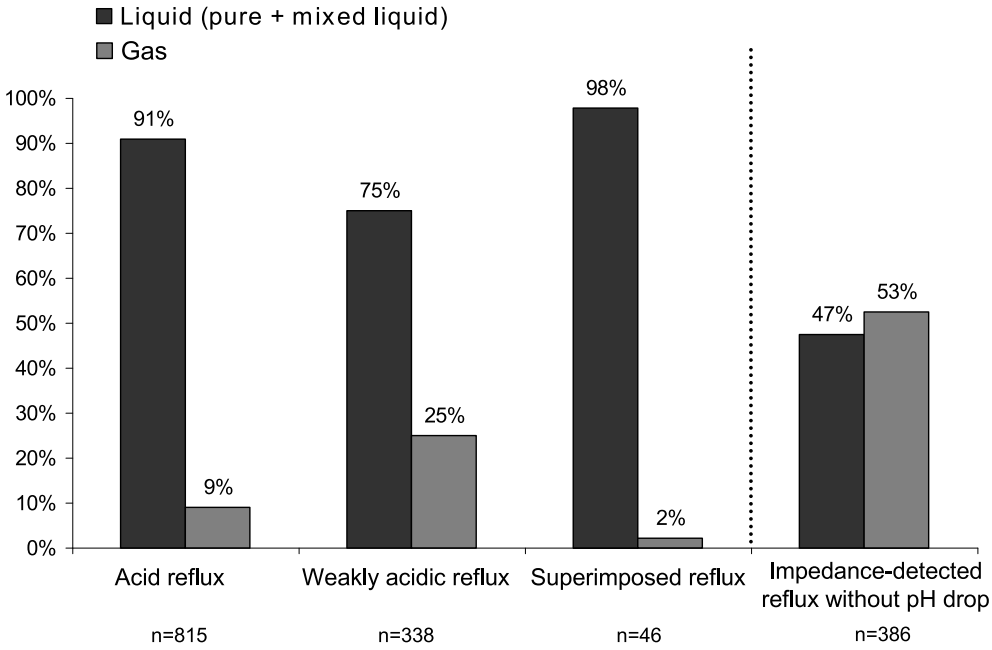


Figure 2. Composition of impedance-detected reflux events. Reflux events associated with a pH drop were more often liquid than events not associated with a pH drop.

DISCUSSION

Esophageal pH recording is considered to be an accurate method for detection of acid reflux, traditionally recognized as pH drops from above to below 4. It has been suggested that by using pH drops as reflux marker other forms of reflux such as weakly acidic reflux (nadir pH between 4 and 7) and superimposed reflux (pH drop starting from a pH already below 4) could also be detected. These types of reflux have become focus of attention after the emergence of esophageal impedance monitoring (5).

Impedance monitoring has become the gold standard for reflux detection since it allows one to detect reflux irrespective of its acidity (3). Although it is generally accepted that impedance monitoring is superior to pH monitoring for detection of gastroesophageal reflux, the majority of practices still use the latter technique. In this study we investigated the value of pH drops, as detected with pH monitoring, for detection of gastroesophageal reflux, using impedance monitoring as the gold standard.

In this study only 51% of all pH drops ≥0.5 corresponded with a “true” reflux event, as detected with impedance monitoring, indicating that almost half of these ”minor” pH drops did not indicate the occurrence of gastro-esophageal reflux and were thus false-positive. Most pH drops that corresponded with an impedance-detected reflux episode were acid, while weakly acidic pH drops were to a lesser extent representative of impedance-detected reflux events. Half of the superimposed pH drops corresponded with impedance-detected reflux events, however, the low number of both pH and impedance-detected superimposed reflux events did not enable us only to draw solid conclusions. Nevertheless, pH drops of any magnitude falling from above to below 4 showed to be fairly useful as diagnostic tool, while the sensitivity of pH drops with a nadir pH above 4 or a starting point below 4 were poor as well.

In this study, weakly alkaline reflux episodes (reflux with a nadir pH above 7) were disregarded as these occur very infrequently and these kinds of pH drops are likely to represent swallowed saliva, rather than gastro-duodeno-esophageal reflux (8).

This study showed that reflux from above 4 to below 4 with a pH drop larger than 0.5 and smaller than 3.3 had a reasonable sensitivity of 94%-70% and low false-positive values of 23% and 13%. In contrast, pH drops with a nadir pH above 4 or a starting point below 4 had for any cut-off value a higher amount of false positives than true positives.

The discrepancy between acid pH drops being a good indicator of reflux and weakly acidic and superimposed pH drops being a poor indicator of reflux has previously been described by others (9-11). However, the occurrence of a swallow during false-positive pH drops was much higher in the study by Hila et al. They found that 80% of the acidic pH drops and 89% of

weakly acidic pH drops coincided with a swallow while in our study this occurred during approximately half of the pH drops (9). This discrepancy could be explained, at least partially, by the inclusion of meal periods in their study. In our study, subjects were not allowed to drink between the restricted standardized meal periods as drinking has been shown to induce pH drops and thus to simulate reflux episodes (12). These meal periods were subsequently excluded from the analysis. However, in our study we still found that several large pH drops, which were not recognized as reflux with impedance monitoring, often occurred simultaneously with a swallow. Besides the possibility of false-positives caused by the ingestion of acidic substances, it is also possible that some reflux episodes, caused by swallow-associated LES relaxations, are missed by impedance due to the concurrent swallowing (4;13;14). In this case the true diagnostic value of pH drops would be higher.

Nevertheless, a substantial part of the pH drops occurs in the absence of swallowing or reflux. A clear explanation is lacking. It could be that these small drops in pH are induced by changes in the position of the pH probe, caused by respiration or changes in body position (15).

As pH monitoring commonly overestimates the number of reflux events, this could lead to an incorrect diagnosis of GERD when this is defined by a certain number of reflux episodes. There are indeed large differences found in percentage of time with pH below 4 calculated according to acidic pH drops compared to percentage of time of pH below 4 calculated with acid reflux events detected also with impedance monitoring (9;11). The symptom association probability index however seems to be less affected by the overestimation of reflux events (16). This is probably because the way the SAP is calculated and corrected for the number of reflux events (6). When GERD is thus defined as the presence of a positive relationship between reflux episodes and symptoms, this diagnose is less dependent on the technique used for reflux detection.

Reflux events with a pH drop most often contained liquids. This was also seen in previous studies in normal volunteers (17). The proximal extent of gas or liquid reflux did not differ between reflux with or without a pH drop although it could be hypothesized that a more proximal extent would induce more frequently a pH drop as it can be regarded as an indirect indicator of a high volume of a reflux episode.

In conclusion, detection of reflux with pH monitoring is clearly inferior to impedance monitoring. When pH monitoring is used for reflux detection, the technique is most reliable when only drops ranging from ≥0.5 and ≤3.3 that fall from above to below pH 4 as considered indicative for reflux. Esophageal pH monitoring is not a suitable technique to monitor weakly acidic and superimposed reflux.

REFERENCES

(1) Bredenoord AJ, Tutuian R, Smout AJ, Castell DO. Technology review: Esophageal impedance monitoring. Am J Gastroenterol 2007; 102(1):187-194.

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

(3) Vandenplas Y, Salvatore S, Vieira MC, Hauser B. Will esophageal impedance replace pH monitoring? Pediatrics 2007; 119(1):118-122.

(4) Roman S, Bruley d, V, Pouderoux P, Chaput U, Mion F, Galmiche JP et al. Ambulatory 24-h oesophageal impedance-pH recordings: reliability of automatic analysis for gastro-oesophageal reflux assessment. Neurogastroenterol Motil 2006; 18(11):978-986.

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

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

(7) Bredenoord AJ, Weusten BL, Timmer R, Smout AJ. Minimum sample frequency for multichannel intraluminal impedance measurement of the oesophagus. Neurogastroenterol Motil 2004; 16(6):713-719.

(8) Singh S, Bradley LA, Richter JE. Determinants of oesophageal 'alkaline' pH environment in controls and patients with gastro-oesophageal reflux disease. Gut 1993; 34(3):309-316.

(9) Hila A, Agrawal A, Castell DO. Combined Multichannel Intraluminal Impedance and pH Esophageal Testing Compared to pH Alone for Diagnosing Both Acid and Weakly Acidic Gastroesophageal Reflux. Clin Gastroenterol Hepatol 2007; 5(2):172-177.

(10) Wenzl TG, Moroder C, Trachterna M, Thomson M, Silny J, Heimann G et al. Esophageal pH monitoring and impedance measurement: a comparison of two diagnostic tests for gastroesophageal reflux. J Pediatr Gastroenterol Nutr 2002; 34(5):519-523.

(11) Woodley FW, Mousa H. Acid gastroesophageal reflux reports in infants: a comparison of esophageal pH monitoring and multichannel intraluminal impedance measurements. Dig Dis Sci 2006; 51(11):1910-1916.

(12) Agrawal A, Tutuian R, Hila A, Freeman J, Castell DO. Ingestion of acidic foods mimics gastroesophageal reflux during pH monitoring. Dig Dis Sci 2005; 50(10):1916-1920.

(13) Mittal RK, Lange RC, McCallum RW. Identification and mechanism of delayed esophageal acid clearance in subjects with hiatus hernia. Gastroenterology 1987; 92(1):130-135.

(14) Srinivasan R, Vela MF, Katz PO, Tutuian R, Castell JA, Castell DO. Esophageal function testing using multichannel intraluminal impedance. Am J Physiol Gastrointest Liver Physiol 2001; 280(3):G457-G462.

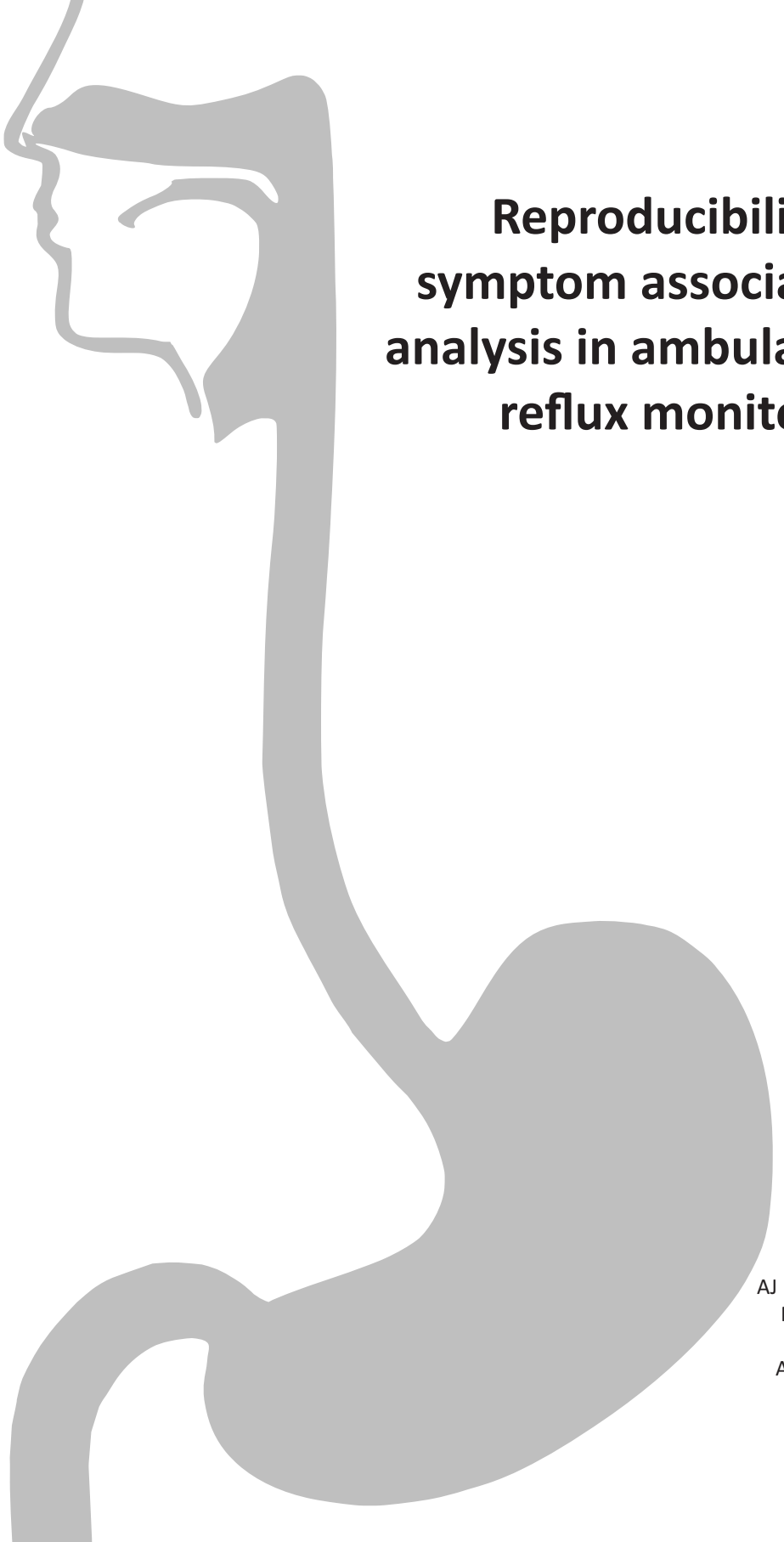
(15) Sifrim D. Acid, weakly acidic and non-acid gastro-oesophageal reflux: differences, prevalence and clinical relevance. Eur J Gastroenterol Hepatol 2004; 16(9):823-830.

(16) Bredenoord AJ, Weusten BL, Timmer R, Conchillo JM, Smout AJ. Addition of esophageal impedance monitoring to pH monitoring increases the yield of symptom association analysis in patients off PPI therapy. Am J Gastroenterol 2006; 101(3):453-459.

(17) Shay SS, Eggli D, Johnson LF. Simultaneous esophageal pH monitoring and scintigraphy during the postprandial period in patients with severe reflux esophagitis. Dig Dis Sci 1991; 36(5):558-564.

Chapter 3

*"My doctor told me to stop having intimate dinners for four. Unless there are **three** other people."*
~ Orson Welles, American Actor



Reproducibility of symptom association analysis in ambulatory reflux monitoring

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ABSTRACT

Background

The temporal relationship between reflux symptoms and reflux episodes during ambulatory reflux monitoring can be studied with symptom association analysis and the strength of the relationship can be expressed using indices such as the SAP (symptom association probability), SI (symptom index) and SSI (symptom sensitivity index). The reproducibility of these indices has not been determined yet.

Methods

Twenty-one patients with typical reflux symptoms (9 males, 53 (38-57) yrs) underwent two 24-h combined pH-impedance recordings off acid-secretory medication with an interval of 1-4 wk. The SAP, SI and SSI were calculated for each measurement. Reproducibility of these indices was determined with Kendall's coefficients of concordance.

Results

The number of reflux events were highly reproducible (Kendall W=0.92, $p<0.01$). The number of symptoms related to reflux events was reproducible (Kendall W=0.91, $p<0.01$) while the number of reported reflux symptoms was not (Kendall W=0.75, p=0.07). The SAP and SSI were highly reproducible (Kendall W=0.90, p=0.01 and W=0.86, $p<0.05$, respectively) but the SI was not (W=0.73, p=0.09).The percentage of patients with two concordant outcomes for the SAP, SI and SSI was respectively 86%, 67% and 86%, respectively.

Conclusion

In 24-h pH-impedance recordings of patients with reflux symptoms the number of reflux events and the number of symptoms related to reflux events were highly reproducible as were the SAP and SSI. This supports the use of these indices to express the relationship between symptoms and reflux episodes in clinical practice.

INTRODUCTION

Reflux symptoms such as heartburn and regurgitation are very common in the western world (1). However, these symptoms are not very specific for gastroesophageal reflux disease and when subjects do not respond satisfactorily to acid-suppressive therapy an upper endoscopy is often carried out (2). When mucosal lesions are found the diagnosis of gastroesophageal reflux disease (GERD) is established but the majority of patients with GERD have no endoscopic abnormalities (3). In this case the next step in the evaluation of these patients is ambulatory gastroesophageal reflux monitoring. With this technique the quantity of reflux can be studied as well as whether a temporal relationship exists between reflux symptoms and reflux events. The relationship between symptoms and reflux episodes can be expressed numerically using symptom association analysis (4).

The most frequently used indices are the symptom association probability (SAP), the symptom index (SI) and the symptom sensitivity index (SSI) (5-7). The SI represents the percentage of reflux events associated with symptoms and the SSI the percentage of symptoms associated with reflux episodes. The SI and SSI are handicapped by the fact that the former does not take the total number of reflux events into account while the latter does not include the total number of symptom episodes in the equation. The SAP however, does take both parameters into account as the index expresses the statistical relationship between the occurrence of symptoms and reflux episodes using the Fisher exact test. The disadvantage of the SAP is that it is complex and difficult to calculate manually (4).

It is known that the detection of reflux events with a pH recording has a reproducibility during the second measurement of approximately 70-80% (8-10). However, nowadays the gold standard to detect reflux events is pH-impedance recording (11). The reproducibility of impedance monitoring in healthy volunteers has been shown to be very acceptable for both stationary and ambulatory recordings. However, the reproducibility of measuring reflux events in GERD patients has not been studied yet (12;13). Furthermore, a high reproducibility for detection of reflux episodes does not imply a similarly high reproducibility for symptoms related to reflux. When symptom association indices are to be used in the diagnosis of GERD it seems essential that their reproducibility is known.

The aim of this study was therefore to better define the reproducibility of detection of reflux events and reflux-symptom association analysis in patients with reflux symptoms.

METHODS

Patients

In this study 24 patients with typical reflux symptoms (11 males; age 51±11 years) underwent a 24-h combined pH-impedance recording twice on two separate days with a minimum interval of 1 week and a maximum interval of 4 weeks (12;14). All acid-suppressive medication had to be discontinued before each pH recording. Proton pump inhibitors were discontinued 7 days in advance and H2-antagonists 3 days before the recording while antacids were prohibited during the recording day. Patients were excluded for the analysis of the indices when they failed to report symptoms during any of both recording. Informed written consent was obtained before the start of the study and the protocol was approved by the Medical Ethics Committee of the University Medical Center, Utrecht.

Combined 24-h pH-impedance monitoring

Prior to each 24-hour pH-impedance recording the lower esophageal sphincter (LES) was identified manometrically using a 10-channel silicone rubber catheter with a reversed sleeve sensor (DentSleeve International Ltd, Mississauga, Ontario, Canada) which was perfused at a rate of 0.2 mL/min with degassed water, using hydraulic flow restrictors (DentSleeve International Ltd, Mississauga, Ontario, Canada). The pressures were recorded with external pressure transducers (Abbott, Sligo, Ireland). After removal of the manometric catheter, a glass pH catheter with in-built reference electrode (Ingold, Urdorf, Switzerland) was placed transnasally 5 cm above the LES. The pH catheter was calibrated with 3.2 and 7.4 pH buffer solutions. The pH catheter was then attached to a digital datalogger (MMS, Enschede, the Netherlands) which used a sampling frequency of 2 Hz.

For impedance monitoring a 7-channel impedance catheter (outer diameter 2.3 mm) was used (Aachen University of Technology, FEMU, Aachen, Germany). The 7 recording segments formed by pairs of ring electrodes at 2-cm intervals were located at 0–2, 2–4, 4–6, 8–10, 10–12, 14–16, and 17–19 cm above the upper border of the manometrically located LES. Impedance signals were stored in a digital system (Aachen University of Technology, FEMU, Aachen, Germany) using a sampling frequency of 50 Hz (15).

Patients were instructed to restrict their intake to 3 meals and 4 drinks at standardized times during the 24 hours. Meals and drinks had to be consumed within 30 and 15 minutes, respectively. Patients were encouraged to maintain their normal daily activities during the 24-hour pH study.

After the 24-hour recording period the data from the dataloggers were transferred to a personal computer. The periods of meal consumption were excluded from the analysis. This procedure was repeated completely for the second measurement in the same patient after 1-4 weeks.

Data analysis

In order to perform symptom–reflux association analysis it was determined for each reflux episode whether it was symptomatic or not. Previously established criteria were used to identify acid and/or weakly acidic reflux episodes and pure gas reflux episodes with impedance-pH monitoring (11).

In order to provide reproducibility data of symptom association analysis when only pH monitoring is available and not impedance monitoring the analysis was performed separately for those reflux episodes that would have been detected by pH monitoring alone (reflux defined by drops in pH from above to below pH 4). A reflux episode was labelled as symptomatic if a symptom occurred within the 2-minute time window starting at the onset of the reflux episode, however an exception was made for the SI for which besides a 2-minute also a 5-minute time window was used (16). Only typical reflux symptoms such as heartburn, regurgitation, and chest pain were evaluated. Thereafter the symptom association indices were calculated.

The SI was calculated according to Wiener et al. as the percentage of symptoms that was reflux-related (7). The SSI was defined according to Breumelhof et al. as the percentage of reflux episodes that was symptomatic (5). The SAP was defined according to Weusten et al. as the statistical relation between symptoms and reflux episodes (6). The SAP is calculated by dividing the 24-h pH data set into consecutive 2-min segments. For each of these 2-min segments, it is determined whether reflux occurred in it, providing the total number of 2-min segments with and without reflux. Subsequently, it is determined whether or not a reflux episode occurred in the 2-min period before each symptom. A 2 × 2 table is then constructed in which the numbers of 2-min segments with and without symptoms and with and without reflux are tabulated. The Fisher exact test is used and the p-value is calculated. Subsequently, the SAP index is calculated as (1−p)×100%. The cut-off values used in this study for a positive test were SI ≥50%, SSI ≥10%, and SAP ≥95% (4).

Statistics

Reproducibility was determined with Kendall's coefficients of concordance (W value). A Kendall W-value of 1 implies perfect agreement and k value of 0 suggests no agreement. In this study a Kendall W-value ≥ 0.80 was considered reproducible. The coefficients were further tested for significance and an error probability of $p \leq 0.05$ was considered statistically significant.

Assessment of reproducibility was facilitated by Bland–Altman plots (17). In these plots, the differences between the first and second measurement (y-axis) are plotted against the mean values of the two measurements (x-axis). If the difference between the two measurements

is small, data points are scattered closely to the x-axis. Symmetrical scattering around the x-axis indicates that there is no trend toward a difference of the measurements of the second day compared to the measurements of the first day and the difference between the two measurements occurs in a random fashion.

Positive test results for the presence of GERD or negative results for the absence of GERD, as determined by the outcome above or below the set cut-off values were considered a reproducible concordant test result and are in the paper expressed in percentages. To statistically determine concordant agreement between the indices a kappa statistics was calculated. A kappa outcome can be interpreted as follows; 0.00 poor agreement, 0.01-0.20 low agreement, 0.21-0.40 fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 substantial agreement and 0.81-1.00 almost perfect agreement (18).

Throughout the manuscript data is presented as means with 95% confidence intervals (CI).

RESULTS

Three patients were excluded, two because they failed to report symptoms during the recording and one because of a technical failure. In total 42 recordings of 21 patients were used in the analysis of the symptom association indices (9 males, age 53 (CI 38-57) years). Four patients underwent an anti-reflux procedure in the past. The mean time between the two recordings was 19 (CI 16-22) days.

Overall, the reproducibility of reflux events detected with 24-h pH-impedance monitoring was very high, with W-values ranging between 0.92 and 0.78 (see Figure 1 and table 1). The number of symptom episodes reported during 24-h recordings was not highly reproducible while symptoms that were related to impedance-detected reflux events were reproducible (see Figures 2 and 3 and table 2).

Reproducibility results of the indices expressing symptom-reflux association are shown in table 3 and in figures 4 to 6. The SAP and the SSI both had the highest reproducibility, reflected by high Kendall W-values.

The SAP index was concordant on both days in 86% (43% positive on both days, 43% negative on both days). The SI showed concordance of 67% with a 2-minute time window (14% positive, 52% negative) and of 81% with a 5-minute time window (33% positive, 48% negative on both days). The concordance's on both days of SSI was 86% (10% positive, 76% negative). The kappa of the SAP index (0.72, p=0.00) was the highest, followed closely by the SI calculated with 5-minute time window (0.62, p=0.00), while the SSI (0.49, p=0.02) and SI calculated with a 2-minute time window (0.42, p=0.06) had the least agreement on the two days.

For pH monitoring alone, the number of pH-detected reflux events was highly reproducible (W-value 0.95, p=0.01). The symptoms related to pH-detected reflux events had low W-values (W-value 0.70, p=0.11). The SAP (W-value 0.83, p=0.03) was reproducible while the

SI (2-min: W-value 0.68, p=0.13, 5-min: W-value 0.59, p=0.27) and the SSI (0.71, p=0.10) were not.

When only pH monitoring was used the concordance for the SAP was 76% (48% positive, 29% negative), SI 2-minute time window 71% (29% positive, 43% negative), 5 minute time-window 67% (29% positive, 38% negative) and SSI 81% (5% positive, 76% negative). The kappa showed the highest outcome for the SSI index (0.63, p=0.00) followed closely by the SAP (0.62, p=0.00). The kappa of SI were lower whether either calculated with 2-minute (0.42, p=0.06) or 5-minute time window (0.33, p=0.33).

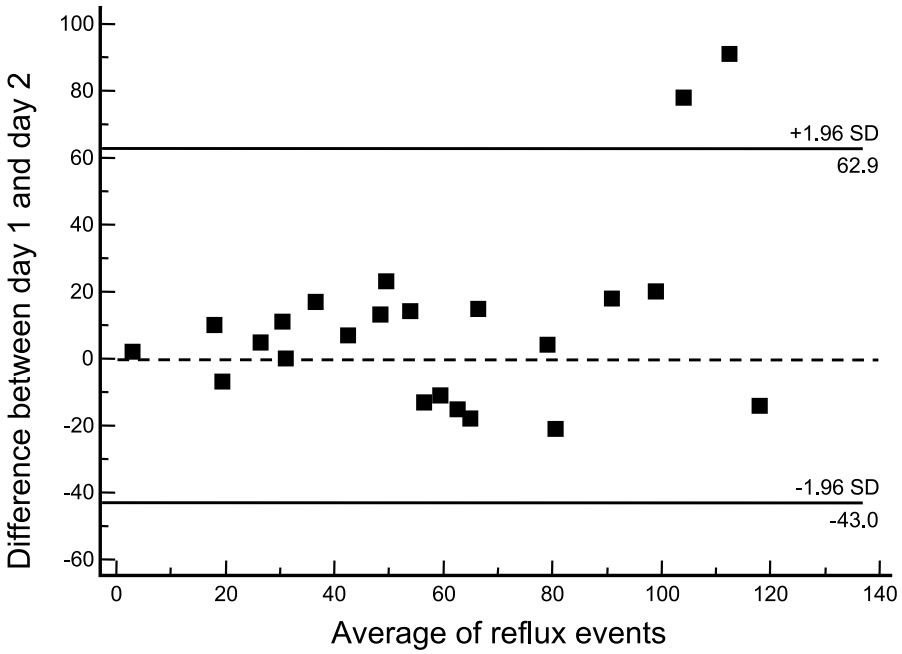

Figure 1. Reproducibility of number of reflux events detected on the basis of impedance drops in 24-h pH-impedance recordings (Bland-Altman plot).

Reflux events (Nr/24 hr)	Day 1	Day 2	Kendall's W	p-values
All reflux	63.8 (47.1-80.6)	53.9 (41.1-66.7)	0.92	0.01
Gas reflux	24.2 (11.5-36.8)	22.6 (10.3-34.6)	0.78	0.05
Acidic reflux	23.6 (13.1-34.0)	17.8 (11.6-24.0)	0.90	0.01
Weakly acidic reflux	40.3 (28.6-51.9)	36.1 (24.9-47.3)	0.90	0.01

Table 1. Reproducibility of reflux episodes detected with 24-h pH-impedance monitoring.

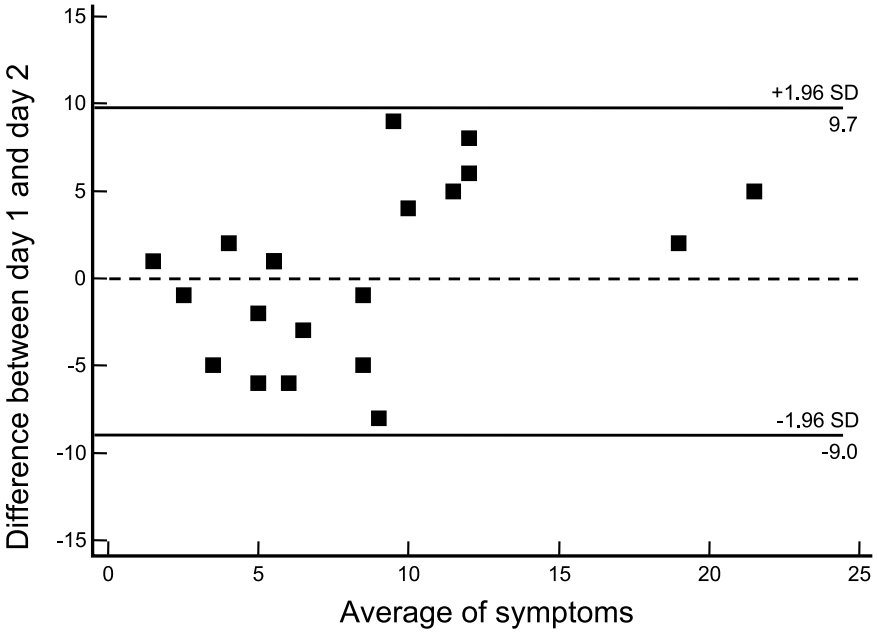

Figure 2. Reproducibility of number of reflux symptoms reported during 24-h pH-impedance recordings (Bland-Altman plot).

Symptoms	Day 1	Day 2	Kendall's W	p-values
All reflux symptoms	8.4 (5.4-11.3)	8.0 (6.0-10.0)	0.75	0.07
Symptoms related to reflux events	3.8 (1.6-5.9)	3.2 (2.1-4.4)	0.91	0.01
Symptoms related to gaseous reflux events	1.0 (0.3-1.7)	0.7 (0.3-1.2)	0.71	0.10
Symptoms related to acid reflux events	2.4 (0.7-4.0)	1.7 (0.9-2.5)	0.74	0.07
Symptoms related to weakly acidic reflux events	1.3 (0.7-2.0)	1.3 (0.5-2.0)	0.66	0.16

Table 2. Reproducibility of reflux symptom reporting during 24-h pH-impedance recording. Symptoms are related to impedance-detected reflux events.

Symptom reflux association	Day 1	Day 2	Kendall's W	p-value
SAP	69.9 (50.9-88.8)	84.5 (73.5-95.5)	0.90	0.01
SI (2-minute)	39.2 (23.6-54.9)	46.0 (32.6-59.5)	0.73	0.09
SI (5-minute)	43.3 (25.7-60.8)	46.9 (34.0-59.7)	0.78	0.06
SSI	5.6 (3.0-8.2)	6.6 (3.7-9.4)	0.86	0.02

Table 3. Reproducibility of symptom-reflux association indices.

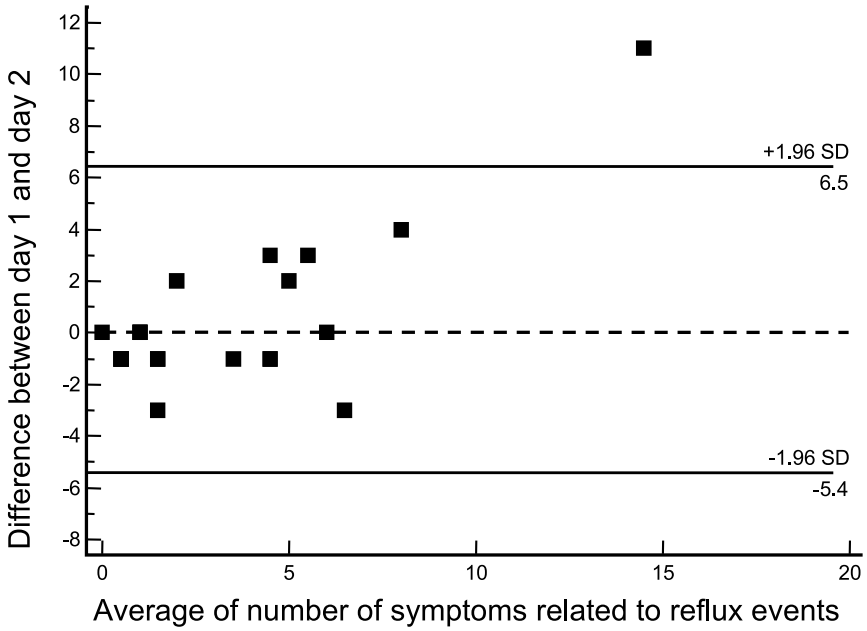

Figure 3. Reproducibility of symptom episodes related to impedance-detected reflux events during 24-h pH-impedance recordings (Bland-Altman plot).

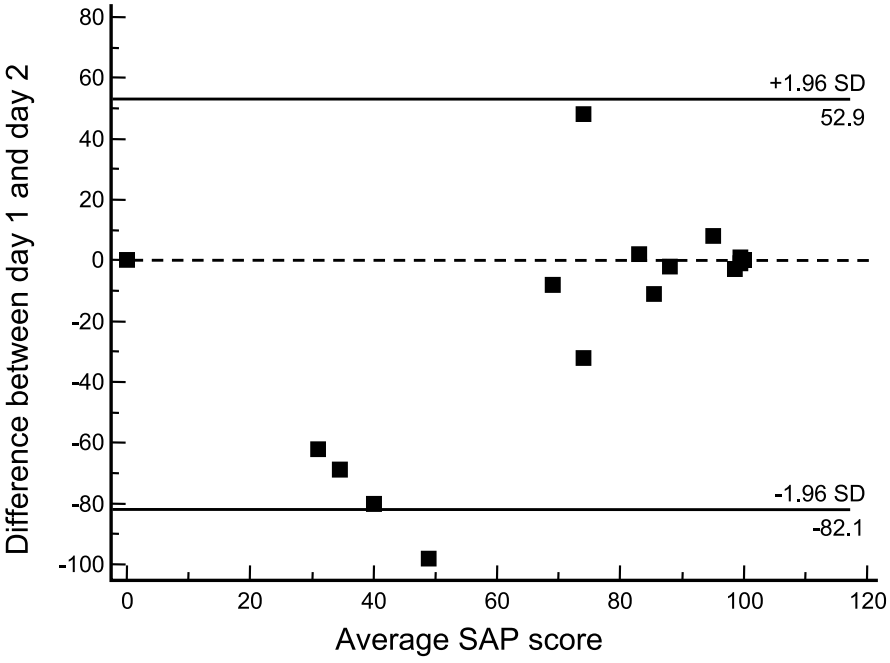

Figure 4. Reproducibility of Symptom Association Probability (SAP) index (Bland-Altman plot).

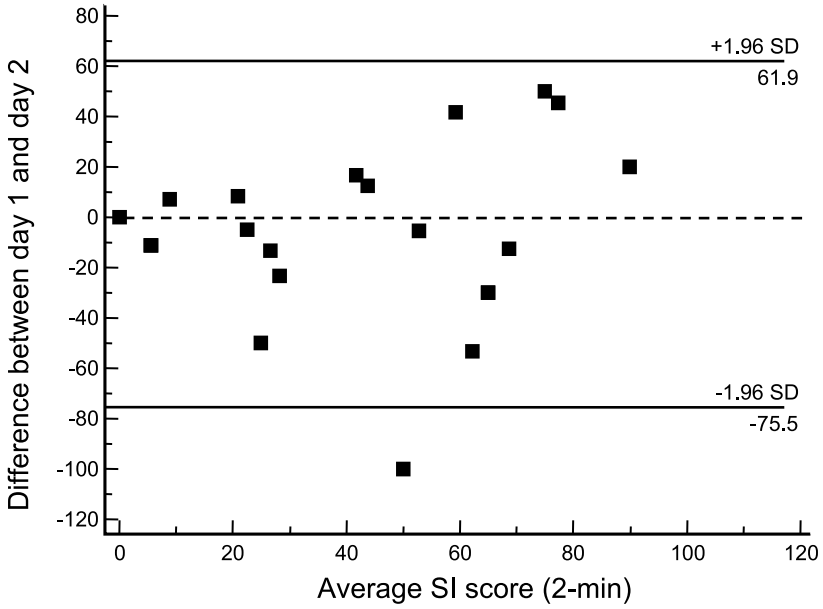

Figure 5a. Reproducibility Symptom Index (SI) calculated with 2-minute time interval (Bland-Altman plot).

DISCUSSION

Symptom-reflux association analysis is often performed to express the strength of the relationship between the occurrence of symptoms and gastroesophageal reflux (4;19). A positive outcome implies that it is highly unlikely that reported symptoms and reflux episodes are independent and suggests causality. The reflux-symptom association indices are thus useful for the evaluation of patients with symptoms suggestive for GERD (20;21). However, it has not been determined yet whether or not these diagnostic tests are reproducible. Furthermore, in order to use the indices for treatment evaluation it is important to know how these tests perform in patients with reflux symptoms under similar circumstances. In healthy volunteers the number of reflux episodes, either detected with pH or impedance monitoring, has been found to be highly reproducible. However, this might be different in GERD patients since the variability in the occurrence of reflux events seems to be larger (12;13;22). Furthermore, the variability in the incidence of reflux symptoms on various days has never been investigated and it is also unknown to what extent this might affect the number of symptoms related to reflux events.

This is the first study to investigate the reproducibility of the reflux-symptom association indices, SAP, SI, and SSI, and the reproducibility of symptom events and reflux events in 24h ambulatory pH-impedance recordings of symptomatic patients.

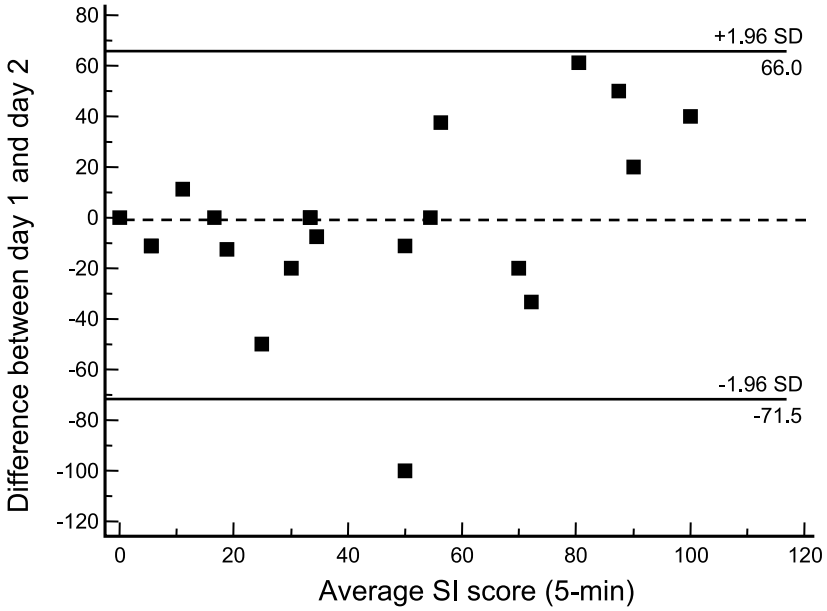

Figure 5b. Reproducibility Symptom Index (SI) calculated with 5-minute time interval (Bland-Altman plot).

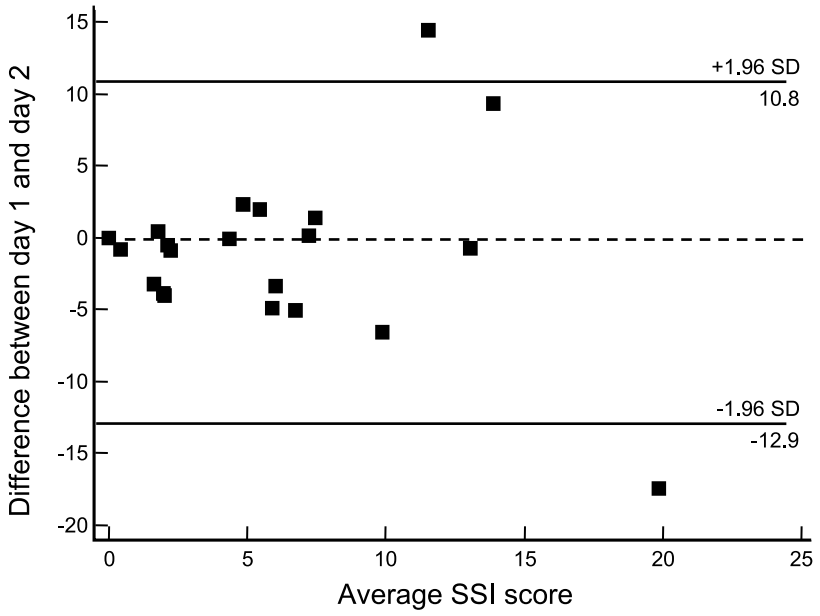

Figure 6. Reproducibility of Symptom Sensitivity Index (SSI) index (Bland-Altman plot).

Our results indicate that, in GERD patients, the SAP and SSI in 24-hour esophageal pH-impedance recordings are reproducible. Furthermore, it was seen that the number of reflux events were very reproducible, irrespective of the reflux detection technique used (impedance or pH). Our GERD patients had similar number of symptoms related to reflux on the two separate days however they did not report a similar number of symptom episodes. This may explain our finding that the SI was less reproducible as this index is calculated by dividing the number of reflux-related symptom events by the total number of symptoms (5;7).

However when a 5-minute time window was used the agreement of the index improved on the two test days as more patients had a negative SI outcome due to reduction of the total symptom but mostly due to the reduction in symptoms related to reflux events.
The SAP had the highest reproducibility of all indices regardless of which technique was used. In contrast, the SSI was less reproducible when only pH data were used (6). The SSI is the number of symptom events related to reflux divided by the number of reflux events and although the number of pH-detected reflux events was highly reproducible, the number of symptoms related to pH-detected reflux was not. Our observation that the SAP was most reproducible may be due to the fact that this index takes all factors involved (number of reflux episodes, number of symptom episodes, number of reflux-associated symptom episodes) into account and therefore is less influenced by a low reproducibility of a single parameter.

The observation that the reproducibility of symptoms related to reflux was higher when reflux was detected with impedance-pH monitoring (both acidic and weakly acidic reflux) than when detected with pH monitoring alone underlines the fact that symptoms are not solely caused by acidic reflux events and indicates the superiority of impedance monitoring for diagnosing GERD. Inclusion of weakly acidic reflux events did make a difference for reproducibility of the number of symptoms related to reflux events.

As confirmed in this study, the number of reported reflux symptoms can vary greatly. It is remarkable, however, to see that the number of reflux events and the symptoms related to reflux events were highly reproducible. This especially is remarkable when considering the fact that our recordings took place in an ambulant setting and not under controlled circumstances. Our patients were neither instructed to use identical meals and beverages on both study days nor to have similar daily routines, although we always instruct patients to “live a normal day” during the measurement and not to restrict physical activities and meal volume. This protocol promotes the realistic circumstances under which recordings are performed. Furthermore, recording patients in their own environment and enabling them to have their own routine is likely to cause less stress and anxiety and therefore to lead to a better correlation between reflux and symptoms episodes (23).

All the three indices showed a concordance above 75% between measurements on two separate days. It was however striking to see that the reproducible positive versus negative outcomes differed considerably between the SAP, SI and SSI. The SAP had predominantly reproducible positive outcomes while the SSI had mainly negative outcomes. Subsequently the question arises which of the indices is optimal for the diagnosis GERD. Taghavi et al.

compared the three indices and found that both the SAP and the SI seemed better predictors than the SSI (20). It was, however, not the aim of this study to determine the best symptom-reflux association index for clinical practice. The SAP, which seems to be the most objective parameter as it eliminates the occurrence of chance that symptoms are caused by reflux, nevertheless did have the best reproducibility (6).

Although not statistically significant, the total number of reflux episodes was lower during the second measurement. Various reasons can account for this, the most important of which could be a regression to the mean effect. In a chronic disorder such as GERD, patients tend to consult a physician in a period with severe symptoms (and probably many reflux episodes) while at the moment of the second measurement there is a tendency to a reduction of reflux episodes. In this study the vast majority patients who reported on the first recording day an average of 9 or more symptoms always reported less symptoms on the second recording day. It is important to realize this, as this in many open-label studies for GERD the observed reduction in reflux episodes is often attributed to the treatment tested. The observed reduction in reflux episodes underlines the need for placebo- and sham-controlled studies before a new treatment is accepted (24;25).

In conclusion, the number of reflux events and the number of symptoms related to reflux events were highly reproducible in GERD patients in 24-h pH-impedance recordings. Subsequently the SAP and SSI were highly reproducible and the SI to a lesser extent. The SAP was the most consistently reproducible irrespective of which reflux detection method was used.

REFERENCES

(1) Locke GR, III, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ, III. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997; 112(5):1448-1456.

(2) Johnsson F, Joelsson B, Gudmundsson K, Greiff L. Symptoms and endoscopic findings in the diagnosis of gastroesophageal reflux disease. Scand J Gastroenterol 1987; 22(6):714-718.

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

(4) Bredenoord AJ, Weusten BL, Smout AJ. Symptom association analysis in ambulatory gastro-oesophageal reflux monitoring. Gut 2005; 54(12):1810-1817.

(5) Breumelhof R, Smout AJ. The symptom sensitivity index: a valuable additional parameter in 24-hour esophageal pH recording. Am J Gastroenterol 1991; 86(2):160-164.

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

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

(8) Emde C, Armstrong D, Castiglione F, Cilluffo T, Riecken EO, Blum AL. Reproducibility of long-term ambulatory esophageal combined pH/manometry. Gastroenterology 1991; 100(6):1630-1637.

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

(10) Johnsson F, Joelsson B. Reproducibility of ambulatory oesophageal pH monitoring. Gut 1988; 29(7):886-889.

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

(12) Bredenoord AJ, Weusten BL, Timmer R, Smout AJ. Reproducibility of multichannel intraluminal electrical impedance monitoring of gastroesophageal reflux. Am J Gastroenterol 2005; 100(2):265-269.

(13) Zerbib F, Bruley DES, V, Roman S, Pouderoux P, Artigue F, Chaput U et al. Normal values and day-to-day variability of 24-h ambulatory oesophageal impedance-pH monitoring in a Belgian-French cohort of healthy subjects. Aliment Pharmacol Ther 2005; 22(10):1011-1021.

(14) Boeckxstaens GE, Hirsch DP, Verkleij CB, Lei A, Holman R, Lehmann A et al. Reproducibility of meal-induced transient lower oesophageal sphincter relaxations in patients with gastro-oesophageal reflux disease. Neurogastroenterol Motil 2005; 17(1):23-28

(15) Bredenoord AJ, Weusten BL, Timmer R, Smout AJ. Minimum sample frequency for multichannel intraluminal impedance measurement of the oesophagus. Neurogastroenterol Motil 2004; 16(6):713-719.

(16) Lam HG, Breumelhof R, Roelofs JM, Berge Henegouwen GP, Smout AJ. What is the optimal time window in symptom analysis of 24-hour esophageal pressure and pH data? Dig Dis Sci 1994; 39(2):402-409.

(17) Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1(8476):307-310.

(18) Fleiss JL. Statistical methods for rates and proportions. 2nd ed. New York: John Wiley & Sons, 1981.

(19) Bredenoord AJ, Smout AJ. Oesophageal pH has a power-law distribution in control and gastro-oesophageal reflux disease subjects. Aliment Pharmacol Ther 2005; 21(7):917.

(20) Taghavi SA, Ghasedi M, Saberi-Firoozi M, izadeh-Naeeni M, Bagheri-Lankarani K, Kaviani MJ et al. Symptom association probability and symptom sensitivity index: preferable but still suboptimal predictors of response to high dose omeprazole. Gut 2005; 54(8):1067-71.

(21) Watson RG, Tham TC, Johnston BT, McDougall NI. Double blind cross-over placebo controlled study of omeprazole in the treatment of patients with reflux symptoms and physiological levels of acid reflux--the "sensitive oesophagus". Gut 1997; 40(5):587-590.

(22) Hendrix TR. pH monitoring: is it the gold standard for the detection of gastroesophageal reflux disease? Dysphagia 1993; 8(2):122-124.

(23) Johnston BT. Stress and heartburn. J Psychosom Res 2005; 59(6):425-426.

(24) Cohen LB, Johnson DA, Ganz RA, Aisenberg J, Deviere J, Foley TR et al. Enteryx implantation for GERD: expanded multicenter trial results and interim postapproval follow-up to 24 months. Gastrointest Endosc 2005; 61(6):650-658.

(25) Mahmood Z, Zaheer A, Ang YS, Mahmud N. Endocinch treatment for gastro-oesophageal reflux (GORD): retention of plications are essential to control GORD. Gut 2007; 56(7):1027.

Chapter 4

*"Strength is the capacity to break a chocolate bar into **four** pieces with your bare hands -- and then eat just one of the pieces."*
~ Judith Viorst, American Journalist

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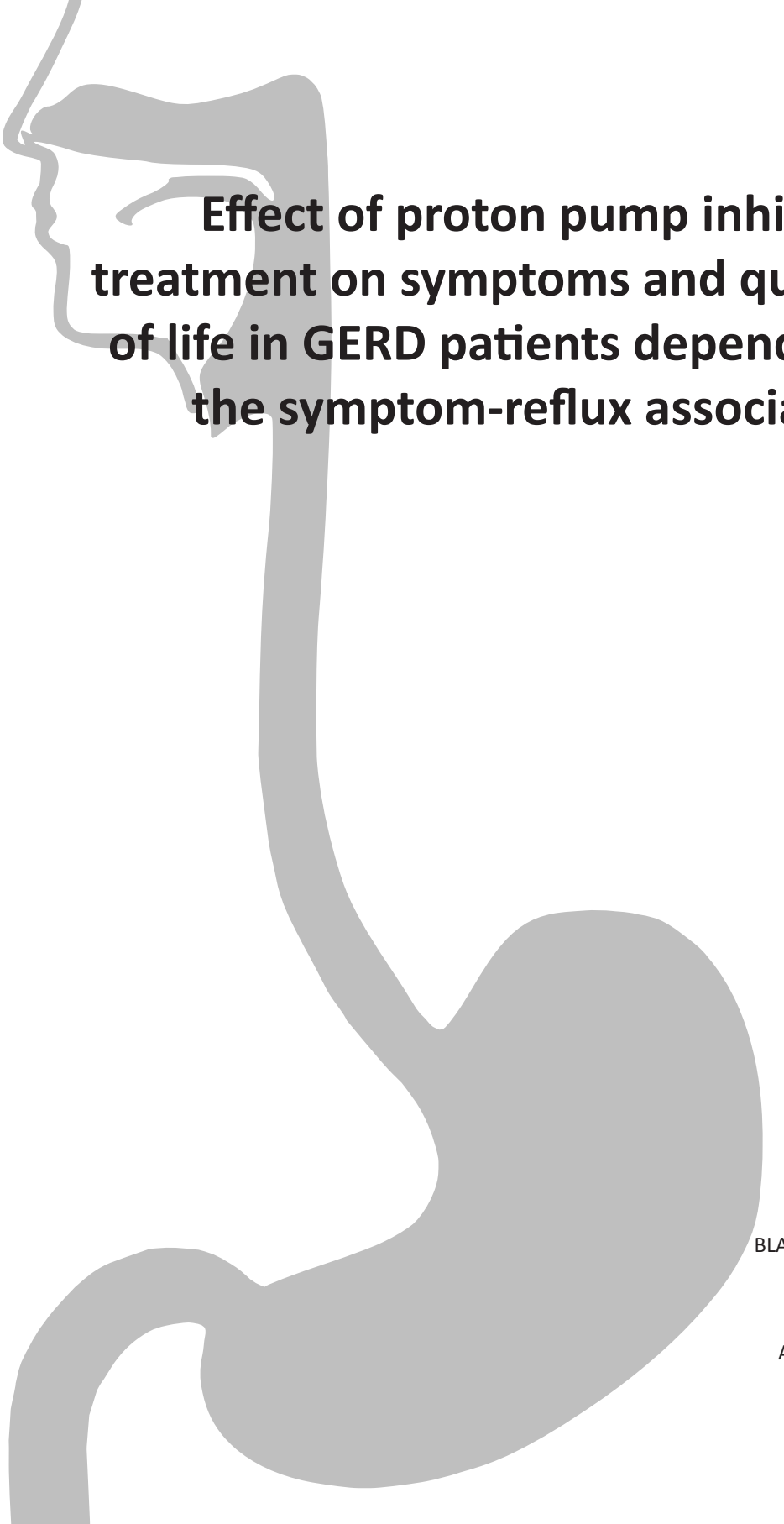


Effect of proton pump inhibitor treatment on symptoms and quality of life in GERD patients depends on the symptom-reflux association

MC Aanen
BLAM Weusten
ME Numans
NJ de Wit
M Samsom
AJPM Smout

ABSTRACT

Backgound

GERD patients demonstrate various pathophysiological backgrounds. Therefore a heterogeneous response to proton-pump inhibitor (PPI) treatment can be expected. We investigated the effect of short-term PPI treatment on symptoms and quality of life (QOL) in primary care patients with and without pathological esophageal acid exposure and in presence or absence of a positive association between symptoms and reflux episodes.

Methods

Seventy-four heartburn patients were categorized into 4 groups according to positive or negative symptom-reflux association, as expressed in symptom index (SI), symptom sensitivity index (SSI) and symptom association probability (SAP) and presence or absence of pathological reflux, defined as esophageal pH<4 for $\geq$6% of the time (pH+/pH-) Overall and specific reflux symptoms were assessed one week before and the last week during a 2-week course of 40mg esomeprazole daily. The QOL was scored by the QOLRAD questionnaire two weeks before treatment and directly after.

Results

Using the SAP to assess symptom-reflux associations, the four groups (SAP+pH+(n=40); SAP+pH-(n=12); SAP-pH+(n=10); SAP-pH-(n=10)) had similar demographic characteristics. The SAP-pH- subgroup had the least overall symptom reduction ((p<0.01) and in the SAP+pH+ subgroup the greatest heartburn symptom reduction was found (p<0.02). The residual symptom scores on treatment were lowest in SAP+pH+ and highest in SAP-pH- subgroups and relatively high in the SAP+pH-. QOL was severely reduced and SAP-pH- patients had the lowest QOL overall. Similar findings were made using SI and SSI.

Conclusion

Symptomatic reflux patients without evidence of reflux disease on a 24-hour pH recording responded less favorably to PPI treatment than patients with a positive symptom-reflux association or with pathological reflux.

INTRODUCTION

Typically, gastroesophageal reflux disease (GERD) patients experience heartburn and regurgitation, but other upper gastrointestinal symptoms may also be reported (1). The presence of GERD-related symptoms has a major impact on a patient's quality of life (QOL) (2). Generic measurements have shown that GERD patients even have a lower QOL than patients with chronic ischemic heart disease (3). However, the QOL can be improved by surgical and/or medical treatment (2;4). Together with life-style advice empirical drug treatment is the first choice therapy for primary care GERD patients. A survey has shown that among general practitioners in the United States the proton pump inhibitors (PPI) are the most commonly prescribed drugs in case of GERD, probably because these drugs have shown to yield the best outcome among the available anti-reflux medication (5;6).

However, GERD has a diverse pathophysiological background and the question remains whether PPIs are equally effective in all types of patients with this disease (7). In a 24-hour pH recording this diversity becomes manifest. Patients can be classified into those with or without pathological reflux and those with or without a positive symptom-reflux association. It can be argued that the best symptom-reflux association index is the symptom association probability (SAP), as it takes into account both the total number of reflux episodes as well as the total number of symptoms, in contrast to the symptom index (SI) and the symptom sensitivity index (SSI) (8).

In the last decade researchers have evaluated the effect of PPI treatment both in patients with GERD in general and in those with erosive reflux disease or non-erosive reflux disease (4;9). Separate treatment evaluation in primary care practice for patients with or without erosive esophageal manifestations seems less relevant as these groups are clinically undistinguishable. Besides, none of these groups has unequivocally been demonstrated to respond differently to short-term PPI treatment (10-12). Studying the effect of PPI treatment in GERD patients who are categorized according to their 24-hour pH recording results might lead to a better insight into this disease. Ideally, knowledge of a patient's pathophysiological background revealed by a distinctive PPI response could support primary care physicians in their management of GERD.

We hypothesized that patients with a positive symptom-reflux correlation would benefit most from PPI treatment as PPIs lead to a reduction of acid reflux events that provoke GERD symptoms. In this study we investigated the effect of short-term PPI treatment on symptoms as well as on the QOL in patients with and without excessive acid exposure and in presence or absence of a positive symptom-reflux association.

METHODS

Patients

Ninety patients suspected of GERD presenting with heartburn at least twice a week for the past 3 months were recruited from the primary care setting, either directly by the primary care physician during consultation (⅓) or indirectly by advertisement (⅔). In addition to heartburn, other symptoms suggestive of GERD (i.e. regurgitation, acid taste, burning sensation in the epigastric region, epigastric pain and chest pain) could be present. None of these patients had used PPIs during the past 3 months and none had used H2-antagonists or prokinetic drugs during the last month. Subjects with a history of gastro-intestinal surgery were excluded, as well as those with alarm symptoms (weight loss, dysphagia or hematemesis). Informed written consent was obtained before the start of the study and the protocol was approved by the Medical Ethics Committee of the University Medical Center, Utrecht.

Measurements

Eighty-eight of the 90 subjects completed the 24-hour esophageal pH monitoring. In 74 subjects an analyzable 24-hour pH data set including at least one reported symptoms episode was obtained. One week after the 24-hour pH recording these 74 patients were treated for two weeks with 40 mg of esomeprazole once a day. Both patients and general practitioners were blinded for the result of the 24-hour pH monitoring until after the study. During one week off treatment and two weeks on treatment subjects kept a diary, scoring their overall reflux symptoms and specific reflux symptoms (i.e. heartburn, regurgitation, acid taste, burning sensation in epigastric region, pain in epigastric region and chest pain) from 0 [absent] to 5 [very severe]. In this study only the mean symptom scores over the seven days before and last seven days on treatment were used.

The QOL was assessed 1 week before the 24-hour recording and 2 weeks after treatment with the Quality of Life in Reflux and Dyspepsia questionnaire (QOLRAD) (13). The QOLRAD, a QOL questionnaire specific for upper gastro-intestinal disease, covers five dimensions: emotional distress, sleep disturbance, problematic food and drink intake, limitations in physical and social functioning and lack of vitality. The validated Dutch QOLRAD is derived from the original English version. Responses to the 25 items are rated on a 7-grade Likert scale in which the lower scores reflect the worst quality of life. This self-administrated questionnaire has been shown to be valid and reliable (13-15).

24-hour pH monitoring

Prior to the 24-hour pH recording the lower esophageal sphincter (LES) was manometrically identified using a 10-channel silicone rubber catheter with a reversed perfused sleeve sensor (DentSleeve International Ltd, Mississauga, Ontario, Canada). All channels were perfused at a rate of 0.2 mL/min with degassed water, using hydraulic flow restrictors (DentSleeve International Ltd, Mississauga, Ontario, Canada). The pressures were recorded with external

pressure transducers (Abbott, Sligo, Ireland). After removal of the manometric catheter, a glass pH catheter with in-built reference electrode (Ingold, Urdorf, Switzerland) was transnasally placed 5 cm above the LES. The pH catheter was calibrated with 3.2 and 7.4 pH buffer solutions. The pH catheter was then attached to a digital datalogger (Orion, MMS, Enschede, the Netherlands) which used a sampling frequency of 2 Hz.

All patients were instructed to record their symptoms by pressing the event marker button on the datalogger and to specify the symptom in a diary card. In the diary card the times of consumption of meals and beverages and the recumbent time were also noted. Patients were instructed to restrict their intake to 3 meals and 3 drinks during the 24 hours. Meals and drinks had to be consumed within 15 and 30 minutes respectively. Patients were encouraged to maintain their normal daily activities during the 24-hour pH study. After the 24-hour recording period the data from the datalogger were transferred to a personal computer.

Registration symptom-reflux association

The 24-hour pH recording data were analyzed automatically (MMS, Enschede, the Netherlands), excluding all eating and drinking periods. Pathological acid exposure was judged to be present when the percentage of time with pH<4 was $\geq$ 6%. The SAP was calculated according to Weusten et al. and was considered positive if it exceeded 95% (16). The SI was defined as the number of reflux-associated symptom episodes divided by the total number of symptom episodes multiplied by 100%. The threshold for a positive SI was set at 50% (17). The SSI was defined as the number of symptom-associated reflux episodes divided by the total number of reflux episodes times 100%. Values above 10% were considered to be positive (18).

Subjects were categorized into 4 subgroups according to the presence or absence of pathological reflux (pH+/pH-) and the presence or absence of a positive symptom-reflux correlation which was determined by the SAP (SAP+/ SAP-), the SI (SI+/SI-) and the SSI (SSI+/SSI+).

Statistical analysis

A chi^2 test was used to determine differences in proportions between the subgroups. Questionnaire scores off and on PPI treatment was analyzed with Wilxocon tests. Kruskall-Wallis tests were used to determine differences between the symptoms or QOLRAD dimensions scores as well as between the 4 subgroups. This analysis was followed by Kruskall-Wallis posthoc tests and Bonferroni corrections. A p value <0.05 was considered statistically significant.
In this study the individual symptom and items scores were summated which resulted in data that was normally distributed. Therefore the data will be presented as means ± standard error of the mean (SEM). However, because of the ordinal discrete nature of the Likert scale non-parametric tests were used for the analysis (19;20).

RESULTS

Basic characteristics of the study population

Gender and age as well as the percentages of patients who consumed alcohol or/and smoked cigarettes were similar in each group. Patients with physiological reflux and a negative symptom-reflux association (SAP-pH-, SI-pH- and SSI-pH-) had a shorter disease history compared to the other 3 subgroups (SAP $p<0.01$, SI $p<0.05$ and SSI $p< 0.05$) (Table 1).

Subgroups		Male	Age	Alcohol	Smoking	Duration symptoms	
						3 months to 1 year	>1 year
	n	(%)	(yr)	(%)	(%)	(n)	(n)
SAP+ pH+	40	63	50.7 ± 2.4	75	18	6	34
SAP+ pH-	12	58	46.3 ± 4.4	58	17	-	34
SAP- pH+	10	70	60.2 ± 3.2	80	10	1	9
SAP- pH-	12	58	50.0 ± 3.6	83	25	7	5
SI+ pH+	38	66	50.5 ± 2.4	76	16	5	33
SI+ pH-	8	38	44.1 ± 4.5	50	13	-	8
SI- pH+	12	58	59.3 ± 3.9	75	17	2	10
SI- pH-	16	69	50.2 ± 3.5	81	25	7	9
SSI+ pH+	20	50	52.9 ± 3.6	70	5	-	20
SSI+ pH-	13	39	45.2 ± 3.8	54	8	2	11
SSI- pH+	30	73	52.4 ± 2.6	80	23	7	23
SSI- pH-	11	82	51.6 ± 4.1	91	36	5	6

Table 1. Basic characteristics of the subgroups of the study population with gastroesophageal reflux disease.

Diary scores in general

At baseline (off medication), the patients indicated to be most bothered by their overall reflux symptoms and in particular by heartburn, burning sensation in epigastrio and regurgitation (Table 2). All symptom scores were significantly reduced during PPI treatment ($p<0.01$, table 2), but the greatest absolute reductions were seen in the scores for heartburn and overall reflux symptoms (Table 2). On treatment, patients found their overall reflux symptoms as well as regurgitation to be more of a nuisance than the other 5 symptoms (Table 2).

Reflux symptoms	Off PPI†	On PPI††	p-value	Delta‡
Overall	2.40 ± 0.09 I	0.94 ± 0.11 I	<0.01	1.38 ± 0.12 III
Heartburn	2.04 ± 0.14 II	0.42 ± 0.10 II	<0.01	1.56 ± 0.15 I
Chest pain	1.20 ± 0.14 VI	0.43 ± 0.11	<0.01	0.71 ± 0.14
Burning sensation in epigastrio	1.85 ± 0.15 III	0.42 ± 0.10	<0.01	1.39 ± 0.15 II
Pain in epigastrio	1.23 ± 0.15 V	0.41 ± 0.10	<0.01	0.78 ± 0.15 V
Acid taste	0.98 ± 0.15	0.43 ± 0.11	<0.01	0.42 ± 0.08
Regurgitation	1.53 ± 0.16 IV	0.59 ± 0.12	<0.01	0.87 ± 0.13 IV

Table 2. Diary scores before (off) and during (on) PPI treatment.

† Posthoc test off PPI

I. Overall vs. heartburn, chest pain, burning epigastrio, pain epigastrio, acid taste, regurgitation p<0.01
II. Heartburn vs. chest pain, burning epigastrio, pain epigastrio, acid taste, regurgitation p<0.01
III. Burning epigastrio vs. chest pain, pain epigastrio, acid taste, regurgitation p<0.01
IV. Regurgitation vs. chest pain, pain epigastrio, acid taste p<0.01
V. Pain epigastrio vs. acid taste p<0.01
VI. Chest pain vs. acid taste p<0.01

†† Posthoc test on PPI

I. Overall vs. heartburn, chest pain, burning epigastrio, pain epigastrio, acid taste, regurgitation p<0.01
II. Regurgitation vs. heartburn, chest pain, burning epigastrio, pain epigastrio, acid taste p<0.01

‡ Posthoc test delta

I. Heartburn vs. overall, chest pain, burning epigastrio, pain epigastrio, acid taste, regurgitation p<0.01
II. Burning epigastrio vs. chest pain, pain epigastrio, acid taste, regurgitation p<0.01
III. Overall vs. chest pain, pain epigastrio, acid taste, regurgitation p<0.01
IV. Regurgitation vs. acid taste, chest pain p<0.01
V. Pain epigastrio vs. acid taste p<0.01

Diary scores of the subgroups

Off medication, the reflux symptoms scores among the 4 subgroups divided according to the presence or absence of pathological reflux (pH+/pH-) and the presence or absence of a positive symptom-reflux correlation were similar (SAP ns, SI ns and SSI ns). However comparison of the absolute reduction in the 4 patient groups demonstrated that the SAP-pH- patients had the least absolute reduction in the overall reflux symptom score following PPI treatment (p<0.01 table 3). For heartburn the greatest absolute score reduction after treatment was found in the SAP+pH+ subgroup (p<0.05 table 3). Patients with SI-pH- had the least absolute reduction for overall symptoms (SI+pH+ 1.69±0.18, SI+pH- 1.55±0.48, SI-pH+ 1.29±0.22, SI-pH- 0.68±0.11, p<0.01).

The symptom scores during treatment differed significantly between the subgroups. Patients with pathological reflux developed the lowest diary symptom scores during treatment while SAP-pH- patients had the highest score for the overall reflux symptoms as well as for the specific symptoms epigastric burning, epigastric pain and chest pain (p<0.01, table 3). Similar findings were found when the subgroups were classified according to SI and SSI.

	SAP+pH+	SAP+pH-	SAP-pH+	SAP-pH-	
On PPI					
Overall	0.67 ± 0.14	1.30 ± 0.31	0.64 ± 0.22	1.70 ± 0.25	p<0.01[I]
Heartburn	0.25 ± 0.10	0.87 ± 0.37	0.23 ± 0.12	0.62 ± 0.29	ns
Epigastric burning	0.20 ± 0.10	0.61 ± 0.27	0.16 ± 0.09	1.13 ± 0.34	p<0.01[II]
Regurgitation	0.30 ± 0.09	0.93 ± 0.42	0.64 ± 0.23	1.08 ± 0.42	ns
Epigastric pain	0.27 ± 0.12	0.44 ± 0.26	0.24 ± 0.20	0.94 ± 0.32	p<0.01[III]
Chest pain	0.22 ± 0.11	0.86 ± 0.40	0.37 ± 0.21	0.65 ± 0.26	p<0.01[IV]
Acid taste	0.20 ± 0.08	0.58 ± 0.35	0.40 ± 0.16	0.99 ± 0.44	ns
Delta					
Overall	1.70 ± 0.16	1.27 ± 0.34	1.20 ± 0.30	0.67 ± 0.14	p<0.01[V]
Heartburn	2.00 ± 0.18	1.20 ± 0.45	1.07 ± 0.29	1.04 ± 0.25	p<0.05[VI]
Epigastric burning	1.69 ± 0.21	1.55 ± 0.41	0.80 ± 0.32	0.79 ± 0.21	
Regurgitation	1.15 ± 0.20	0.89 ± 0.32	0.47 ± 0.30	0.35 ± 0.15	
Epigastric pain	0.83 ± 0.23	1.08 ± 0.39	0.30 ± 0.14	0.68 ± 0.32	
Chest pain	0.87 ± 0.20	0.68 ± 0.41	0.10 ± 0.08	0.79 ± 0.29	
Acid taste	0.46 ± 0.12	0.26 ± 0.19	0.56 ± 0.21	0.36 ± 0.19	

Table 3. Diary symptom scores during PPI treatment (on PPI) and the absolute reduction (delta) before and during PPI treatment in the 4 subgroups classified by SAP. SI and SSI had similar outcomes.
Posthoc tests symptom scores

I. SAP+pH+ vs SAP-pH-; SAP+pH- vs SAP-pH+; SAP-pH+ vs SAP-pH- p<0.01 and SAP+pH+ vs SAP+pH-; SAP+pH- vs SAP-pH- p<0.05
II. SAP+pH+ vs SAP-pH-; SAP-pH+ vs SAP-pH- p<0.01 and SAP+pH+ vs SAP+pH-; SAP+pH- vs SAP-pH+ p<0.05
III. SAP+pH+ vs SAP-pH-; SAP+pH- vs SAP-pH-; SAP-pH+ vs SAP-pH- p<0.01
IV. SAP+pH+ vs SAP-pH-; SAP-pH+ vs SAP-pH- <0.01 and SAP+pH+ vs SAP+pH- p<0.05
V. SAP+pH+ vs SAP-pH-; SAP+pH- vs SAP-pH-; SAP-pH+ vs SAP-pH- p<0.01
VI. SAP+pH+ vs SAP-pH-; SAP+pH+ vs SAP-pH+ p<0.01 and SAP+pH+ vs SAP+pH- p<0.05

Dimensions	Pre-treatment†	Post-treatment	p-value	Delta‡
Total	5.4 ± 0.1	6.6 ± 0.1	<0.01	-1.08 ± 0.97
Emotional	5.5 ± 0.2	6.6 ± 0.1	<0.01	-1.13 ± 1.27
Sleep	5.4 ± 0.2	6.6 ± 0.1	<0.01	-1.18 ± 1.24
Food & drink	4.7 ± 0.2	6.4 ± 0.1	<0.01	-1.66 ± 1.20
Social & physical	6.6 ± 0.1	6.7 ± 0.1	<0.05	-0.18 ± 0.64
Vitality	5.2 ± 0.2	6.5 ± 0.1	<0.01	-1.29 ± 1.23

Table 4. QOLRAD scores pre- and post-treatment and the differences between these (delta).
† Posthoc pre-treatment

I. Food & drink vs total, emotional, sleep, social & physical, vitality p<0.01
II. Social and physical vs total, emotional, sleep, vitality p<0.01
III. Emotional vs vitality p<0.05

‡ Posthoc delta

I. Food & drink vs total, emotional, sleep, social & physical, vitality p<0.01
II. Physical & social vs total, emotional, sleep, vitality p<0.01

Quality of life (QOL)

Off medication the QOLRAD dimension problematic food and drink intake had the lowest scores while the dimension social and physical functioning the highest (Table 4). Similar baseline QOL dimension scores were seen among the 4 subgroups (SAP, SI or SSI). The PPI treatment significantly improved all QOLRAD scores (Table 4). The greatest absolute improvement in the QOL was found in the problematic food and drink intake domain and the smallest reduction was seen in the physical and social functioning domain (Table 4). In the QOL analysis in the subgroups we found that SAP-pH- had least improvement and SAP+pH- had the best absolute improvement for the dimension physical and social ($p<0.05$, table 5). SSI-pH- patients had the least absolute improvement in the QOL dimension problematic food and drink intake (SSI+pH+ -1.60$\pm$0.24, SSI+pH- -1.62$\pm$0.32, SSI-pH+ -2.00$\pm$0.22, SSI-pH- -0.91$\pm$0.36, $p<0.05$).

No significant differences between the dimensions were found after PPI treatment in the whole study group (Table 4). However, differences did exist between the subgroups. SAP+pH+ patients reached the highest scores followed closely by SAP+pH- and SAP-pH+ for the total QOLRAD score, the dimension problematic food and drink intake and the dimension sleep ($p<0.05$, Table 5). For the dimensions emotional and vitality patients with pathological reflux had the best scores ($p<0.05$, Table 5). In the subgroups formed according to SI and SSI similar findings were seen.

	SAP+pH+	SAP+pH-	SAP-pH+	SAP-pH-	
post PPI					
Total	6.71 ± 0.10	6.48 ± 0.19	6.57 ± 0.17	6.10 ± 0.26	$p<0.01^{I}$
Emotional	6.75 ± 0.10	6.43 ± 0.24	6.80 ± 0.13	6.00 ± 0.36	$p<0.05^{II}$
Sleep	6.71 ± 0.12	6.60 ± 0.24	6.47 ± 0.23	6.13 ± 0.28	$p<0.05^{III}$
Food & drink	6.62 ± 0.13	6.30 ± 0.26	6.26 ± 0.28	5.86 ± 0.27	$p<0.05^{IV}$
Social & physical	6.80 ± 0.07	6.76 ± 0.09	6.80 ± 0.12	6.47 ± 0.19	ns
Vitality	6.69 ± 0.11	6.23 ± 0.22	6.56 ± 0.20	6.11 ± 0.32	$p<0.05^{V}$
Delta					
Total	-1.27 ± 0.15	-0.94 ± 0.17	-1.19 ± 0.46	-0.89 ± 0.32	ns
Emotional	-1.14 ± 0.20	-0.92 ± 0.19	-1.09 ± 0.56	-1.13 ± 0.39	ns
Sleep	-1.21 ± 0.22	-1.06 ± 0.28	-1.11 ± 0.36	-0.98 ± 0.39	ns
Food & drink	-1.81 ± 0.18	-1.42 ± 0.37	-1.67 ± 0.49	-1.04 ± 0.35	ns
Social & physical	-0.21 ± 0.07	-0.56 ± 0.32	-0.16 ± 0.26	0.22 ± 0.17	$p<0.01^{VI}$
Vitality	-1.53 ± 0.18	-0.80 ± 0.26	-1.04 ± 0.60	-0.89 ± 0.42	ns

Table 5. QOLRAD scores after PPI treatment (post PPI) and the absolute reduction after treatment (delta) in the subgroups classified according to SAP. SI and SSI had similar results.
Posthoc tests QOLRAD scores

I. SAP+pH+ vs. SAP-pH-; SAP-pH+ vs. SAP-pH- $p<0.01$ & SAP+pH+ vs. SAP+pH- $p<0.05$
II. SAP+pH+ vs. SAP+pH-; SAP+pH+ vs. SAP-pH-; SAP+pH- vs. SAP-pH+; SAP-pH+ vs. SAP-pH-$p<0.01$
III. SAP+pH+ vs. SAP-pH-; SAP+pH- vs. SAP-pH+; SAP-pH+ vs. SAP-pH-$p<0.01$
IV. SAP+pH+ vs. SAP-pH-; SAP+pH- vs. SAP-pH-; SAP-pH+ vs. SAP-pH- $p<0.01$
V. SAP+pH+ vs. SAP+pH-; SAP+pH- vs. SAP-pH+ $p<0.01$ & SAP+pH+ vs. SAP-pH-; SAP-pH+ vs. SAP-pH- $p<0.05$
VI. SAP+pH+ vs. SAP-pH-; SAP+pH- vs. SAP-pH+; SAP+pH- vs. SAP-pH- $p<0.01$ & SAP-pH+ vs. SAP-pH- $p<0.05$

DISCUSSION

Up to now many studies on the therapy of GERD have either treated GERD patients as a uniform group or have classified them on the basis of endoscopic findings, i.e. as suffering from erosive reflux disease (ERD) or non-erosive reflux disease (NERD) (4;9). Although it has been suggested that ERD patients have a better response to PPI treatment, direct comparisons between ERD and NERD patient groups did not demonstrate major differences (6;11;21-24). Evidence is accumulating, however, that the mechanisms involved in the pathogenesis of GERD are diverse and that GERD patients actually form a heterogeneous group (11;25). We hypothesized that the symptomatic response to short-term PPI treatment is determined more by the characteristics of the reflux and reflux perception than by the severity of mucosal damage. In this study we evaluated the effect of a short-term PPI treatment in patients who were classified according to their 24-hour pH recording as having a positive symptom-reflux association and/or a pathological reflux or neither of these outcomes. This resulted in the finding that, despite a general good improvement of symptom and quality of life scores, patients divided according to their pathophysiological characteristics did not respond similarly.

The main differences in response to treatment were:
1) The symptomatic response to short-term PPI treatment was poorest in patients without any evidence of reflux disease on esophageal pH recording while patients with a positive SAP as well as pathological reflux had the best response. Residual symptom scores during treatment were lowest in patients with pathological reflux and highest in patients without evidence of reflux disease.

2) Reflux disease had a severe impact on the quality of life. Upon PPI treatment patients with a positive SAP and physiological reflux had the greatest improvement in the QOL domain social and physical well-being. In general the QOL after treatment was lowest in patients without any evidence of reflux disease on 24-hour pH recording.

In this study, no major differences were found between the indices of symptom-reflux association (SI, SSI and SAP) used. The best responders to PPI treatment were those who had either a positive SAP or SI or SSI in combination with pathological reflux. Thus, although studies have suggested a bad concordance between SAP, SI and SSI, the symptomatic response to PPI treatment was predicted equally well by the SAP, the SI and the SSI (26;27). Nevertheless, we still feel that the SAP better indicates whether symptoms are caused by reflux events as this index incorporates both symptoms and reflux events. The SI overestimates the strength of the association between symptoms and reflux when reflux events are frequent and the SSI does so when symptoms are abundantly expressed (8;17;18).

Patients with a positive symptom-reflux association have a proven relationship of symptomatic response to acidic reflux, therefore we had expected that these patients would experience the greatest symptom reduction and the greatest improvement of QOL on PPI treatment, irrespective of the severity of esophageal acid exposure. Even though patients with pathological reflux and positive SAP performed overall best, patients with physiological reflux and positive SAP showed only a modest response. This latter finding probably reflects

the presence of a more pronounced visceral hypersensitivity in patients with a positive SAP and non-pathological reflux. During adequate PPI treatment these patients still appear to perceive the presence of small amounts of acid and/or non-acid gastric fluids in their esophagus (26). Whether this hypersensitive reaction is due to the presence of microscopic esophageal tissue lesions or due to the occurrence of longitudinal muscle contractions remains to be studied (25).

The PPI treatment effect was smallest in patients with a negative SAP and physiological reflux. One of the possible explanations of this finding is that in this subgroup of patients, the 24-hour pH recording fails to demonstrate a relationship between symptoms and acid reflux because these patients are also hypersensitive to non-acidic reflux (26;28). During PPI treatment acid reflux becomes predominantly non-acidic (26;29). However, when non-acid reflux is included in the SAP calculation, approximately 10% of patients shifts from a negative to a positive SAP (28). Therefore, in some patients the pathophysiological origin of their presenting symptom and reduced QOL remains unknown and the question is whether one should consider these patients as having functional GERD or as not having GERD at all. It has been shown that an overlap exists between GERD and other functional gastro-intestinal disorders, indicating a possible common pathophysiological origin (30;31). In addition, perhaps higher levels of psychological stress exist in this subgroup of patients, increasing thereby the perception of reflux symptoms (32;33).

Reflux symptoms can resolve spontaneously but the vast majority of GERD patients will have symptomatic GERD throughout their life-time. Luckily most primary care patients do not develop any GERD-related complications when treated adequately (34;35). Although the response to a prolonged PPI treatment was not investigated in this study it is likely that some subjects eventually will become “non-responders” (36). It has been reported that a bad symptomatic response to a PPI in the first week is predictive of PPI treatment failure (37). Although real evidence is still lacking, our results might indicate that due to their poor response to short-term PPI treatment patients with a negative SAP and physiological reflux might be to ones who become non-responders.

Information on a patient’s reflux characteristics and esophageal sensitivity might be helpful in the management of GERD, especially when symptoms are resistant to therapy. However, treatment options for functional and hypersensitive GERD patients seem to be limited. It has been shown that these patients not only fail to respond to acid-reducing medications, but also are not the ideal candidates for surgical anti-reflux treatment (38;39). It has been suggested that low doses of an anti-depressant may be helpful in this group but clinical trials are still lacking (40). In order to identify adequate treatment for these patients, further research is needed, especially in the subgroups of patients with physiological reflux.

In conclusion, we demonstrated that patients with reflux symptoms in whom no evidence of reflux disease is found on a 24-hour pH recording respond less favorably to PPI treatment than patients with a positive symptom-reflux association or pathological reflux. This poor response concerns symptoms as well as QOL. Management of patients with physiological reflux, with or without a positive symptom-reflux association is likely to pose the greatest problems.

REFERENCES

(1) Rothman M, Farup C, Stewart W, Helbers L, Zeldis J. Symptoms associated with gastroesophageal reflux disease: development of a questionnaire for use in clinical trials. Dig Dis Sci 2001; 46(7):1540-1549.

(2) Irvine EJ. Quality of life assessment in gastro-oesophageal reflux disease. Gut 2004; 53 Suppl 4:35-39.

(3) Wiklund I. Review of the quality of life and burden of illness in gastroesophageal reflux disease. Dig Dis 2004; 22(2):108-114.

(4) Bytzer P. Goals of therapy and guidelines for treatment success in symptomatic gastroesophageal reflux disease patients. Am J Gastroenterol 2003; 98(3 Suppl):S31-S39.

(5) Chey WD, Inadomi JM, Booher AM, Sharma VK, Fendrick AM, Howden CW. Primary-care physicians' perceptions and practices on the management of GERD: results of a national survey. Am J Gastroenterol 2005; 100(6):1237-1242.

(6) van Pinxteren B, Numans ME, Lau J, de Wit NJ, Hungin AP, Bonis PA. Short-term treatment of gastroesophageal reflux disease. J Gen Intern Med 2003; 18(9):755-763.

(7) Jones R, Galmiche JP. Review: what do we mean by GERD?--definition and diagnosis. Aliment Pharmacol Ther 2005; 22 Suppl 1:2-10.

(8) Bredenoord AJ, Weusten BL, Smout AJ. Symptom association analysis in ambulatory gastro-oesophageal reflux monitoring. Gut 2005; 54(12):1810-1817.

(9) Fass R, Fennerty MB, Vakil N. Nonerosive reflux disease--current concepts and dilemmas. Am J Gastroenterol 2001; 96(2):303-314.

(10) Johnsson F, Weywadt L, Solhaug JH, Hernqvist H, Bengtsson L. One-week omeprazole treatment in the diagnosis of gastro-oesophageal reflux disease. Scand J Gastroenterol 1998; 33(1):15-20.

(11) Kulig M, Leodolter A, Vieth M, Schulte E, Jaspersen D, Labenz J et al. Quality of life in relation to symptoms in patients with gastro-oesophageal reflux disease-- an analysis based on the ProGERD initiative. Aliment Pharmacol Ther 2003; 18(8):767-776.

(12) van Pinxteren B, Numans M, Bonis P, Lau J. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev 2006; 3:CD002095.

(13) Talley NJ, Fullerton S, Junghard O, Wiklund I. Quality of life in patients with endoscopy-negative heartburn: reliability and sensitivity of disease-specific instruments. Am J Gastroenterol 2001; 96(7):1998-2004.

(14) Borgaonkar MR, Irvine EJ. Quality of life measurement in gastrointestinal and liver disorders. Gut 2000; 47(3):444-454.

(15) Wiklund IK, Junghard O, Grace E, Talley NJ, Kamm M, Veldhuyzen van Zanten S et al. Quality of Life in Reflux and Dyspepsia patients. Psychometric documentation of a new disease-specific questionnaire (QOLRAD). Eur J Surg Suppl 1998;(583):41-49.

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

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

(18) Breumelhof R, Smout AJ. The symptom sensitivity index: a valuable additional parameter in 24-hour esophageal pH recording. Am J Gastroenterol 1991; 86(2):160-164.

(19) Clason DL, Dormody TJ. Analyzing data measured by individual likert-type items. Journal of Agricultural Education 1994; 35(4):31-35.

(20) Whitley E, Ball J. Statistics review 6: Nonparametric methods. Crit Care 2002; 6(6):509-513.

(21) Bate CM, Green JR, Axon AT, Tildesley G, Murrays FE, Owen SM et al. Omeprazole is more effective than cimetidine in the prevention of recurrence of GERD-associated heartburn and the occurrence of underlying oesophagitis. Aliment Pharmacol Ther 1998; 12(1):41-47.

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

(23) Johnsson F, Hatlebakk JG, Klintenberg AC, Roman J. Symptom-relieving effect of esomeprazole 40 mg daily in patients with heartburn. Scand J Gastroenterol 2003; 38(4):347-353.

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

(25) Orlando RC. The pathogenesis of gastroesophageal reflux disease: the relationship between epithelial defense, dysmotility, and acid exposure. Am J Gastroenterol 1997; 92(4 Suppl):3S-5S.

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

(27) Taghavi SA, Ghasedi M, Saberi-Firoozi M, izadeh-Naeeni M, Bagheri-Lankarani K, Kaviani MJ et al. Symptom association probability and symptom sensitivity index: preferable but still suboptimal predictors of response to high dose omeprazole. Gut 2005; 54(8):1067-71.

(28) Bredenoord AJ, Weusten BL, Timmer R, Conchillo JM, Smout AJ. Addition of esophageal impedance monitoring to pH monitoring increases the yield of symptom association analysis in patients off PPI therapy. Am J Gastroenterol 2006; 101(3):453-459.

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

(30) Kennedy TM, Jones RH, Hungin AP, O'flanagan H, Kelly P. Irritable bowel syndrome, gastro-oesophageal reflux, and bronchial hyper-responsiveness in the general population. Gut 1998; 43(6):770-774.

(31) Talley NJ. A unifying hypothesis for the functional gastrointestinal disorders: really multiple diseases or one irritable gut? Rev Gastroenterol Disord 2006; 6(2):72-78.

(32) Bradley LA, Richter JE, Pulliam TJ, Haile JM, Scarinci IC, Schan CA et al. The relationship between stress and symptoms of gastroesophageal reflux: the influence of psychological factors. Am J Gastroenterol 1993; 88(1):11-19.

(33) Wright CE, Ebrecht M, Mitchell R, Anggiansah A, Weinman J. The effect of psychological stress on symptom severity and perception in patients with gastro-oesophageal reflux. J Psychosom Res 2005; 59(6):415-424.

(34) Pace F, Bollani S, Molteni P, Bianchi PG. Natural history of gastro-oesophageal reflux disease without oesophagitis (NERD)--a reappraisal 10 years on. Dig Liver Dis 2004; 36(2):111-115.

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

(36) Fass R, Shapiro M, Dekel R, Sewell J. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease--where next? Aliment Pharmacol Ther 2005; 22(2):79-94.

(37) Talley NJ, Armstrong D, Junghard O, Wiklund I. Predictors of treatment response in patients with non-erosive reflux disease. Aliment Pharmacol Ther 2006; 24(2):371-376.

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

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

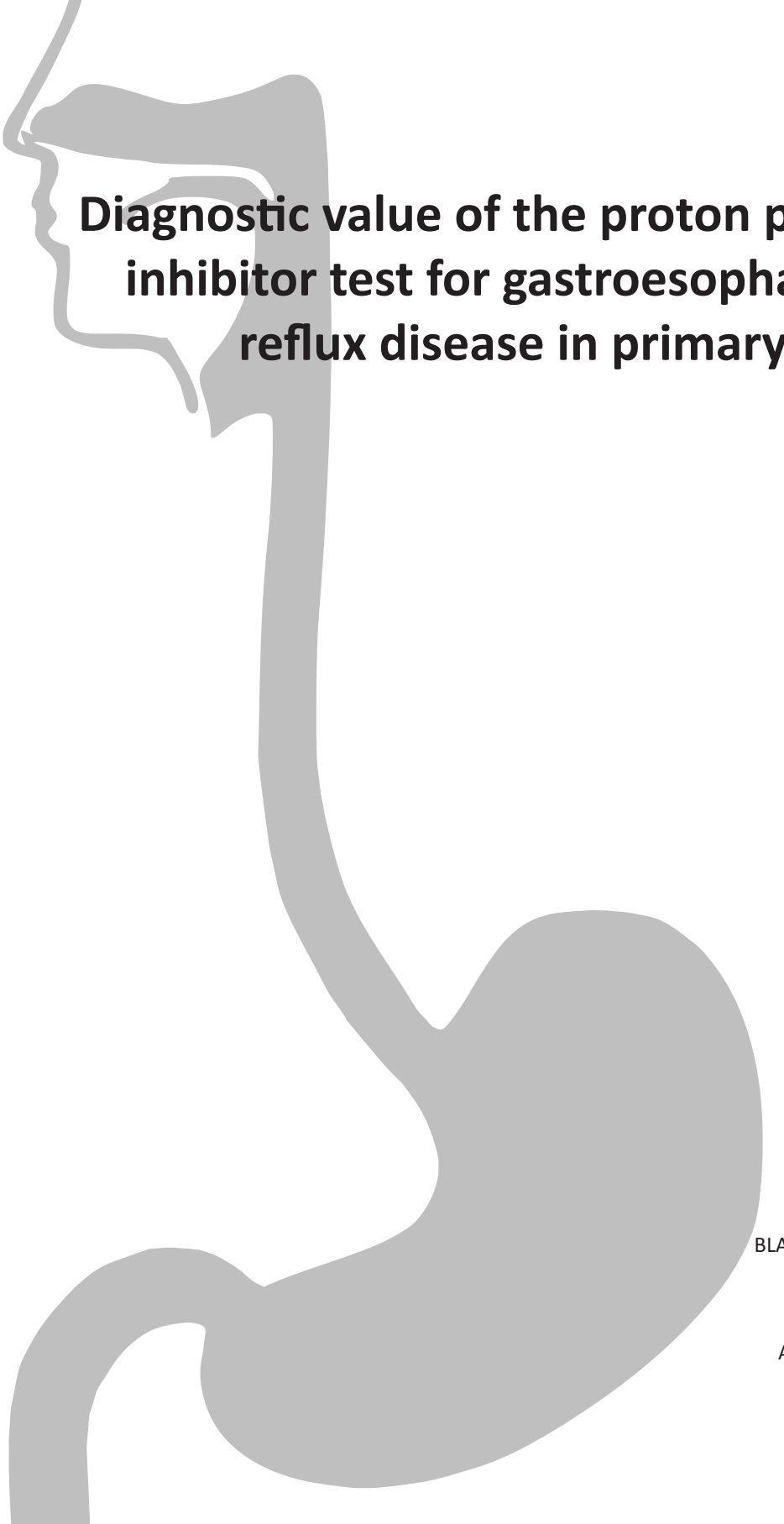
(40) Fass R, Tougas G. Functional heartburn: the stimulus, the pain, and the brain. Gut 2002; 51(6):885-892

Chapter 5

*"He who asks is a fool for **five** minutes,*
but he who does not ask remains a fool forever."
~ Chinese Proverb

Alimentary Pharmacology Therapeutics 2006

Diagnostic value of the proton pump inhibitor test for gastroesophageal reflux disease in primary care



MC Aanen
BLAM Weusten
ME Numans
NJ de Wit
A Baron
AJPM Smout

ABSTRACT

Background

To assess the diagnostic accuracy of the proton pump inhibitor test in a primary care population as well as its additional value over reflux history, using the symptom association probability outcome during 24-h esophageal pH recording as reference test for gastroesophageal reflux disease.

Methods

Subjects with symptoms suggestive of gastroesophageal reflux disease were recruited from primary care. After a 24-h pH recording with calculation of the symptom association probability, subjects started using 40 mg esomeprazole once daily for 13 days. The proton pump inhibitor test was considered positive when the subjects reported adequate symptom suppression. Data are presented as means with 95% confidence intervals.

Results

Successful 24-h pH recording was accomplished in 84 of the 90 subjects, while the symptom association probability was calculable in 74. The symptom association probability was positive in 70% of the subjects. The sensitivity of the proton pump inhibitor test was 0.91 (CI 0.78–0.96) and the specificity was 0.26 (CI 0.10–0.49). The mean likelihood ratio was 1.2 (CI 0.9–1.6) with little variation over the 13 consecutive proton pump inhibitor test days. The likelihood ratios of gastroesophageal reflux disease symptoms were comparable, ranging around 1.

Conclusion

In primary care patients with reflux symptoms gastroesophageal reflux disease is highly prevalent. Under these conditions the additional value of short-term treatment with a proton pump inhibitor for diagnosing gastroesophageal reflux disease is limited.

INTRODUCTION

Reflux symptoms are very common in the general population and most of the care-seeking patients wit these symptoms are managed in the general practice (1). It has been shown that diagnosing gastroesophageal reflux disease (GERD) on the basis of the presence of the typical reflux symptoms heartburn and acid regurgitation is suboptimal. An overall diagnosis made by gastroenterologists based on symptoms had a specificity of 78% and sensitivity of 60% (2;3). Therefore, the response to a short course of an acid suppressant is often used as an additional diagnostic tool, in particular by general practitioners. This method has been labelled the proton pump inhibitor (PPI) test.

However, it is not known what a PPI test adds to reflux history, and, despite many studies, evidence concerning the diagnostic accuracy of the PPI test for the general population is lacking (4-13). Up to now, most studies on the diagnostic value of the PPI test were carried out in secondary and tertiary referral patients resulting in referral or spectrum bias (14). Furthermore, disputable reference tests have been used, such as the presence of oesophagitis, pathological reflux or both, thereby excluding a large group of patients who do not exhibit these features, but nevertheless do have GERD (15;16).

The symptom–reflux association analysis therefore seems to be a better test as it determines whether symptoms are caused by reflux events (17). Several calculations are possible such as the symptom index (SI), symptom sensitivity index (SSI) and symptom association probability (SAP) (17-20). Of these three methods the SAP provides the best assessment of the relationship between reflux and symptoms as it takes both the total number of reflux episodes as well as the total number of symptoms into account, in contrast to SI and SSI (17). A recent study has shown that the SSI and the SAP are both significantly related to the symptomatic response to a high dose of omeprazole (21).

The aim of this study was to determine the diagnostic accuracy of the PPI test in a primary care population using the SAP outcome as reference test. Furthermore, we wished to evaluate the additional value of the PPI test over a reflux history in the diagnosis of GERD.

METHODS

Patients

Patients with 'typical' reflux symptoms who were considered likely to have GERD were recruited from primary care practices and by local advertisement. The general practitioner (in case of primary care recruitment) or the research nurse (in case of recruitment by advertisement) judged whether the patient had symptoms suggestive of reflux disease (i.e. heartburn, regurgitation, acid taste, burning sensation in the epigastric region, epigastric pain and chest pain). Patients had to have these symptoms for at least twice a week for the past 3 months or longer to be included. Patients with atypical reflux symptoms, such as hoarseness, coughing and 'gastric asthma', were not eligible for the study. Subjects were not included when they had undergone gastro-intestinal surgery or when they needed endoscopic evaluation because of alarm symptoms (weight loss, dysphagia or haematemesis). In order to avoid interference with drug effects, patients who had used PPIs longer than 30 days in the past 3 months or used H2-antagonists or prokinetic drugs during the last month, were excluded. Pregnant and lactating women were not allowed to participate in the study, and phenytoin and diazepam were prohibited because of possible drug interaction. Informed written consent was obtained before the start of the study and the protocol was approved by the Medical Ethics Committee of the University Medical Center, Utrecht.

Study protocol

On day 1 of the study, at baseline, the frequency and severity of symptoms suggestive of GERD were scored on a 6-point Likert scale (0 none to 5 daily/very bothersome). Subsequently, the frequency and severity scores were multiplied. Seven days later the patient underwent a 24-h esophageal pH monitoring. After the recording the patient used 40 mg of esomeprazole daily for 2 weeks. During these 2 weeks the patient had to answer daily whether his or her reflux symptoms were adequately suppressed (yes/no) (16). The response to this question was used to judge whether the PPI test was positive or negative. Patients and general practitioners were blinded to the results of the 24-h pH monitoring until the end of the study.

24-h pH monitoring

Prior to the 24-h pH recording the lower esophageal sphincter (LES) was manometrically identified using a 10-channel silicone rubber catheter with a reversed sleeve sensor (DentSleeve International Ltd, Mississauga, ON, Canada) which was perfused at a rate of 0.2 mL/min with degassed water, using hydraulic flow restrictors (DentSleeve International Ltd). The pressures were recorded with external pressure transducers (Abbott, Sligo, Ireland). After removal of the manometric catheter, a glass pH catheter with in-built reference electrode (Ingold, Urdorf, Switzerland) was transnasally placed 5 cm above the LES. The pH catheter was calibrated with 3.2 and 7.4 pH buffer solutions. The pH catheter was then attached to a digital datalogger (MMS, Enschede, the Netherlands) which used a sampling frequency of 2 Hz.

All patients were instructed to record each of their symptoms by pressing the event marker button on the datalogger as well as by specifying the symptom in a diary card. The times of consumption of meals and beverages and the recumbent time were also noted. Patients were instructed to restrict their intake to three meals and three drinks during the 24 h at standardized times. Meals and drinks had to be consumed within 15 and 30 min respectively. Patients were encouraged to maintain their normal daily activities during the 24-h pH study. After the 24-h recording period, data from the datalogger were transferred to a personal computer.

Data analysis

The 24-h pH recording data were analyzed automatically (MMS), excluding all eating and drinking periods. The SAP was calculated according to Weusten et al. and was considered positive if it exceeded 95% (20).

The SI was defined as the number of reflux-associated symptom episodes divided by the total number of symptom episodes multiplied by 100%. The threshold for a positive SI was set at 50% (19). The SSI was defined as the number of symptom-associated reflux episodes divided by the total number of reflux episodes multiplied by 100%. Values above 10% were considered to be positive (18).

The sensitivity, specificity and predictive values were calculated using a 2 x 2 contingency table. For each of the 13 PPI test days, comparisons were made between the symptomatic response and with each of the three symptom–reflux association indices: SAP, SI and SSI. Therefore, only patients with calculable symptom–reflux associations were further analyzed (see Figure 1).

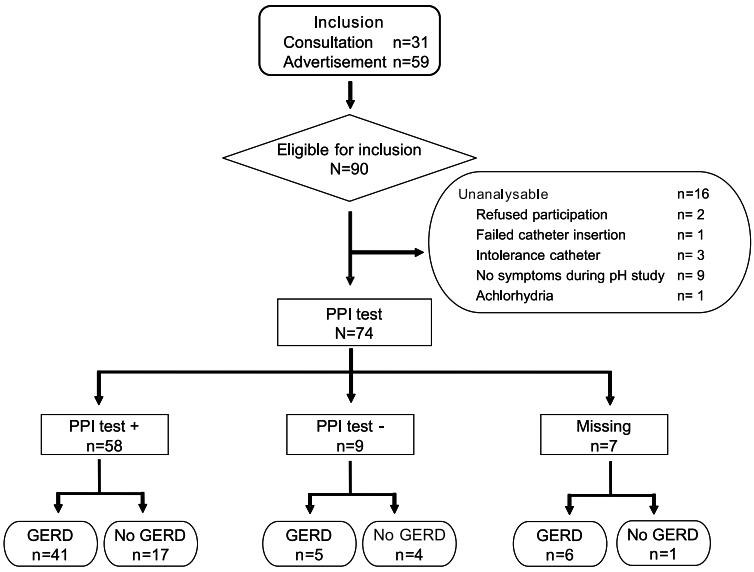


Figure 1. Flowchart showing the inclusion as well as the number of patients during the final proton pump inhibitor (PPI) test (day 13) who did and did not have gastroesophageal reflux disease (GERD). The missing number reflects the number of patients who did not answer whether their symptoms were adequately suppressed by the PPI and were excluded from analysis.

The presence of a reflux symptom (i.e. positive result), indicated when a score higher than 0 was present after multiplying the frequency and severity scores of the reflux symptoms of the past 4 weeks found at baseline, was compared to the SAP outcome.

The sensitivity of the PPI test or the presence of a reflux symptom was defined as the fraction of all individuals with the disease in whom a positive result was obtained, specificity was calculated as the fraction of those without the disease who yielded a negative test result. Predictive values indicated the chance of whether the test result was really true. Likelihood ratios, which express the discriminating power of the test, were calculated by dividing the sensitivity by 1 minus specificity.

Statistical analysis

In order to determine whether the recruitment of patients directly by GP and indirectly by advertisement led to spectrum bias, a chi-squared test was performed with a Yates continuity correction (14;22). Differences between outcomes assessed by the three symptom–reflux association indices were assessed by an ANOVA test and Bonferroni post hoc tests. Statistically significant differences were judged to be present when $p < 0.05$. Results are presented as mean with a 95% confidence interval (CI).

RESULTS

Ninety patients with reflux symptoms of which 74 were analyzable were included between 2003 and 2005 in the study (see Figure 1). The 74 subjects had a median age of 51 years (41–62). Sixty-two per cent were male, 21% smoked and 74% used alcoholic beverages. Four patients had used a PPI and four patients an H2-antagonist in the past. Thirty-nine patients used antacids before this study. Three patients had undergone eradication therapy for Helicobacter pylori and one patient had a history of gastric ulcers.

The prevalence of symptoms and symptom scores of the 74 patients found at baseline are shown in Table 1. Heartburn was the most frequently reported symptom (82% of the patients). In total, the SAP, SI and SSI calculations indicated a positive symptom–reflux association in 70%, 62% and 45% of the patients respectively. The 24-h pH monitoring data are shown in Table 2.

	Symptom prevalence (%)	Symptom score, mean (95% CI)
Reflux symptoms	**Total**	**Total**
Heartburn	82	10.1 (8.3–11.7)
Regurgitation	75	5.6 (3.8–7.4)
Epigastric burning	70	8.4 (6.6–10.2)
Acid taste	48	5.3 (3.5–7.1)
Chest pain	46	4.7 (3.0–6.5)
Epigastric pain	44	7.7 (5.8–9.5)
Chest pain	46	4.7 (3.0–6.5)
Epigastric pain	44	7.7 (5.8–9.5)

Table 1. Symptom scores and the prevalence of reflux symptoms at baseline
CI: confidence interval

		Percentiles		
	Median	**25th**	**75th**	**Reference**
Time with pH <4 upright (%)	9.6	4.4	15.6	9
Time with pH <4 supine (%)	2.9	0.2	9.3	2
Time with pH <4 total (%)	7.7	4.9	11.4	7
Number of reflux episodes upright (n)	47.5	27.8	72.0	29
Number of reflux episodes supine (n)	3.5	1.0	11.0	1
Number of reflux episodes total (n)	53.0	33.8	78.5	29
Number of symptom episodes (n)	9.0	4.8	13.3	0
Number of reflux-related episodes (n)	5.0	2.0	9.3	0

Table 2. Results of 24-h pH measurement and reference values (28)

The SAP outcome as well as the outcomes of the 13 PPI tests in the group recruited by GP were similar to those in the group recruited by advertisement. The sensitivities of the PPI test obtained with the SAP (0.91, CI 0.78 -0.96) and the SI (0.90, CI 0.77–0.96) as reference standard were statistically higher than those obtained with the SSI as standard (0.83, CI 0.65–0.93) (SAP vs. SSI, SI vs. SSI $p < 0.01$, see Figure 2a).

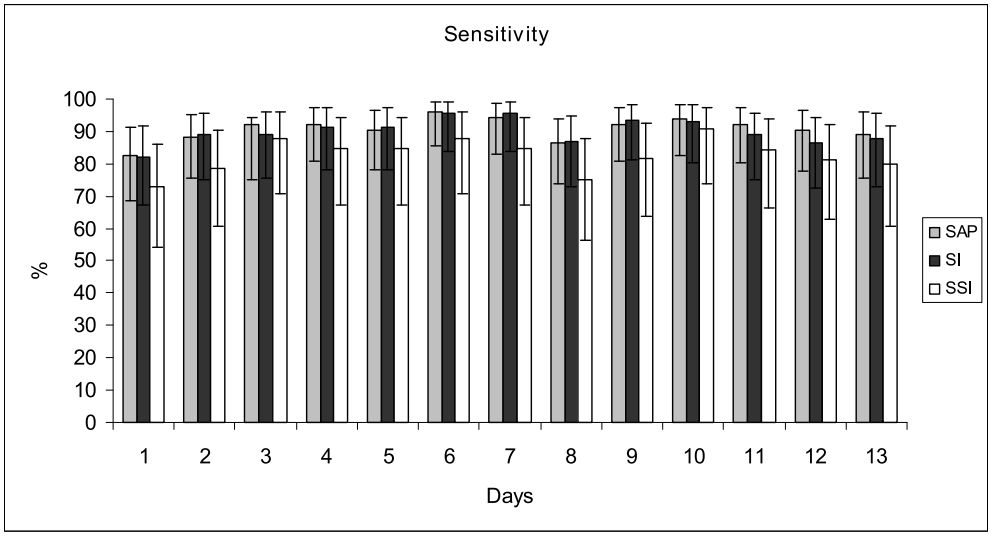
The specificities of the PPI test calculated with SAP (0.26, CI 0.10–0.49) and SI (0.21, CI 0.09–0.42) as reference standard differed significantly from the specificity obtained by the SSI (0.11, CI 0.04–0.26) (SAP vs. SSI, SI vs. SSI $p < 0.01$, see Figure 2b).

The sensitivity and specificity of the found reflux suggestive symptoms are shown in Table 3. The presence of all reflux suggestive symptoms gave a sensitivity of 0.59 (CI 0.45–0.72) and a specificity of 0.43 (CI 0.23–0.65) with the SAP as reference test.

The positive predictive value of the PPI test with the SAP as reference standard (0.75, CI 0.62–0.85) was significantly higher than with SSI (0.43, CI 0.31– 0.57) and SI (0.66, CI 0.53–0.77) as reference (SAP vs. SSI, SAP vs. SI, SSI vs. SI $p < 0.00$). The negative predictive values of the PPI test obtained with SAP, SI and SSI were 0.54 (CI 0.22–0.81), 0.58 (CI 0.25–0.83) and 0.45 (CI 0.17–0.76) respectively (SSI vs. SI $p < 0.05$).

Reflux symptoms	Sensitivity		Specificity	
	(%)	95% CI	(%)	95% CI
Heartburn	87	0.74–0.94	27	0.12–0.50
Regurgitation	82	0.69–0.91	41	0.21–0.63
Burning sensation in epigastric region	73	0.59–0.84	38	0.19–0.61
Acid taste	45	0.31–0.60	45	0.60–0.67
Chest pain	42	0.29–0.57	45	0.25–0.67
Epigastric pain	40	0.27–0.55	48	0.26–0.70

Table 2. Sensitivity and specificity of the symptoms scored at baseline calculated with SAP as reference standard



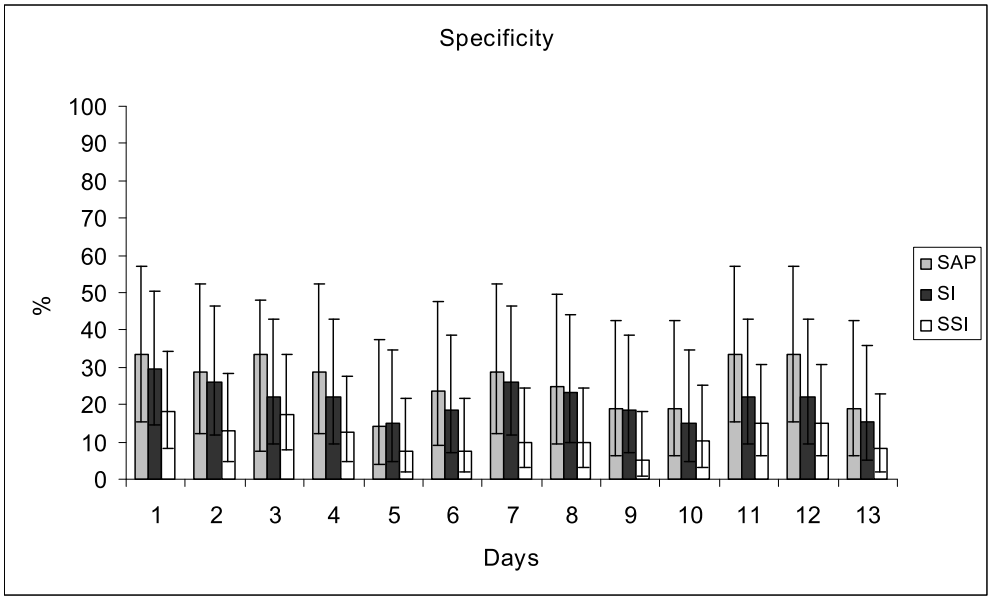


Figure 2. Sensitivity (a) and specificity (b) of the proton pump inhibitor test in percentages with symptom association probability (SAP), symptom index (SI) and symptom sensitivity index (SSI) as reference test for gastroesophageal reflux disease for each of the 13 test days.

The likelihood ratios of the PPI test were highest with the SAP as reference standard (1.2, CI 0.9–1.6) compared to SI (1.2, CI 0.9–1.4) and SSI (0.9, CI 0.8– 1.1) (SAP vs. SSI, SSI vs. SI $p < 0.01$, SAP vs. SI $p < 0.05$, see Figure 3).

The sensitivity, specificity, positive and negative predictive value did not differ significantly for each test day (see Figure 2), neither did the likelihood ratios differ (see Figure 3). The likelihood ratios of the reflux symptoms (1.0, CI 0.66–1.46) were similar to PPI test likelihood ratios with the SAP reference (see Figure 4).

DISCUSSION

This study has shown that the PPI test is unable to determine the presence or absence of GERD in a group of primary care patients and subsequently does not add any additional value to an adequate reflux history. Several studies have been performed on this topic, however this is the first study that has tested the accuracy of the PPI test in a study population similar to the 'normal' test population and has made use of the reference test that seems most appropriate for GP patients.

In a GP practice the doctor often encounters patients with reflux symptoms (1). The reason for the occurrence of these symptoms can be explained by various pathophysiological mechanisms (23). However, we believe that in the case of GERD the decisive feature is that symptoms are caused by reflux events (17). The presence of excessive pathological reflux does not provide evidence whether symptoms are caused by the acidic reflux episodes. We therefore believe that the unequivocal evidence for reflux disease is provided by the symptom–reflux association analysis. This study has made no use of endoscopy because it does not seem to be the most appropriate test for GP patients. About two-thirds of the general population do not have any signs of mucosal breaks and secondly, half of the patients with esophagitis are asymptomatic which does not apply to the 'normal' PPI test population (15;24).

In our opinion the best symptom association index for GERD is the SAP, as it takes into account both the total number of reflux episodes as well as the total number of symptoms (17). However, the choice of the reference test remains a difficult issue in all diagnostic studies. In contrast to our approach, Taghavi et al. tested the value of the indices of symptom–reflux association against the response to a short course of PPI as reference test (21). Their conclusion was that the SAP, SSI and SI are bad predictors for GERD. This conclusion is disputable because of the large placebo response of the PPI test which was seen in several other studies, including our study (4-13).

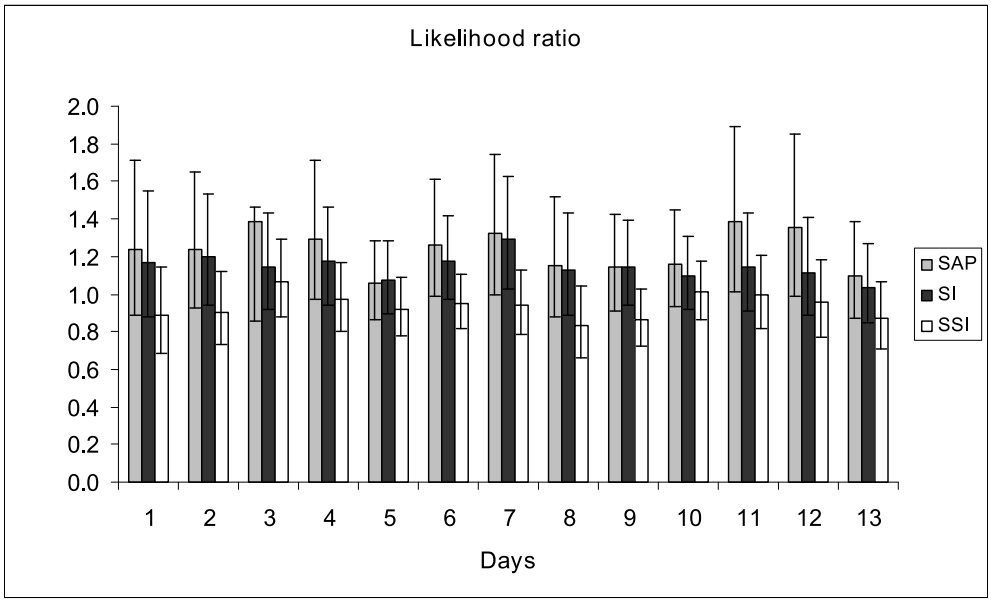


Figure 3. Likelihood ratio of the proton pump inhibitor test evaluated with the reference standards symptom association probability (SAP), symptom index (SI) and symptom sensitivity index (SSI) for each of the 13 test days.

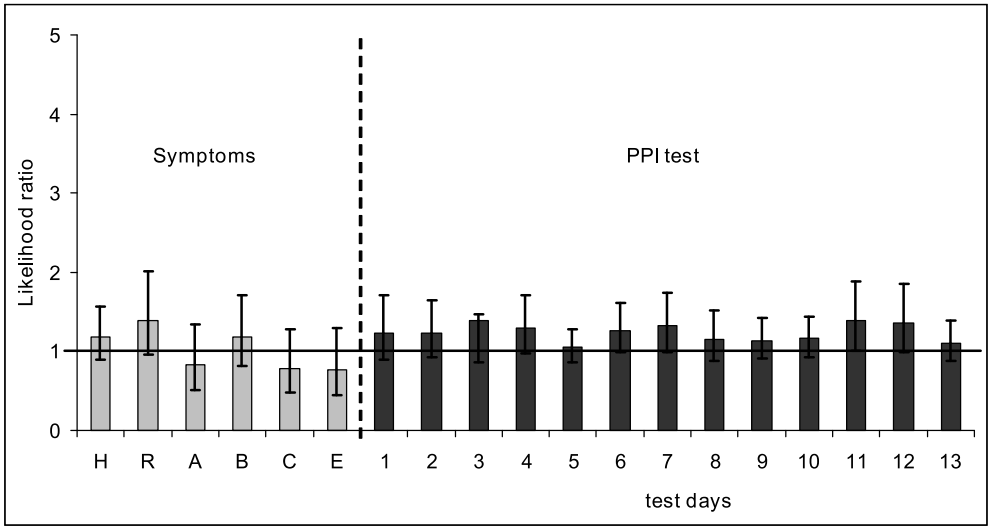


Figure 4. Likelihood ratios for the pre-test reflux symptoms [heartburn (H), regurgitation (R), acid taste (A), burning sensation in the epigastric region (B), chest pain (C) and epigastric pain (E)] and for the proton pump inhibitor (PPI) test for each of the 13 days using the symptom association probability as reference standard. A likelihood ratio of 1 (see line) indicates that the test result does not influence the final diagnostic outcome.

In a recent study using rabeprazole as the PPI test in a primary care setting, esophagitis, prolonged esophageal acid exposure or positive SAP were used as reference. Under these conditions the PPI test was not found to be a useful test (25). Our study population consisted of patients on which a GP would perform a PPI test, namely patients with mild-to-moderate symptoms suggestive of reflux disease. These study patients were not only included during GP consultation but also by advertisement. We did not find any difference in GERD prevalence or in PPI test outcome between the two subgroups that would question the presence of spectrum bias (14).

Gastroesophageal reflux disease was highly prevalent in our primary care population; 70% had a positive SAP. Nevertheless, the PPI diagnosed even more people with GERD, thereby confirming the unspecific nature of this sensitive diagnostic tool (4;6;8;10;11;26). However, due to the frequent occurrence of GERD in the general population, the positive predictive value with SAP as reference standard was 75% (73.6–76.7) and the negative predictive value 57.1% (44.1–63.6). This implies that a positive test result is reasonably trustworthy, as 25% of the patients with a positive PPI test could not have the disease. However, in case of a negative test, there still is a 50% chance that the subject could have the disease.

The likelihood ratio of a test indicates how much the chance of having the disease increases when the test is positive. In our study the likelihood ratio of the PPI test was close to 1.0 for each of the 13 test days. This outcome corresponds with the results of previous studies confirming the ambivalence of the test (27). Further, the likelihood ratios for the 13 test days were comparable, indicating that a long test period is not necessary to use a PPI test.

In the studies by Johnsson et al. and Klauser et al. the diagnostic value of the symptoms heartburn and acid regurgitation were evaluated with esophageal acid exposure (time with pH below 4) and/or endoscopic erosions as reference. Both concluded that the symptoms were specific of GERD (2;3). In contrast, we found that regurgitation and heartburn are sensitive but not specific for GERD. The discrepancy between our results and those obtained in other studies might be due to the fact that our population consisted solely of primary care patients, rather than of secondary or tertiary referral patients. Our findings indicate that the presence of reflux symptoms in primary care patients does not imply that these subjects have GERD.

As our patients were recruited on the basis of having symptoms that were judged to be caused by gastroesophageal reflux, the pre-test probability of GERD was high. In such a population, the likelihood of having GERD did not improve by the presence of specific reflux symptoms (all likelihood ratios were close to 1). Hence, the combination of symptoms and PPI test will also yield a likelihood ratio of 1. Consequently, it may be concluded that the PPI test does not add much to the GP's history-based judgment on presence or absence of GERD. Whether a PPI test would have greater diagnostic value in patients with less typical reflux symptoms remains to be seen, although this is probably unlikely as the PPI test was not even able to diagnose GERD in typical reflux patients. We hope that future studies will elucidate the topic further.

In conclusion, in this study we have assessed the value of the PPI test using the pH monitoring-derived symptom–reflux association indices as reference standard. It was found that the use of the SAP as reference test led to the highest sensitivity, specificity, positive and negative predictive values of the PPI test, as well as to the highest likelihood ratios. However, in primary care patients with symptoms suggestive of reflux, GERD is highly prevalent. Under these conditions the additional value of a short-term treatment with a PPI as a diagnostic tool for GERD is relatively poor.

REFERENCES

(1) Locke GR, III, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ, III. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997; 112(5):1448-1456.

(2) Johnsson F, Joelsson B, Gudmundsson K, Greiff L. Symptoms and endoscopic findings in the diagnosis of gastroesophageal reflux disease. Scand J Gastroenterol 1987; 22(6):714-718.

(3) Klauser AG, Schindlbeck NE, Muller-Lissner SA. Symptoms in gastro-oesophageal reflux disease. Lancet 1990; 335(8683):205-208.

(4) Bate CM, Riley SA, Chapman RW, Durnin AT, Taylor MD. Evaluation of omeprazole as a cost-effective diagnostic test for gastro-oesophageal reflux disease. Aliment Pharmacol Ther 1999; 13(1):59-66.

(5) Brun J, Sorngard H. High dose proton pump inhibitor response as an initial strategy for a clinical diagnosis of gastro-oesophageal reflux disease (GERD). Swedish multi-centre group in primary health care. Fam Pract 2000; 17(5):401-404.

(6) Fass R, Fennerty MB, Ofman JJ, Gralnek IM, Johnson C, Camargo E et al. The clinical and economic value of a short course of omeprazole in patients with noncardiac chest pain. Gastroenterology 1998; 115(1):42-49.

(7) Fass R, Ofman JJ, Gralnek IM, Johnson C, Camargo E, Sampliner RE et al. Clinical and economic assessment of the omeprazole test in patients with symptoms suggestive of gastroesophageal reflux disease. Arch Intern Med 1999; 159(18):2161-2168.

(8) Fass R, Ofman JJ, Sampliner RE, Camargo L, Wendel C, Fennerty MB. The omeprazole test is as sensitive as 24-h oesophageal pH monitoring in diagnosing gastro-oesophageal reflux disease in symptomatic patients with erosive oesophagitis. Aliment Pharmacol Ther 2000; 14(4):389-396.

(9) Ofman JJ, Gralnek IM, Udani J, Fennerty MB, Fass R. The cost-effectiveness of the omeprazole test in patients with noncardiac chest pain. Am J Med 1999; 107(3):219-227.

(10) Schenk BE, Kuipers EJ, Klinkenberg-Knol EC, Festen HP, Jansen EH, Tuynman HA et al. Omeprazole as a diagnostic tool in gastroesophageal reflux disease. Am J Gastroenterol 1997; 92(11):1997-2000.

(11) Schindlbeck NE, Klauser AG, Voderholzer WA, Muller-Lissner SA. Empiric therapy for gastroesophageal reflux disease. Arch Intern Med 1995; 155(16):1808-1812.

(12) Johnsson F, Hatlebakk JG, Klintenberg AC, Roman J, Toth E, Stubberod A et al. One-week esomeprazole treatment: an effective confirmatory test in patients with suspected gastroesophageal reflux disease. Scand J Gastroenterol 2003; 38(4):354-359.

(13) Gerson LB, Triadafilopoulos G. A prospective study of oesophageal 24-h ambulatory pH monitoring in patients with functional dyspepsia. Dig Liver Dis 2005; 37(2):87-91.

(14) Mower WR. Evaluating bias and variability in diagnostic test reports. Ann Emerg Med 1999; 33(1):85-91.

(15) Dent J. Gastro-oesophageal reflux disease. Digestion 1998; 59:433-445.

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

(17) Bredenoord AJ, Weusten BL, Smout AJ. Symptom association analysis in ambulatory gastro-oesophageal reflux monitoring. Gut 2005; 54(12):1810-1817.

(18) Breumelhof R, Smout AJ. The symptom sensitivity index: a valuable additional parameter in 24-hour esophageal pH recording. Am J Gastroenterol 1991; 86(2):160-164.

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

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

(21) Taghavi SA, Ghasedi M, Saberi-Firoozi M, izadeh-Naeeni M, Bagheri-Lankarani K, Kaviani MJ et al. Symptom association probability and symptom sensitivity index: preferable but still suboptimal predictors of response to high dose omeprazole. Gut 2005; 54(8):1067-71.

(22) Yates F. Contingency table involving small numbers and the chi square test. Journal of the Royal Statistical Society (Supplement) 1934; 1:217-235.

(23) Heikkinen M, Pikkarainen P, Eskelinen M, Julkunen R. GPs' ability to diagnose dyspepsia based only on physical examination and patient history. Scand J Prim Health Care 2000; 18(2):99-104.

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

(25) des Varannes SB, Sacher-Huvelin S, Vavasseur F, Masliah C, Le Rhun M, Aygalenq P et al. Rabeprazole test for the diagnosis of gastro-oesophageal reflux disease: results of a study in a primary care setting. World J Gastroenterol 2006; 12(16):2569-2573.

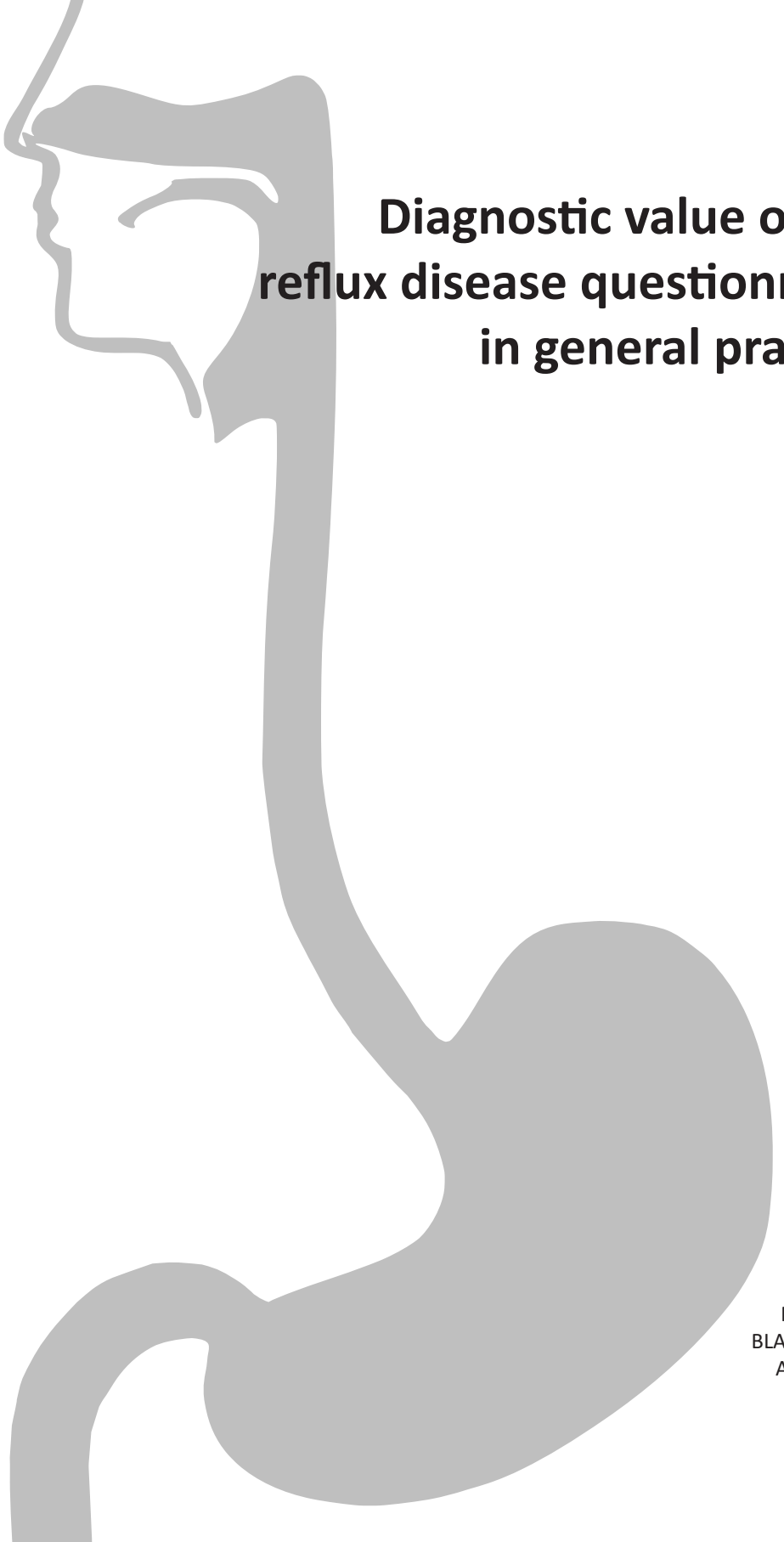
(26) Johnsson F, Weywadt L, Solhaug JH, Hernqvist H, Bengtsson L. One-week omeprazole treatment in the diagnosis of gastro-oesophageal reflux disease. Scand J Gastroenterol 1998; 33(1):15-20.

(27) Numans ME, Lau J, de Wit NJ, Bonis PA. Short-term treatment with proton-pump inhibitors as a test for gastroesophageal reflux disease: a meta-analysis of diagnostic test characteristics. Ann Intern Med 2004; 140(7):518-527.

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

Chapter 6

*"I stopped believing in Santa Claus when I was **six**. Mother took me to see him in a department store and he asked for my autograph."*
~ Shirley Temple, American Actress



Diagnostic value of the reflux disease questionnaire in general practice

MC Aanen
ME Numans
BLAM Weusten
AJPM Smout

ABSTRACT

Background

This study determined the diagnostic and therapeutic response of the Reflux Disease Questionnaire (RDQ) using the symptom association probability (SAP) as reference. In addition, the RDQ's construct validity and its relationship to quality of life (QOL) were ascertained.

Methods

Seventy-four patients with GERD symptoms (age 51 years (22–78); ♂ 62%) derived from primary care completed the RDQ, GSRS and QOLRAD before and after a 2-week course of esomeprazole 40 mg daily. The SAP was determined by a 24-hour pH recording before PPI treatment. The diagnostic abilities of the RDQ (total and 4 dimensions scores) were assessed with the area under the curve (AUC) of a receiver operating curve. RDQ scores before and after PPI treatment were compared with Wilcoxon tests. Multiple linear regressions assessed the RDQ's construct validity (GSRS) and relationship to QOL (QOLRAD).

Results

The AUCs were low for all RDQ dimensions (AUC <0.6). In the SAP-positive patients all RDQ dimensions improved ($p < 0.0001$) while the scores of the SAP negatives did not (heartburn $p < 0.01$; GERD and total score $p < 0.05$; regurgitation and dyspepsia n.s.). The RDQ was related to the total and reflux GSRS dimensions while the food and drink QOL dimension was linearly associated with the RDQ.

Conclusion

The RDQ is a valid and reliable questionnaire with excellent construct validity and a good relationship to QOL. The diagnostic value of the RDQ in primary care is limited, but combination with an additional PPI treatment course might improve the RDQ's ability to discriminate GERD patients according to their SAP outcome.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is common in the western population (1). Most GERD patients are diagnosed and treated in the primary care setting. Despite the fact that the disease itself is benign since the prevalence of complications and severe GERD-related morbidity is low, GERD can severely reduce a patient's quality of life (2;3). This is why GERD treatment is usually started empirically in an early stage. Following treatment start, diagnostic procedures are postponed and a favorable response to proton pump inhibitors (PPI) is widely accepted to validate the diagnosis (4). However, the increase in long-term use of PPIs without a proper diagnosis has urged researchers to look for other means to improve GERD diagnostics. One of the tools that might help the general practitioner (GP) is a validated GERD questionnaire to support diagnostic accuracy. It is likely that the use of a questionnaire would reduce the inter-observer variability in comparison with clinical history taking. Besides aiding in the diagnosis of GERD, a questionnaire would also enable the physician to quantify therapeutic response.

The Reflux Disease Questionnaire (RDQ) is a promising new questionnaire that was specially designed to be used in the primary care setting (5). Extensive research has found this questionnaire to be reliable, valid, responsive and above all practical (5-7). Furthermore, the RDQ outcome seems to correlate well with quality of life (6;8). However, data on its diagnostic validity is still lacking (7).

This validation should be performed in a population that represents patients in whom primary care physicians consider the diagnosis of GERD and in this population the most relevant diagnostic reference test for GP patients should be used, which, in our opinion, is a measure of the symptom-reflux association, such as the symptom association probability (SAP) (9). The SAP objectively determines with a Fisher exact test whether symptoms are due to reflux events taking all symptom episodes and reflux events into account.

The aim of this study was therefore to assess the diagnostic and therapeutic response of the RDQ questionnaire using the SAP outcome as determined by 24-hour pH recording as reference standard in a primary care population. The secondary aim was to ascertain the construct validity of the questionnaire and to specify the RDQ's relationship with quality of life.

METHODS

Patients

Seventy-four patients (mean age 51 years (22–78); 62% male) who completed a 24-hour pH recording and exhibited symptoms during this recording were analyzed in this study. These patients were recruited directly during a GP consultation (34%) or indirectly by advertisement in a local newspaper (66%). In case of recruitment by advertisement the patient's GP was consulted before inclusion. All patients had symptoms suggestive of reflux disease (i.e. heartburn, regurgitation, acid taste, burning sensation in the epigastric region, epigastric pain and chest pain) for at least twice a week for the past 3 months. The subjects had not used an acid-suppressant drug for at least 4 weeks before entry. Furthermore, none of the subjects had undergone gastrointestinal surgery.

Informed written consent was obtained before the start of the study and the protocol was approved by the Medical Ethics Committee of the University Medical Center, Utrecht.

Study protocol

All patients with symptoms suggestive of GERD were asked to fill in the RDQ. In order to assess the RDQ's construct validity and the RDQ's assessment of quality of life, the Gastrointestinal Rating Scale (GSRS) and Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaires were simultaneously completed with the RDQ 1 week before a 24-hour pH recording (5;10;11). After the pH recording patients used 40 mg esomeprazole daily during 2 weeks. After these 2 weeks the patients completed the three questionnaires again. The SAP was determined after the pH recording but the patients and their physician were kept oblivious of the results until the protocol was completed.

24-Hour pH Monitoring

The 24-hour pH recording was performed after identification of the lower esophageal sphincter (LES) with manometry. The manometric recording was performed with a 10-channel silicone rubber catheter with a reversed sleeve sensor (DentSleeve International Ltd., Mississauga, Ont., Canada) which was perfused at a rate of 0.2 ml/min with degassed water, using hydraulic f low restrictors (DentSleeve International Ltd, Mississauga, Ont., Canada). The pressures were recorded with external pressure transducers (Abbott, Sligo, Ireland). The 24-hour pH recording was performed with a glass pH catheter with in-built reference electrode (Ingold, Urdorf, Switzerland) that was transnasally placed 5 cm above the LES. The pH catheter was calibrated with 3.2 and 7.4 pH buffers solutions. The pH catheter was then attached to a digital datalogger (MMS, Enschede, the Netherlands) which used a sampling frequency of 2 Hz. All patients were instructed to record their symptoms by pressing the event marker button on the datalogger and at the same time specifying the symptom in a diary card. In the diary card also the times of consumption of meals and beverages and the recumbent time were noted. Patients were instructed to restrict their intake to 3 meals and 3 drinks during the 24 h at standardized times. Meals and drinks had to be consumed within

30 and 15 min, respectively. Patients were encouraged to maintain their normal daily activities during the 24-hour pH study.After the 24-hour recording period the data from the datalogger was transferred to a personal computer.

Analysis of 24-Hour pH Data

The 24-hour pH data were analyzed automatically (MMS, Enschede, the Netherlands), excluding all eating and drinking periods. The SAP is calculated by dividing 24-hour pH data into consecutive 2-min segments. For each of these 2-min segments, it is determined whether reflux occurred, providing the total number of two-minute segments with (total R+) and without (total R–) reflux. Then, for each symptom episode, it is determined whether reflux did (S+R+) or did not (S+R–) occur in the preceding two-minute period. Subtraction of S+R+ from total R+ results in S–R+ and subtraction of S+R– from total R– results in S–R–.

A 2 x 2 contingency table is then constructed in which the number of 2-min segments with and without symptoms and with and without reflux are tabulated. Fisher's exact test is used to calculate the probability (p) that the observed distribution could have been brought about by chance. The SAP is calculated as (1–p) x 100%. By statistical convention, the SAP is considered positive if it exceeds 95% (9;12).

Analysis of Questionnaires

The English version of the RDQ comprises 12 questions assessing the frequency and severity of heartburn, acid regurgitation and dyspeptic complaints which are scored on a 5-point Likert scale (5). We used the Dutch version of RDQ which has been translated from English to Dutch and re-translated back for validity. The 12 items are combined into 3 dimensions: heartburn, regurgitation, dyspepsia. The mean of all three dimensions gives a total score ranging from 0 to 5. The specific GERD dimension is determined by the mean of the dimensions heartburn and regurgitation.

The QOLRAD, a disease-specific quality-of-life questionnaire, covers five dimensions: emotional distress, sleep disturbance, problems with eating and drinking (food and drink problems), limitations in physical and social functioning and lack of vitality. The Dutch QOLRAD is similar to the original English version. Responses were rated on a 7-grade Likert scale. The lower the score, the more severe the impact was on daily functioning during the past week. The QOLRAD has been shown to be reliable and valid (11;13).

The GSRS includes 15 items combined into five symptom clusters addressing to what extent different gastrointestinal symptoms were bothersome in the past week. The five symptom clusters depict reflux, abdominal pain, indigestion, diarrhea and constipation. The GSRS has a seven-graded Likert type scale where 1 represents absence of bothersome symptoms and 7 very bothersome symptoms. All questions were translated into Dutch. The GSRS is documented to be reliable and valid (13;14).

Statistics

In order to determine significant differences a Mann-Whitney test was used for unpaired data and a Wilcoxon test for paired data. A $p < 0.05$ was considered statistically significant. Data is presented in median and interquartiles (25–75th). The ability of the RDQ to discriminate SAP-positive from SAP-negative patients was quantified by using the receiver operating curve (ROC) (15). The area under the curve (AUC) denotes the discriminative power of a diagnostic model and can range from 0.5 (no discrimination, like flipping a coin) to 1.0 (perfect discrimination). A value of 0.7–0.8 is considered to represent a reasonable diagnostic test and a value of >0.8 represents a good discriminative diagnostic test (16). In case of a good discriminative AUC, an optimal cut-off point can be determined at the largest angle of the curve, most closely related to the left upper corner of the figure.

To compare the RDQ dimensions with the pretreatment quality of life outcome of the QOLRAD and to assess the construct validity with the GSRS a stepwise multiple regression was performed. The 5 RDQ dimensions were subsequently chosen as the dependent factor. In a multiple linear regression model, adjusted R square (adjR^2) measure the proportion of the variation in the dependent variable accounted for by the explanatory variables thereby making adjustments for the number of explanatory variables inserted into the model. The adjusted R squares can take on any value between 0 and 1, with a value closer to 1 indicating that a greater proportion of variance is accounted for by the model. In this study all adjusted R squares are shown in percentages.

RESULTS

Similar pretreatment scores were found for the five RDQ dimensions that were studied. Also posttreatment the symptom scores of the five RDQ dimensions were also similar. However, PPI treatment significantly reduced all RDQ symptom scores (figure 1).

Seventy percent of the studied subjects had a positive SAP. Patients with and without a positive SAP had similar pretreatment RDQ scores (table 1). On PPI treatment, patients with a positive SAP appeared to have a greater improvement of their RDQ scores: only in subjects with a positive SAP all RDQ dimensions scores were significantly reduced (table 1). Treatment decreased the total score significantly more in SAP-positive than in SAP-negative patients ($p < 0.05$).

The ROC analysis showed that all RDQ dimension scores had an AUC < 0.6 with the SAP as reference standard (table 2). The RDQ dimension scores from patients recruited by advertisement or by their GP showed similar AUC values both below 0.6 (data not shown). No RDQ cut-off value could be determined that would separate SAP-positive from SAP-negative patients (figure 2). The RDQ dimensions GERD and heartburn were found to be linearly related with the GSRS reflux score and they could be explained by the GSRS for 57% and 29%, respectively. Also regurgitation and the total RDQ score were positively related to GSRS reflux score (regurgitation adjR2 40% $p<0.001$; total RDQ adjR2 44% $p<0.001$). By adding the total score of bothersome gastrointestinal symptoms the regression model improved

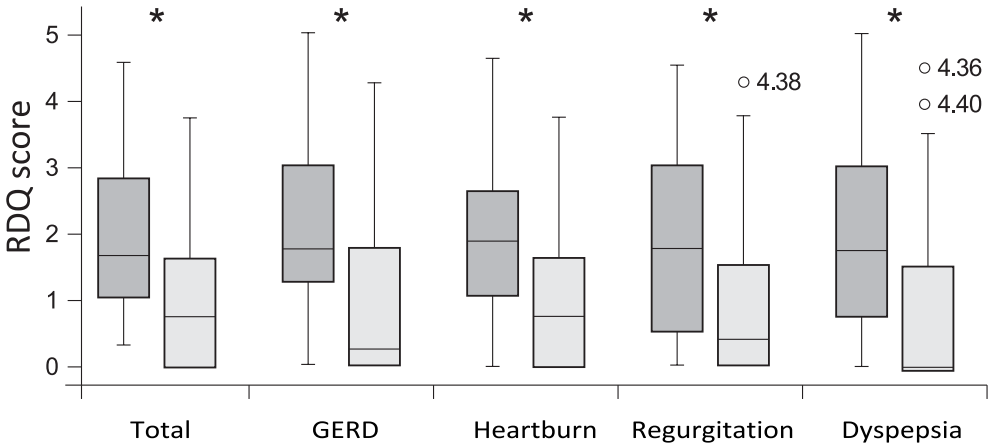


Figure 1. Pre-treatment (shaded boxes) and post-treatment (open boxes) RDQ scores. Both before and after treatment the dimensions scores were similar. Treatment significantly reduced the RDQ scores for all dimensions. *Pre-treatment vs. post-treatment scores p<0.01.

Dimension	Pre-treatment		Post-treatment		p-value
	Median	25th-75th	Median	25th-75th	
SAP-positive					
Heartburn	1.75	1.50-3.44	0.00	0.00-1.50	<0.0001
Regurgitation	1.75	0.94-2.81	0.25	0.00-1.50	<0.0001
Dyspepsia	1.88	0.94-3.06	0.00	0.00-1.25	<0.0001
GERD	2.13	1.00-2.63	0.63	0.00-1.50	<0.0001
Total score	**1.83**	**1.33-2.88**	**0.42**	**0.00-1.50**	**<0.0001**
SAP-negative					
Heartburn	2.13	0.38-3.13	0.50	0.00-2.31	<0.01
Regurgitation	1.38	0.00-3.25	0.75	0.00-2.50	ns
Dyspepsia	1.50	0.25-3.13	0.75	0.00-2.75	ns
GERD	1.56	1.09-3.16	1.25	0.00-1.78	<0.05
Total score	**1.67**	**0.88-3.04**	**1.00**	**0.42-1.96**	**<0.05**

Table 1. Pre-treatment and post-treatment scores for all RDQ dimensions for SAP-positive and SAP-negative patients. The p-values relate to differences between pre- and post-treatment scores.

(regurgitation: reflux and total adjR^2 47% p <0.05; total RDQ: reflux and total adjR^2 60% p = 0.01). The dyspepsia dimension was solely related to the total GSRS score (adjR^2 34% p <0.001).

Assessment of the relationship between the QOLRAD scores and the RDQ scores showed that the total RDQ score and the RDQ dimension GERD could both be explained for 40% and the RDQ dimension heartburn for 33% by the QOLRAD dimension food and drink problems (all 3 regressions p<0.001). Regurgitation was also associated with problematic food and drink intake and the variance of this dimension could be explained for by 19% (p<0.01). The dimension physical and social dysfunction accounted for an extra 5% elucidation of regurgitation (p<0.05), but this was due to three outliers. After exclusion of these outliers regurgitation was only associated with food and drink problems (adjR^2 17%, p<0.001). The dyspepsia dimension did not relate to a specific QOLRAD domain but was linearly related to the total QOLRAD score (adjR^2 16%, p<0.001).

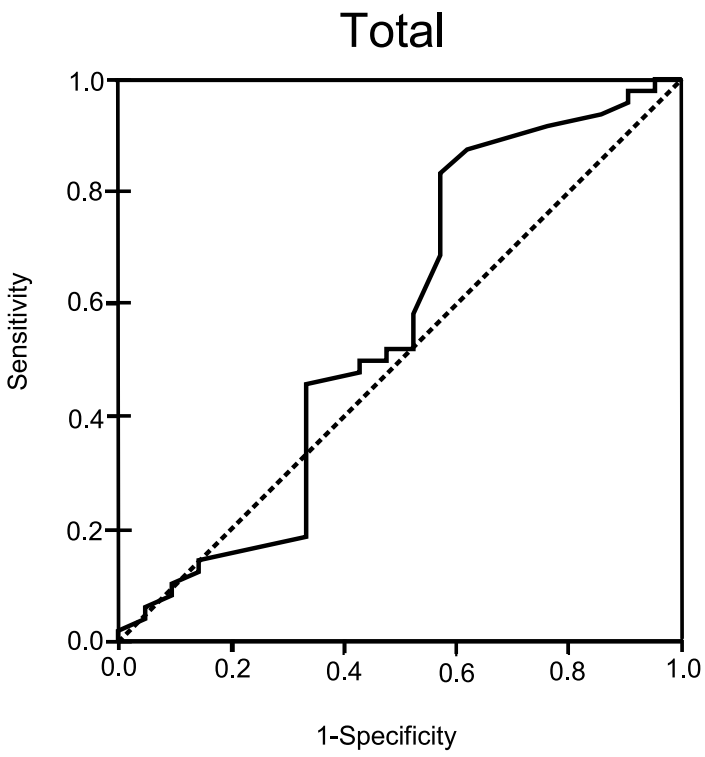


Figure 2.
ROC curves of the total RDQ scores and the 4 RDQ dimensions versus the SAP outcome. The sensitivity represents the true-positive fraction and the 1-specificity the false positive fraction at different cut-off points.

Indices	Dimensions	AUC	SEM	95% Confidence Interval	
				lower	upper
SAP	Heartburn	0.51	0.08	0.36	0.66
	Regurgitation	0.54	0.08	0.38	0.70
	Dyspepsia	0.52	0.08	0.37	0.67
	GERD	0.55	0.08	0.40	0.70
	Total score	0.56	0.08	0.40	0.73

Table 2. Area under the curve (AUC) for all RDQ dimensions found during ROC analysis against the SAP outcome as reference standards. All AUCs are shown with standard error of the mean and 95% asymptotic confidence intervals.

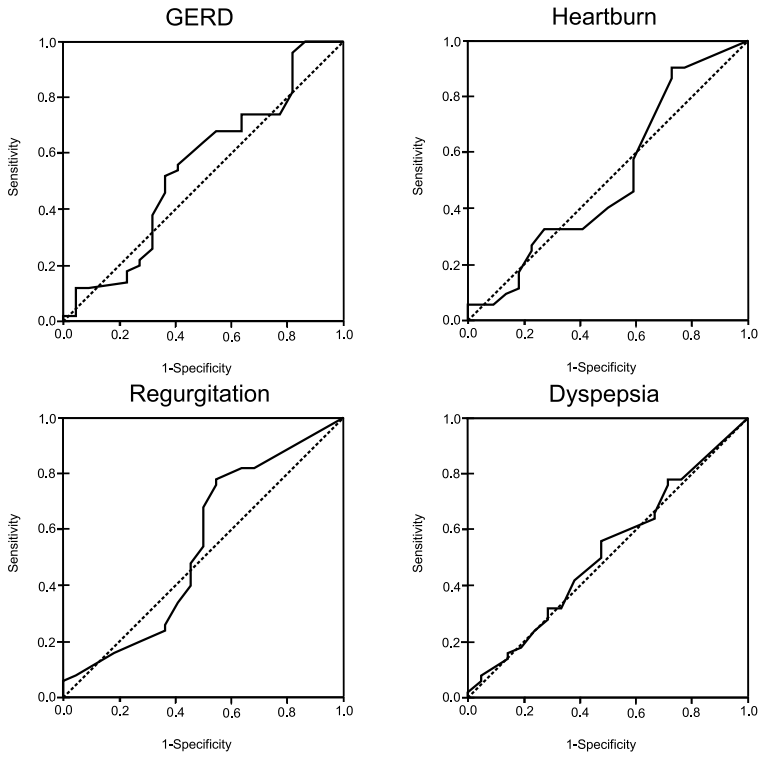


Figure 2 ***continued*****.**
All dimensions scores followed the broken reference line indicating that every improvement in false positive rate is matched by a corresponding decline in the false negative rate corresponding with areas under the curves below 0.6 (see table 2). Therefore no diagnostic cut-off point could be identified.

DISCUSSION

The main findings of our study are:

1) The RDQ cannot be used to identify GERD patients as defined by a positive SAP outcome. The areas under curves were lower than 0.6 for all dimensions and subsequently no optimal cut-off value could be determined.

2) After PPI treatment all RDQ scores were significantly reduced in SAP-positive patients but not in SAP-negative patients and the reduction in total RDQ score after treatment was greater in SAP-positive than in SAP-negative patients.

3) The RDQ questionnaire is specific for reflux symptoms but not for other bothersome gastrointestinal symptoms as assessed by GSRS. (4) The RDQ relates to QOL, i.e. to the dimension food and drink problems.

The RDQ, assessing frequency and severity of reflux symptoms to facilitate the diagnosis of GERD in primary care, presently is the best-designed GERD-specific questionnaire, due to the fact that both expert opinions and patient's interview analyses were used in its development (5;7). According to our study results, however, RDQ does not deliver the solution for misclassification problems in primary care. This finding needs further discussion. It has been shown that clinical history taking alone has a low specificity for diagnosing GERD and is riddled with a high interobserver variability, despite a high sensitivity (17). Nowadays, most GPs have adopted the PPI test for diagnosing GERD, although this has also shown to yield a low specificity, despite a high sensitivity (17-19). Due to the rebound effect of PPIs even more patients are false-positively labeled (20). This leads to the conclusion that currently no adequate diagnostic test for GERD can be performed in primary care and thus, the vast majority of patients with suspected GERD symptoms have to be treated empirically. Subsequently, in most patients a diagnosis is never made, which may lead to a life-long treatment with a PPI without knowing whether this is the best treatment option.

Performing a more invasive and costly investigation in every patient is not possible in a primary care setting. Furthermore, due to the fact that no absolute gold standard exists, it is unclear which diagnostic test would be most useful. Endoscopy is irrelevant in a primary care population in which the majority of GERD patients do not have acid-induced esophageal lesions (3;17). We believe that the occurrences of GERD symptoms are caused by reflux events. Calculation of the SAP determines whether a true relationship exists between symptoms and reflux events and is therefore a more relevant procedure than only an assessment of the percentage of time with esophageal pH below 4 (9;12). For the evaluation of the diagnostic properties as well as the responsiveness to treatment of the RDQ questionnaire we have used the SAP outcome as the reference standard for presence of GERD. A questionnaire validated against the SAP that would demonstrate whether reflux symptoms of primary care patients are due to acidic reflux events would greatly improve GERD diagnosis in primary care (12).

Disappointingly however, the RDQ was unable to discriminate SAP-positive from SAP-negative patients, despite the fact that our study population was comprised of patients in whom a GP indeed might use a questionnaire and/or short-term PPI treatment to support diagnostic decisions (18;21;22). Although our study population was 'GERD-enriched', this does not influence the characteristic test properties, i.e. sensitivity and specificity (23). The observation that patients recruited from two different sources did not show different outcomes in AUC suggests that the performance of the RDQ is not due to issues related to patient selection.

Several studies have shown that the response to PPI treatment, when simply evaluated with symptom improvement or patient satisfaction scores, results in a large group of false-positively labeled patients (18;19). It is possible that the additional use of the RDQ would enable physicians to improve the diagnostic test characteristic of the PPI test. Our data suggest that patients with a positive SAP had significantly better posttreatment RDQ scores than patients with a negative SAP while the reduction in total RDQ score was significantly greater in SAP-positive patients. However, these results only show differences between groups and may not be applicable to individual patients. Nevertheless, our results suggest that the RDQ could be used as an additional help in differentiating GERD from non-GERD in the relevant population of patients suspected of GERD in primary care, when short-term empirical treatment with PPI is considered. Further research is needed to determine whether the response of the RDQ scores to PPI treatment can indeed be used diagnostically.

The RDQ has been shown to have excellent construct validity for GERD which we confirmed with the GSRS questionnaire (5;7). All reflux-specific RDQ domains were strongly related to the reflux dimension of the GSRS as the reflux dimension could explain 50–30% of the variation for most RDQ domains. Concerning the QOL, most RDQ dimensions were related to problems encountered during eating and drinking (food and drink problems) indicating that the QOL of patients was diminished due to the fact that they had less appetite, avoided eating due to their reflux symptoms and that certain food items increased their symptoms. In contrast, other studies suggested that the RDQ correlates with all QOL dimensions of the QOLRAD. However, the highest degree of correlation was found also with food and drink problems (6;8). It is known that GERD patients experience the most problems with the consumption of food and drink and little for social and physical functioning (6;24). The total RDQ scores and 3 of the 4 RDQ dimensions scores (GERD, heartburn and regurgitation) could be explained for 20–40% by the specific QOLRAD dimension food and drink problems.

In conclusion, the RDQ is a valid and reliable questionnaire with excellent construct validity and a good relationship to quality of life. However, in our primary care population the diagnostic value of the RDQ with a positive SAP as reference was limited. An empirical short term PPI treatment course with pre- and post-treatment evaluation might improve the RDQ's ability to discriminate between individuals with and without GERD.

REFERENCES

(1) Locke GR, III, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ, III. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997; 112(5):1448-1456.

(2) Irvine EJ. Quality of life assessment in gastro-oesophageal reflux disease. Gut 2004; 53 Suppl 4:35-39.

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

(4) DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol 2005; 100(1):190-200.

(5) Shaw MJ, Talley NJ, Beebe TJ, Rockwood T, Carlsson R, Adlis S et al. Initial validation of a diagnostic questionnaire for gastroesophageal reflux disease. Am J Gastroenterol 2001; 96(1):52-57.

(6) Kulig M, Leodolter A, Vieth M, Schulte E, Jaspersen D, Labenz J et al. Quality of life in relation to symptoms in patients with gastro-oesophageal reflux disease-- an analysis based on the ProGERD initiative. Aliment Pharmacol Ther 2003; 18(8):767-776.

(7) Shaw M. Diagnostic utility of reflux disease symptoms. Gut 2004; 53 Suppl 4:25-27.

(8) Nocon M, Kulig M, Leodolter A, Malfertheiner P, Willich SN. Validation of the Reflux Disease Questionnaire for a German population. Eur J Gastroenterol Hepatol 2005; 17(2):229-233.

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

(10) Svedlund J, Sjodin I, Dotevall G. GSRS--a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci 1988; 33(2):129-134.

(11) Wiklund IK, Junghard O, Grace E, Talley NJ, Kamm M, Veldhuyzen van Zanten S et al. Quality of Life in Reflux and Dyspepsia patients. Psychometric documentation of a new disease-specific questionnaire (QOLRAD). Eur J Surg Suppl 1998;(583):41-49.

(12) Bredenoord AJ, Weusten BL, Smout AJ. Symptom association analysis in ambulatory gastro-oesophageal reflux monitoring. Gut 2005; 54(12):1810-1817.

(13) Talley NJ, Fullerton S, Junghard O, Wiklund I. Quality of life in patients with endoscopy-negative heartburn: reliability and sensitivity of disease-specific instruments. Am J Gastroenterol 2001; 96(7):1998-2004.

(14) Dimenas E, Glise H, Hallerback B, Hernqvist H, Svedlund J, Wiklund I. Well-being and gastrointestinal symptoms among patients referred to endoscopy owing to suspected duodenal ulcer. Scand J Gastroenterol 1995; 30(11):1046-1052.

(15) Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982; 143(1):29-36.

(16) Swets JA. Measuring the accuracy of diagnostic systems. Science 1988; 240(4857):1285-1293.

(17) Aanen MC, Weusten BL, Numans ME, de Wit NJ, Baron A, Smout AJ. Diagnostic value of the proton pump inhibitor test for gastro-oesophageal reflux disease in primary care. Aliment Pharmacol Ther 2006; 24(9):1377-1384.

(18) Johnsson F, Hatlebakk JG, Klintenberg AC, Roman J, Toth E, Stubberod A et al. One-week esomeprazole treatment: an effective confirmatory test in patients with suspected gastroesophageal reflux disease. Scand J Gastroenterol 2003; 38(4):354-359.

(19) Numans ME, Lau J, de Wit NJ, Bonis PA. Short-term treatment with proton-pump inhibitors as a test for gastroesophageal reflux disease: a meta-analysis of diagnostic test characteristics. Ann Intern Med 2004; 140(7):518-527.

(20) Waldum HL, Arnestad JS, Brenna E, Eide I, Syversen U, Sandvik AK. Marked increase in gastric acid secretory capacity after omeprazole treatment. Gut 1996; 39(5):649-653.

(21) Bate CM, Riley SA, Chapman RW, Durnin AT, Taylor MD. Evaluation of omeprazole as a cost-effective diagnostic test for gastro-oesophageal reflux disease. Aliment Pharmacol Ther 1999; 13(1):59-66.

(22) Juul-Hansen P, Rydning A. Endoscopy-negative reflux disease: what is the value of a proton-pump inhibitor test in everyday clinical practice? Scand J Gastroenterol 2003; 38(12):1200-1203.

(23) Loong TW. Understanding sensitivity and specificity with the right side of the brain. BMJ 2003; 327(7417):716-719.

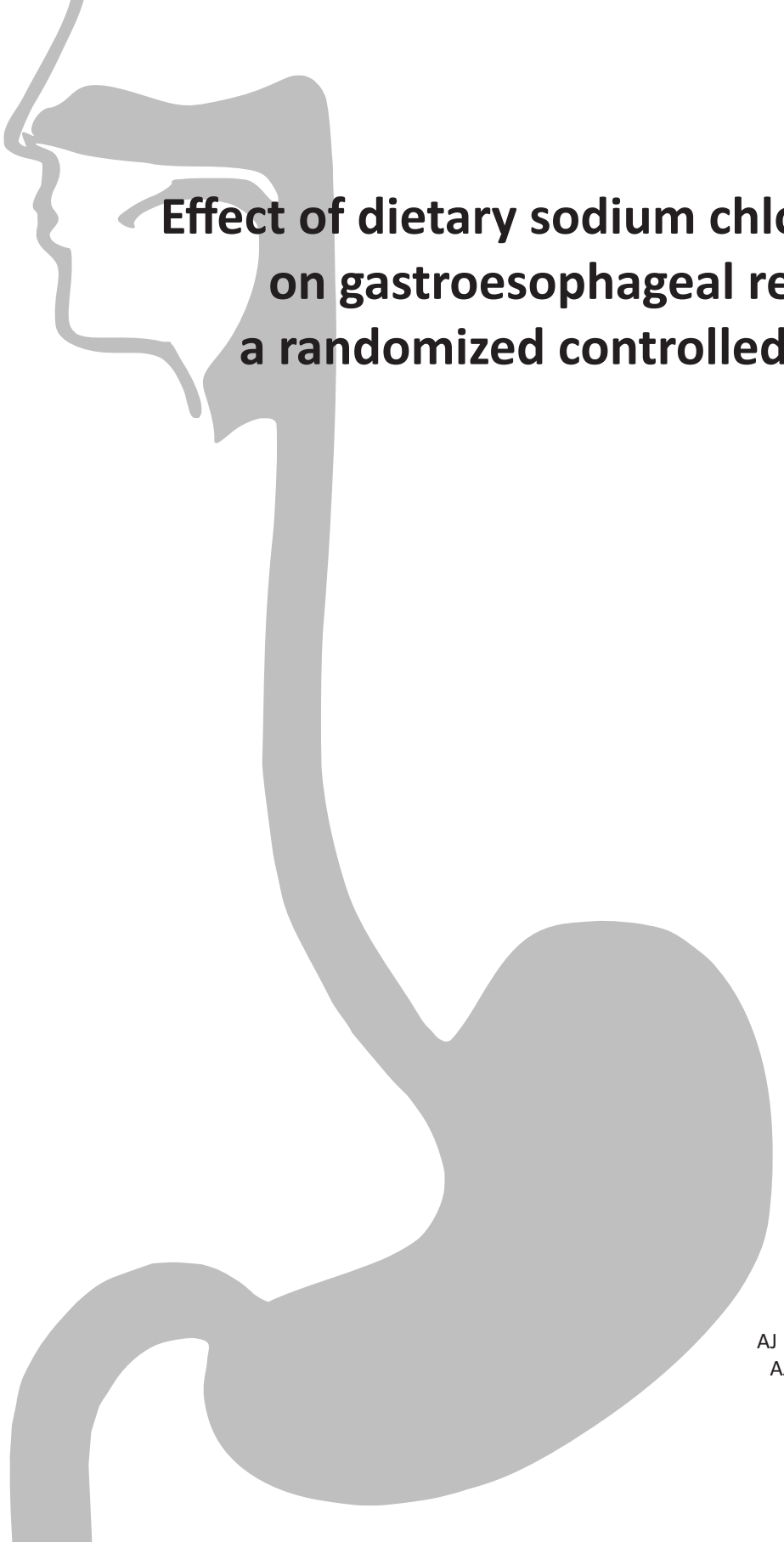
(24) Pace F, Negrini C, Wiklund I, Rossi C, Savarino V. Quality of life in acute and maintenance treatment of non-erosive and mild erosive gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2005; 22(4):349-356.

Chapter 7

*"**Seven** days without laughter makes one weak."*
~ Mort Walker, American Comic Artist

Scandinavian Journal of Gastroenterology 2006

Effect of dietary sodium chloride on gastroesophageal reflux: a randomized controlled trial



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ABSTRACT

Background

It has been suggested that a high consumption of sodium chloride (NaCl) is associated with reflux symptoms. The objective of this study was to investigate the effect of increased dietary NaCl intake on gastroesophageal reflux and reflux mechanisms.

Methods

In this double-blind, placebo-controlled, crossover study 10 healthy male subjects received 5 g NaCl or placebo in capsules per day for one week, after which concurrent manometric, pH and impedance monitoring was carried out for 4.5 h.

Results

Esophageal acid exposure time (pH<4) was similar for placebo (median 11% (25th 3-75th 36)) and NaCl (9% (1-36)). No differences in the numbers of reflux episodes were found for NaCl (16 (13.5-22)) and placebo (23 (14.8-27)). Furthermore, similar numbers of liquid acid reflux episodes (placebo 12 (6.5-17.3); NaCl 10 (2.3-14.3)), liquid weakly acidic reflux episodes (placebo 5.5 (4-12.3); NaCl 6.5 (3-10.8)) and gaseous reflux episodes (placebo 1 (0-1.8); NaCl 2 (0-3)) were seen. In both conditions transient lower esophageal sphincter relaxations (TLESRs) were the most common reflux mechanism, followed by swallow-induced reflux. High salt intake lowered LES pressure overall and in the first postprandial hour ($p<0.01$).

Conclusion

High dietary sodium intake does not increase gastroesophageal reflux in healthy volunteers, despite a decrease in LES pressure.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is common in the Western world. At least 20% of the general population experience symptoms of heartburn and regurgitation once a week, and 60% experience symptoms on an intermittent basis (1). In most GERD patients, quality of life is significantly affected (2). Reflux symptoms are primarily caused by reflux of acidic gastric contents into the esophagus. However, studies using the new technique of impedance monitoring have shown that non-acidic reflux can also provoke GERD symptoms (3).

Although GERD is most prevalent in Western Europe and North America, the disease is also becoming more common in Asia (4). This might partially be explained by lifestyle modifications, such as an increase in the consumption of hyperosmolar products like dietary salt (5;6). Increasing our knowledge of the association between lifestyle and reflux could lead to minimization of the GERD population as well as reducing disease-associated costs. Several lifestyle modifications have been proposed, but only a few are evidence based (7).

Recently, a large epidemiological study of GERD patients in Norway showed that a frequent consumption of salted dishes and/or adding extra salt to regular meals increases the risk of GERD symptoms (8). A study involving twins also showed a relationship between salt intake and reflux symptoms (9). In addition, it has been shown that saline delays gastric emptying and increases pancreaticobiliary secretion, mechanisms that could lead to an increase in both gastroesophageal reflux and reflux symptoms (10).

No other study has ever investigated the relationship between a high salt intake and gastroesophageal reflux. The aim of this study was therefore to investigate the effect of an increase in dietary salt (sodium chloride) intake on gastroesophageal reflux and reflux mechanisms in healthy volunteers.

METHODS

Patients

A total of 10 healthy male volunteers were enrolled for this double-blind, randomized, placebo-controlled, crossover trial which was based on a sample size estimation that the study had a probability of 80% to detect a difference of 30% between placebo and salt at a two-sided significance level of 0.05 (11;12).

Randomization of all volunteers into equal groups took place 7 days prior to the first combined stationary manometric, pH and impedance recording session. Randomization was performed by an independent researcher, ensuring a blind assignment for both the primary investigator and the volunteers. The subjects consumed 10 standardized capsules daily for 7 days. Each capsule contained 500 mg of either placebo (microcrystalline cellulose, Avicel ®) or NaCl. The selected daily dose of NaCl (5 g) represents a 50% increase of the average normal daily sodium intake in the Netherlands. After a 6-day washout period and another week of capsule intake, containing the other substance as decided by randomization, the second recording took place. Prior to each recording, the volunteers collected their 24-h urine in which sodium excretion was determined.

All volunteers were free of gastrointestinal symptoms and were not taking any medication. During the study all volunteers refrained from using alcohol and tobacco. Informed written consent was obtained before the start of the study and the protocol was approved by the Medical Ethics Committee of the University Medical Center, Utrecht.

Study protocol

After an overnight fast, a manometry catheter (described below) was inserted through the nose. After positioning of the manometry catheter, the impedance and the pH catheters were introduced transnasally. The position of the pH and impedance catheters was based on the manometric findings. All subjects were in a seated position during the recording and were asked to minimize head movements. After 1 h and 15 min of continuous recording, a reflux-eliciting meal was consumed consisting of a hamburger (McDonald's Quarter Pounder), 20 g fresh onions, 44 g chips, and 475 ml orange juice (in total 967 kCal and 2.8 g NaCl). The meal had to be finished within 20 min. Thereafter, a postprandial recording period of 3 h completed the protocol.

Manometry and pH monitoring

A water-perfused 10-channel silicone rubber assembly with an inner diameter of 0.4 mm and outer diameter of 4 mm (DentSleeve International Ltd., Mississauga, Ontario, Canada) was used for the manometry. The catheter was equipped with a 6 cm-long reversed perfused sleeve sensor. Pressures were recorded from 4 pharyngeal side-holes (at 24, 26, 28, 30 cm proximal to the upper border of the sleeve), 3 esophageal side-holes (at 4, 9 and 14 cm

proximal to the upper border of the sleeve) and a gastric side-hole (2 cm from the distal side of the catheter). The manometric catheter was positioned with the sleeve sensor straddling the lower esophageal sphincter (LES). The sleeve sensor, gastric and esophageal side-holes were perfused at a rate of 0.2 ml/min with degassed water, using hydraulic flow restrictors (DentSleeve International Ltd.). The pharyngeal side-hole that registered the pharyngeal contraction best was selected and perfused with air at a rate of 0.8 ml/min, while the other pharyngeal side-holes were not used, in order to prevent mechanically stimulated transient LES relaxations (TLESR) (13). The pressures were recorded with external pressure transducers (Abbott, Sligo, Ireland).

Intraluminal pH monitoring was performed with a glass pH electrode catheter (Ingold AG, Urdorf, Switzerland). The pH electrode was positioned 5 cm above the manometrical upper border of the LES. The pH data were stored together with the manometric data in digital format in two 12-channel dataloggers (MMS, Enschede, The Netherlands), using a sample frequency of 8 Hz. At the end of the study all data were transferred to the hard disc of the computer.

Impedance monitoring

For impedance monitoring, a 7-channel impedance catheter (outer diameter 2.3 mm) was used (Aachen University of Technology, FEMU, Aachen, Germany). The 7 recording segments were located at 0-2, 2-4, 4-6, 8-10, 10-12, 14-16 and 17-19 cm above the upper border of the manometrically located LES. Impedance signals were stored in a digital system (Aachen University of Technology) using a sampling frequency of 50 Hz (14).

Data analysis

In the impedance signals, reflux episodes were identified and classified as either liquid (liquid and mixed reflux) or gaseous reflux based on previously described criteria (15). Furthermore, using the pH tracings, the liquid reflux episodes were classified as either acidic (pH<4) or weakly acidic (pH>4). For each reflux episode the underlying mechanism was classified into five categories: TLESRs-associated, swallow-associated, strain-associated, low LES pressure-associated and other/unknown mechanisms. TLESRs were scored according to the Holloway criteria (16). Reflux was considered to be swallow-induced if it occurred during a swallow-induced LES relaxation. Straining was defined as a simultaneous increase in pressure in all manometric channels. LES pressure (LESP) was determined by subtracting the fundic pressure from the end-expiratory sleeve pressure. A low LESP was defined as a pressure below 0.5 kPa.

The liquid volume clearance time was defined as the time interval between a drop of ≥50% of baseline impedance until recovery above this point. The pH, pressure and impedance tracings were divided into four periods; the 1.15-h fasting period and three 1-h postprandial periods. The meal period was excluded from the analysis.

Statistics

In the analysis of differences between NaCl and placebo, a paired Wilcoxon signed-rank test was used. A Friedman test was used for multiple comparisons. A p-value of less than 0.05 was considered statistically significant. Throughout the article, data are presented as median values (interquartile range).

RESULTS

The volunteers were 24 years (22±27 years) of age with a body mass index (BMI) of 22 kg/m^2 (20±23). In all subjects 24-h sodium excretion was increased after NaCl intake (placebo 150 mmol (130±190); NaCl 270 mmol (250±310), p <0.01).

Esophageal acid exposure (the percentage of time with pH<4) was similar after placebo (11% (3-36) and NaCl (9% (1-36)) administration. Twenty-three (14.8-27) reflux episodes were found in the placebo tracings and 16 (13.5-22) in NaCl recordings, the difference not being significantly different (Figure 1). When the fasting period and the three postprandial time periods were analysed separately, there were no statistically significant differences in acid exposure and reflux episodes between placebo and NaCl.

More liquid than gaseous reflux episodes were found (liquid 17.5 (13-24); gas 2 (1-3)) and 60% (215/358) of all liquid reflux episodes were acidic (pH<4). Liquid acidic reflux was more common than weakly liquid acidic or gaseous reflux. No differences were found between placebo and NaCl for the number of liquid acidic reflux episodes (placebo 12 (6.5-17.3); NaCl 10 (2.3-14.3)), or for liquid weakly acidic reflux episodes (placebo 5.5 (4-12.3); NaCl 6.5 (3-10.8)); see Figure 1. Also the number of gaseous reflux episodes did not differ between placebo (1 (0-1.8)) and NaCl (2 (0-3))

The median proximal extent of gaseous reflux (placebo 18 cm (18-17.5); NaCl 18 cm (18-18)) and the proximal extent of liquid reflux (placebo 6.5 cm (7-10); NaCl 7 cm (7-10)) were similar under placebo and NaCl conditions. The nadir pH values of all acidic reflux episodes were the same under both conditions (placebo 2.7 (2.3-3); NaCl 2.5 (1.5-2.7)).

Liquid volume clearance times (placebo 15.8 s (13.5-18.6); NaCl 14.3 s (12.9-20.1)) and acid clearance times (placebo 19.8 seconds (14-25); NaCl 16.5 s (9-20.1)) did not differ between placebo and NaCl conditions.

Nineteen (15-22.5) TLESRs were recorded after placebo intake and 18.5 (12.8-21.5) after NaCl supplementation, which was not significantly different. Most TLESRs were seen in the first postprandial hour in both conditions (p<0.01). The TLESRs were distributed equally in the fasting and postprandial time periods after NaCl and placebo supplementation.

Under both placebo and high salt conditions the most common reflux mechanism was a TLESR (placebo 83% (70-91), NaCl 83% (58-94), NS). The second most identified mechanism for reflux was swallow-associated reflux (placebo 8% (3-21), NaCl 9% (0-33), NS). Low LESP-

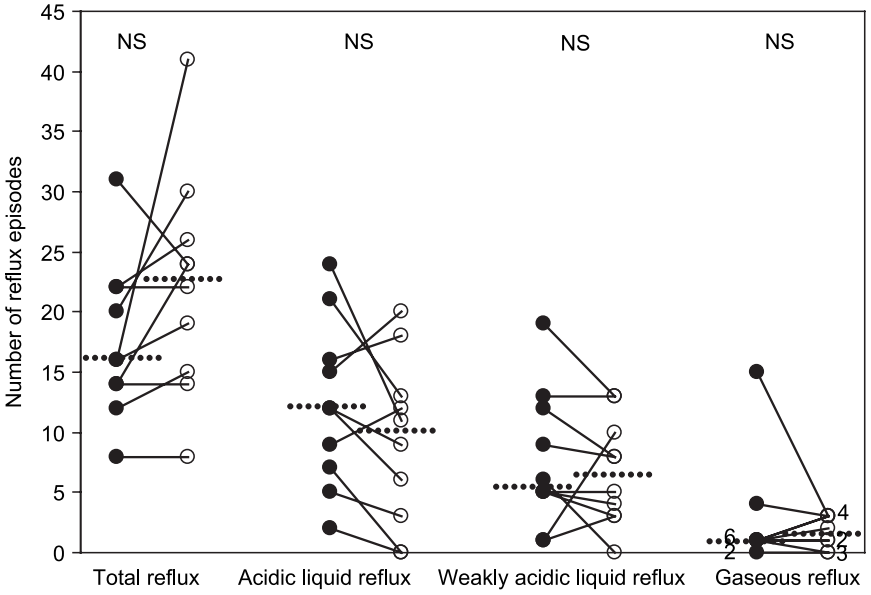

Figure 1. Number of reflux episodes (total, acidic liquid, weakly acidic liquid and gaseous reflux) for each subject after 7 days of high salt intake (○) and after 1 week of placebo (●). Medians are presented as a dotted line. The numbers at the dots and circles of gaseous reflux represent the number of subjects with the identical outcome. NS=not significant.

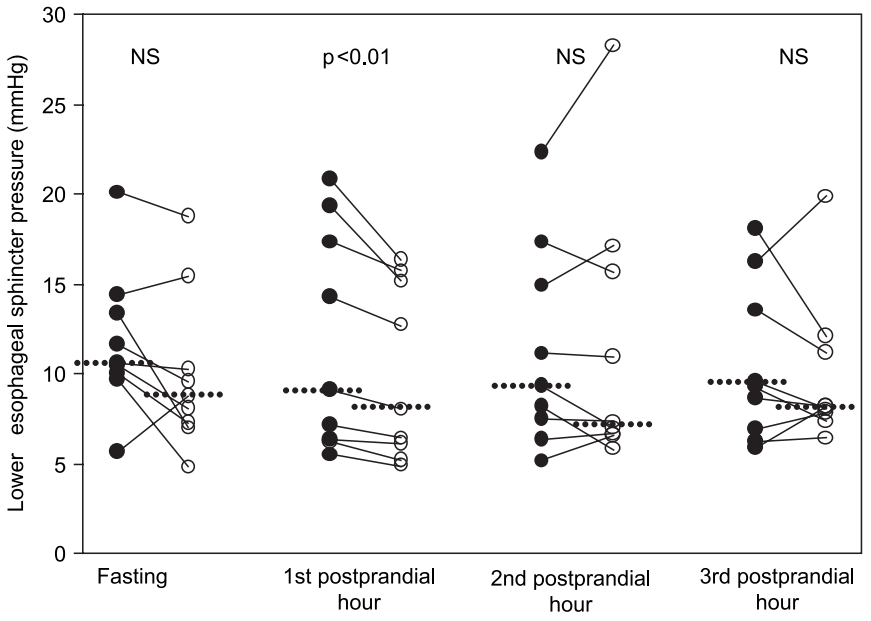

Figure 2. Lower esophageal sphincter (LES) pressures during the fasting and three postprandial 1-h periods. Circles (○) represent the pressures after increased NaCl exposure and dots (●) after placebo exposure. The dotted lines are the median values. During the high-NaCl diet, a lower LES pressure was seen in the first postprandial hour. No differences were seen between the four time periods. NS=not significant.

associated reflux (placebo 0% (0-5), NaCl 0% (0-5), NS), strain-induced reflux (placebo 2% (0-4), NaCl 0% (0-1), NS) and other/unknown reflux mechanisms (placebo 2% (0-6), NaCl 0% (0-1), NS) were rarely seen. Owing to a technical failure, abnormal high LESP was measured in one recording. This subject was therefore excluded in the analysis of the LESP. Lower pressures were found after high salt intake compared to placebo overall (placebo 9.9 mmHg (6.7-15.3); NaCl 8 mmHg (6.7-14.5), $p<0.01$), and during the first postprandial hour ($p<0.01$); see Figure 2. No differences in LESP were seen between the four time periods.

The swallow frequency per hour was similar after placebo and NaCl supplementation (placebo 62 (31.3-95.8); NaCl 69 (42-92.5)).

DISCUSSION

In a large epidemiological study conducted in Norway, dietary salt was found to increase the risk of severe recurrent heartburn and regurgitation dose-dependently (8). Another study concerning monozygotic and dizygotic twins showed that an increased intake of sodium was associated with GERD symptoms (9). It has been suggested that duodenal hypertonicity delays gastric emptying and increases the output of pancreaticobiliary secretions (10). Both mechanisms can increase the number of gastroesophageal reflux episodes. We therefore hypothesized that sodium chloride-associated symptoms might be caused by an increase in gastroesophageal acid or weakly acidic reflux and we tested this hypothesis in healthy volunteers by means of a double-blind, placebo-controlled, crossover trial.

In our study all participating subjects adhered to their capsule intake regimen, as could be observed after analysis of their 24-h sodium excretion. The results of this study show that there was no noticeable difference in the number of reflux episodes when the subjects increased their daily salt intake by 50% for a week. Similar incidences of acid, weakly acidic and gaseous reflux episodes were found under control and high-salt conditions. In accordance with other studies in normal healthy volunteers, most of the reflux episodes in this study were acidic (17).

The reflux mechanisms were similar after NaCl supplementation and after placebo. The most common reflux mechanism was a TLESR, which is in accordance with the literature (18). The number of TLESRs was similar after placebo and NaCl supplementation, including the first postprandial hour during which the incidence of TLESRs was the highest. The second most common reflux mechanism was the swallow-induced LES relaxation. Low LESP-induced, strain-induced and other unknown reflux mechanisms were rare.

Postprandial LESP was significantly lower after 7 days of high NaCl intake. But as demonstrated in this study, a low LESP did not correlate with an increase in reflux episodes in healthy volunteers (19). Finally, the percentage of time of pH below 4 in this study did not differ between the two recordings. The acidity of the reflux episodes was similar in both conditions as was the proximal extent to which the refluxate reached. Also the liquid and acid clearing time per reflux episode did not differ.

The results of our study suggest that an increase in dietary salt has no major effect on the occurrence or contents of gastroesophageal reflux in healthy volunteers. This might be due to a type II statistical error; however, it is also possible that salt only affects the occurrence of reflux episodes in GERD patients. Two previous studies in which the effects of a high salt intake were investigated were performed exclusively in patients with reflux symptoms (8;9). Nevertheless, if sodium chloride in the duodenum increases the number of gastroesophageal reflux events by delaying gastric emptying and increasing the output of pancreaticobiliary secretions, it is likely that this would also be visible in healthy subjects.

Given the findings of our study, it may well be that salt only affects the perception and not the incidence of reflux episodes or esophageal acid exposure. Observations have shown that saline and intraluminal nutrients in the duodenum are able to modulate the perception of events in the upper gastrointestinal tract (20;21). Other studies have focused on the direct irritating influence of hypertonic products such as salt. Price et al. found that in 66 patients with a positive Bernstein test, direct esophageal instillation with hyperosmolar solutions (orange juice, tomato mixtures and coffee) can cause similar symptoms to those caused by hydrochloric acid (0.1M) instillation (22). The symptoms still occurred when the pH of the hypertonic mixtures was adjusted to a pH above 7. LIoyd et al. demonstrated that hypertonic saline (630 mOsm/kg) and hypertonic sucrose (630 mOsm/kg) could evoke pain in 54% and 82% of acid-sensitive patients, respectively (23). In animal studies it has been shown that hypertonic luminal environments can impair the esophageal defence system, making the cells more susceptible to acid injury (24;25). Both studies using instillation of hyperosmolar solutions were performed after an acid perfusion test, which may have affected the esophageal mucosa as well. Therefore, Fletcher et al. (26) investigated the influence of hypertonic saline (1030 mOsm/kg) without previous acid exposure in healthy volunteers and GERD patients with and without Barrett's esophagus. Their study clearly showed that only GERD patients responded to the hypertonic provocation, while all subjects responded to acidic and hypertonic acidic solutions. These findings indicate that a symptomatic response to hypertonicity only occurs in GERD patients, which suggests that other factors such as the condition of the esophageal mucosal layer play a role.

In the case of damaged mucosa, i.e. esophagitis, it has been suggested that acid and hyperosmolar substances can directly interfere with chemosensitive nociceptors. However, the majority of patients with reflux symptoms have a normal-appearing mucosa at endoscopy. With this in mind, new mechanisms have been proposed. These mechanisms concern a dysfunction in the epithelial barrier function (27;28).The junctions between the esophageal epithelial cells are damaged by acid or by noxious substances, which can result in increased paracellular permeability for water, electrolytes and small molecules. This enables a direct stimulation of the chemosensitive nociceptors, which are known to respond with pain to low acidic environments (5.2-6.9) or altered osmolality (24;25). The increase in salt and water flow across the junctions also leads to an early lesion of GERD, namely dilated intracellular spaces (29;30).

In conclusion, our data suggest that salt does not increase the number of acidic or weakly acidic gastroesophageal reflux episodes despite a decrease in LES pressure. We highly recommend further investigations on the relation between esophageal perception and the intake of sodium chloride and other hypertonic solutions.

REFERENCES

(1) Locke GR, III, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ, III. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997; 112(5):1448-1456.

(2) Irvine EJ. Quality of life assessment in gastro-oesophageal reflux disease. Gut 2004; 53 Suppl 4:35-39.

(3) Tutuian R, Castell DO. Reflux monitoring: role of combined multichannel intraluminal impedance and pH. Gastrointest Endosc Clin N Am 2005; 15(2):361-371.

(4) Goh KL. Changing epidemiology of gastroesophageal reflux disease in the Asian-Pacific region: an overview. J Gastroenterol Hepatol 2004; 19 Suppl 3:S22-S25.

(5) Sung JJ. Westernisation of gastrointestinal diseases in Asia. Gut 2004; 53(1):152.

(6) Watanabe Y, Fujiwara Y, Shiba M, Watanabe T, Tominaga K, Oshitani N et al. Cigarette smoking and alcohol consumption associated with gastro-oesophageal reflux disease in Japanese men. Scand J Gastroenterol 2003; 38(8):807-811.

(7) DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol 2005; 100(1):190-200.

(8) Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Lifestyle related risk factors in the aetiology of gastro-oesophageal reflux. Gut 2004; 53(12):1730-1735.

(9) Mohammed I. Are diet and physical activity risk factors for gastro-oesophageal reflux disease symptoms: a study of discordant twins? Gastroenterology 2005; 128(4 Suppl 2):M1760.

(10) Tanaka T, Mizumoto A, Muramatsu S, Mochiki E, Haga N, Suzuki H et al. Postprandial normal saline intake delays gastric emptying of solids in conscious dogs: partial involvement of CCK in its mechanism. Dig Dis Sci 1999; 44(8):1516-1524.

(11) Allen ML, Mellow MH, Robinson MG, Orr WC. The effect of raw onions on acid reflux and reflux symptoms. Am J Gastroenterol 1990; 85(4):377-380.

(12) Bredenoord AJ, Weusten BL, Timmer R, Smout AJ. Reproducibility of multichannel intraluminal electrical impedance monitoring of gastroesophageal reflux. Am J Gastroenterol 2005; 100(2):265-269.

(13) Trifan A, Shaker R, Ren J, Mittal RK, Saeian K, Dua K et al. Inhibition of resting lower esophageal sphincter pressure by pharyngeal water stimulation in humans. Gastroenterology 1995; 108(2):441-446.

(14) Bredenoord AJ, Weusten BL, Timmer R, Smout AJ. Minimum sample frequency for multichannel intraluminal impedance measurement of the oesophagus. Neurogastroenterol Motil 2004; 16(6):713-719.

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

(16) Holloway RH, Penagini R, Ireland AC. Criteria for objective definition of transient lower esophageal sphincter relaxation. Am J Physiol 1995; 268(1 Pt 1):G128-G133.

(17) Shay S, Tutuian R, Sifrim D, Vela M, Wise J, Balaji N et al. Twenty-four hour ambulatory simultaneous impedance and pH monitoring: a multicenter report of normal values from 60 healthy volunteers. Am J Gastroenterol 2004; 99(6):1037-1043.

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

(19) Mittal RK, Holloway R, Dent J. Effect of atropine on the frequency of reflux and transient lower esophageal sphincter relaxation in normal subjects. Gastroenterology 1995; 109(5):1547-1554.

(20) Janig W, Khasar SG, Levine JD, Miao FJ. The role of vagal visceral afferents in the control of nociception. Prog Brain Res 2000; 122:273-287.

(21) Meyer JH, Lembo A, Elashoff JD, Fass R, Mayer EA. Duodenal fat intensifies the perception of heartburn. Gut 2001; 49(5):624-628.

(22) Price SF, Smithson KW, Castell DO. Food sensitivity in reflux esophagitis. Gastroenterology 1978; 75(2):240-243.

(23) Lloyd DA, Borda IT. Food-induced heartburn: effect of osmolality. Gastroenterology 1981; 80(4):740-741.

(24) Long JD, Marten E, Tobey NA, Orlando RC. Effects of luminal hypertonicity on rabbit esophageal epithelium. Am J Physiol 1997; 273(3 Pt 1):G647-G654.

(25) Long JD, Marten E, Tobey NA, Orlando RC. Luminal hypertonicity and the susceptibility of rabbit esophagus to acid injury. Dis Esophagus 1998; 11(2):94-100.

(26) Fletcher J, Gillen D, Wirz A, McColl KE. Barrett's esophagus evokes a quantitatively and qualitatively altered response to both acid and hypertonic solutions. Am J Gastroenterol 2003; 98(7):1480-1486.

(27) Barlow WJ, Orlando RC. The pathogenesis of heartburn in nonerosive reflux disease: a unifying hypothesis. Gastroenterology 2005; 128(3):771-778.

(28) Castell DO, Murray JA, Tutuian R, Orlando RC, Arnold R. Review article: the pathophysiology of gastro-oesophageal reflux disease - oesophageal manifestations. Aliment Pharmacol Ther 2004; 20 Suppl 9:14-25.

(29) Calabrese C, Fabbri A, Bortolotti M, Cenacchi G, Areni A, Scialpi C et al. Dilated intercellular spaces as a marker of oesophageal damage: comparative results in gastro-oesophageal reflux disease with or without bile reflux. Aliment Pharmacol Ther 2003; 18(5):525-532.

(30) Tobey NA, Carson JL, Alkiek RA, Orlando RC. Dilated intercellular spaces: a morphological feature of acid reflux--damaged human esophageal epithelium. Gastroenterology 1996; 111(5):1200-1205.

Summary

SUMMARY

In the introduction the definition of GERD is described as well as the epidemiology and demographics of this disease. Insights into the pathophysiology of GERD are provided and the complexity of the perception of reflux events as GERD symptoms is discussed. Diagnosing GERD is difficult when no esophageal lesions are found, which is the case in the majority of GERD patients. Then, the most appropriate technique is ambulatory reflux monitoring, in order to assess esophageal acid exposure and to determine a relationship between reflux symptoms and reflux events with the use of symptom association indices such as the SAP, SI and SSI. Impedance-pH monitoring is the gold standard for detecting reflux events. Finally, this chapter addresses the challenge of diagnosing GERD in primary care without the use of the above-described techniques. The general reflux history and PPI test are the main tools used in a primary care practice.

At the end of the chapter the aims of this thesis are presented.

Chapter 1

Relaxation of the lower esophageal sphincter (LES) causing an open connection between the esophagus and the stomach is often accompanied by simultaneous intraesophageal pressure rise to gastric pressure level, which can be recognized on manometry as a “common cavity phenomenon”. The manometric common cavity phenomenon has been used as indicator of gastroesophageal reflux of liquid or of gaseous substances.

In our study combined pH and impedance recording was used as reference standard in an assessment of the value of the common cavity as indicator of gastroesophageal reflux. Ten healthy male subjects underwent combined stationary pressure, pH and impedance recording for 4.5 h. A common cavity was found in 43% of all reflux events detected by impedance, while only a minority of the common cavities found was unrelated to a reflux episode. In 54% of the reflux, events detected by impedance during which a common cavity was not detected, the common cavity could possibly have been obscured by either contractile activity or artefacts of various origins. The types of reflux associated with a common cavity (liquid 60%, mixed 31%, gas 9%) and without a common cavity (liquid 59%, mixed 29%, gas 12%) did not differ, nor did the acidity of the reflux episodes, most of which were acidic. We concluded that the common cavity is a specific but not a sensitive marker of gastroesophageal reflux. Furthermore, common cavities are not specific for a particular type of reflux.

Chapter 2

Despite the introduction of impedance monitoring, esophageal pH monitoring is still a frequently used technique to measure gastroesophageal reflux. pH drops from above to below pH 4 and pH drops of ≥1 pH unit are used as marker for gastroesophageal reflux. In this chapter the accuracy of pH drops for detection of gastroesophageal reflux was

investigated, using impedance monitoring as gold standard. All pH drops and impedance reflux events were determined in combined 24-h pH-impedance recording of 19 GERD patients who were studied off acid-suppressive therapy.

Most of the pH drops found were acidic (nadir pH<4) and weakly acidic (nadir pH between pH 7-4), while only a few pH drops were indicative of superimposed reflux events (pH drop starting below pH 4). We found that, compared to impedance monitoring, the detection of reflux with pH monitoring is clearly inferior. When drops ≥1 pH unit irrespective of nadir pH are used as an indicator of reflux episodes, the number of reflux episodes is overestimated. Drops from above to below 4 with a magnitude ≥0.5 and <3.3 are most indicative for true reflux episodes.

Chapter 3

The temporal relationship between reflux symptoms and reflux episodes reported and observed during ambulatory reflux monitoring can be studied with symptom association analysis. The symptom index (SI) represents the percentage of reflux events associated with symptoms and the symptom sensitivity index (SSI) is the percentage of symptoms associated with reflux episodes, whereas the symptom association probability (SAP) expresses the statistical relationship between the occurrence of symptoms and reflux episodes in two-minute segments of the recording using the Fisher exact test.

In this chapter the reproducibility of these symptom association indices were studied in 21 patients with typical reflux symptoms who underwent two 24-h combined pH-impedance recordings off acid secretion inhibiting medication with an interval of 1-4 weeks. The SAP, SI and SSI were calculated for both measurements and the reproducibility of these indices was determined with Kendall's coefficient of concordance. In the 24-h pH-impedance recordings of patients with reflux symptoms the number of symptoms reported was not reproducible while, in contrast, the reflux events and the number of symptoms related to reflux events were highly reproducible. The SI was found to be less reproducible than the SAP and SSI. Overall, the SAP was the most consistently reproducible index irrespective of which reflux detection method was used. Therefore, we advocate the use of the SAP to express the relationship between symptoms and reflux episodes in clinical practice.

Chapter 4

GERD patients appear to be heterogeneous with respect to the pathophysiological mechanisms involved in the generation of their symptoms. Therefore, a mixed response to proton pump inhibitor (PPI) treatment can be expected. In this chapter the effect of short-term PPI treatment on symptoms and quality of life (QOL) in primary care patients with and without pathological esophageal acid exposure and in the presence or absence of a positive association between symptoms and reflux episodes was investigated.

The population studied consisted of 74 heartburn patients with heartburn and these were categorized into 4 groups according to positive or negative symptom-reflux association, as

expressed in symptom index (SI), symptom sensitivity index (SSI) and symptom association probability (SAP) and presence or absence of pathological reflux. Overall and specific reflux symptoms were assessed one week before and in the last week during a 2-week course of 40 mg esomeprazole daily. The QOL was scored by the QOLRAD questionnaire two weeks before treatment and directly after treatment. It was found that the symptomatic reflux patients without evidence of reflux disease on a 24-hour pH recording responded less favorably to PPI treatment than patients with a positive symptom-reflux association or with pathological reflux. This poor response concerned symptoms as well as quality of life.

Chapter 5

In general practice, the response to a short course of an acid suppressant, the so-called proton pump inhibitor (PPI) test, is used as a diagnostic tool to diagnose GERD. In this chapter the diagnostic accuracy of the proton pump inhibitor test in a primary care population as well as its additional value over reflux history was assessed by using the symptom association probability (SAP) outcome during 24-h esophageal pH recording as reference test for presence of gastroesophageal reflux disease. Primary care patients with symptoms suggestive of GERD underwent a 24-h pH recording to determine the SAP. Subsequently, subjects started using 40 mg esomeprazole once daily for 13 days. The PPI test was considered positive when the subjects reported adequate symptomatic relief. We found that in primary care patients with reflux symptoms gastroesophageal reflux disease was highly prevalent as 70% of the subjects had a positive SAP. The sensitivity of the PPI test was high while the specificity was low. The ambivalence of the PPI is shown by the mean likelihood ratio which was 1.2 (CI 0.9–1.6) during the consecutive 13 days. We concluded that, due to the frequent occurrence of GERD, the additional value of short-term treatment with a PPI for diagnosing gastroesophageal reflux disease is limited.

Chapter 6

A questionnaire to diagnose GERD could improve the diagnostic accuracy in primary care practice and could offer the possibility to quantify the response to therapy. In this chapter the diagnostic and therapeutic response of the Reflux Disease Questionnaire (RDQ) was determined using the symptom association probability (SAP) as a reference test. Secondly, the RDQ's construct validity and its relationship to quality of life (QOL) was ascertained. Seventy-four primary care patients with GERD symptoms completed the RDQ, GSRS and QOLRAD before and after a 2 weeks' course of esomeprazole 40 mg daily. The SAP was determined by 24-hour pH recording before PPI treatment. The diagnostic abilities of the RDQ (total and 4 dimensions scores) were assessed with the area under the curve (AUC) of a receiver operating curve. Using multiple linear regression analysis the RDQ's construct validity (GSRS) and relationship to QOL (QOLRAD) were assessed. The RDQ showed to be a valid and reliable questionnaire with excellent construct validity and a good relationship to QOL. The diagnostic value of the RDQ in primary care was limited. However, the combination with an additional PPI treatment course might improve the RDQ's ability to discriminate GERD patients according to their SAP outcome.

Chapter 7

It has been suggested that a high consumption of sodium chloride (NaCl) is associated with reflux symptoms. Therefore, in this chapter the effect of increased dietary NaCl intake on gastroesophageal reflux and reflux mechanisms was investigated. A double-blind, placebo-controlled, crossover study was carried out in 10 healthy male subjects who received 5 g NaCl per day or placebo in capsules for one week, after which concurrent manometric, pH and impedance monitoring was carried out for 4.5 h. This study showed that a high-sodium intake does not increase gastroesophageal reflux in healthy volunteers, despite a decrease in LES pressure.

The questions that were formulated at the end of the introduction can be answered as follows:

1. Is the manometric common cavity specific for a certain type of reflux?
The manometric common cavity is a highly specific but insensitive marker of gastroesophageal reflux. However, it showed not to be exclusive for a certain reflux type. A common cavity is often associated with acidic liquid reflux, however, weakly acid as well as gaseous reflux can also be seen.

2. Can pH recordings still clinically be used for diagnosis of GERD?
The pH recording is inferior compared to impedance for detection of reflux and leads to an overestimation of the number of detected reflux events. However, the symptom association probability (SAP) index is less affected by the overestimation of reflux events. When diagnosing GERD with ambulatory esophageal pH recording it is best to use the SAP.

3. Are the symptom-reflux association analysis indices reproducible?
Symptoms related to reflux events and detected reflux events are highly reproducible. SAP and SSI indices are better reproducible than the SI.

4. What patients groups seem to benefit most from PPI treatment?
Patients with either a positive SAP or pathological percentage of acidic reflux or both have the best response to PPI treatment. Symptomatic reflux patients without any evidence of GERD respond less favorably.

5. Is the PPI test a useful addition to reflux history?
In primary care patients GERD is highly prevalent under patients with GERD symptoms. Under these conditions the additional value of a short-term treatment with a PPI as diagnostic tool is limited.

6. Is the RDQ a useful diagnostic tool in general practice?
Despite its excellent construct validity the RDQ is not able to discriminate patients with and without GERD according to the SAP outcome. Consequently, the RDQ is not useful as diagnostic tool in primary care practice. The discriminative power could improve however by comparing pre- and post-PPI treatment outcomes, but more research is needed.

7. Does a direct causal relationship exist between an increased salt intake and gastroesophageal reflux?
An increased dietary salt intake lowers LES pressure but does not increase gastroesophageal reflux in healthy volunteers. However, this observation does not rule out the possibility that increased intake of dietary salt affects esophageal perception and thus leads to an increase in reflux symptoms.

Nederlandse Samenvatting

Nederlandse Samenvatting

In de algemene inleiding wordt de gastro-oesofageale refluxziekte gedefinieerd. De epidemiologie en de demografie worden behandeld en daarnaast worden de huidige inzichten van de pathofysiologie van gastro-oesofageale refluxziekte beschreven. Het blijkt dat de relatie tussen de perceptie van refluxsymptomen en het optreden van reflux-episoden erg complex is. Vervolgens worden de mogelijkheden die bestaan voor het diagnosticeren van gastro-oesofageale refluxziekte weergegeven. Endoscopie is het minst geschikte onderzoek voor het diagnosticeren van gastro-oesofageale reflux omdat de meeste refluxpatiënten geen oesofageale laesies hebben. De meest geëigende manier om gastro-oesofageale refluxziekte te diagnosticeren is om een relatie aan te tonen tussen refluxepisodes en refluxsymptomen. Hiervoor worden indexen gebruikt zoals de Symptom Association Probability (SAP), Symptom Index (SI) en Symptom Sensitivity Index (SSI). De referentiestandaard voor refluxdetectie is de pH-impedantie-meting.

In dit hoofdstuk wordt ook aandacht besteed aan het diagnosticeren van gastro-oesofageale refluxziekte in de huisartsenpraktijk en de uitdagingen die hieraan kleven gezien het feit dat huisartsen niet beschikken over de bovenbeschreven technieken. De refluxanamnese en de zogenaamde proton pump inhibitor (PPI) test zijn de screeningsmethoden waarvan de huisarts gebruikt maakt. Tenslotte worden aan het einde van het hoofdstuk de doelstellingen van deze dissertatie besproken.

Hoofdstuk 1

Tijdens de relaxatie van de onderste slokdarmsfincter ontstaat er een open verbinding tussen de oesofagus en de maag, die vaak leidt tot een simultane intra-oesofageale drukverhoging totaan het drukniveau in de maag. Deze drukverhoging kan manometrisch herkend worden als een “common cavity” fenomeen. Het “common cavity” fenomeen wordt veelvuldig gebruikt voor het detecteren van reflux-episodes die specifiek zijn voor gas of een vloeibare consistentie. Door gebruik te maken van pH-impedantie-metingen als referentie was het mogelijk om te testen hoe goed een “common cavity” fenomeen reflux detecteert. Tien gezonde mannen ondergingen een stationaire drukmeting en pH-impedantiemeting gedurende 4.5 uur. Een “common cavity” fenomeen werd gezien bij 43% van alle door middel van impedantie gedetecteerde reflux-episoden en slechts weinig “common cavity” fenomenen waren niet gerelateerd aan reflux. Bij de 54% van de impedantie-gedetecteerde reflux-episodes waar geen “common cavity” fenomeen werd gezien, zou dit mogelijk gemist zijn door het gelijktijdige optreden van plotselinge contractiele activiteit en artefacten met verschillende origine. De consistentie van reflux episodes met een “common cavity” fenomeen (vloeibaar 60%, gemixed 31%, gas 9%) verschilde niet van reflux zonder het “common cavity” fenomeen (vloeibaar 59%, gemixed 29%, gas 12%). Ook de zuurgraad van de reflux-episodes, waarvan de meeste een pH beneden de 4 hadden, verschilde niet. Er werd geconcludeerd dat het “common cavity” fenomeen een specifieke marker is voor gastro-oesofageale reflux maar dat een “common cavity” fenomeen niet specifiek is voor een bepaald type reflux.

Hoofdstuk 2

Ondanks de introductie van een nieuwe referentie standaard, de gecombineerde pH-impedantie-meting, worden pH-metingen nog steeds frequent gebruikt om gastro-oesofageale reflux episodes te detecteren. Hierbij wordt een pH daling van boven 4 naar onder 4 en dalingen groter dan 1 pH eenheid gezien als indicatief voor gastro-oesofageale reflux. In dit hoofdstuk wordt de nauwkeurigheid van deze pH-dalingen voor de detectie van gastro-oesofageale reflux onderzocht met de nieuwe pH-impedantie techniek. Bij 19 gastro-oesofageale refluxpatienten die op dat moment geen zuursuppressie medicatie gebruikten werden alle pH- en impedantiedalingen suggestief voor reflux-episodes opgespoord. De meeste gevonden pH-dalingen gingen door de pH grens van 4, en/of bleven tussen pH 4 en pH 7. Slechts weinig pH-dalingen werden gezien wanneer de pH al beneden de pH 4 grens was. De detectie van reflux-episoden met behulp van pH-metingen was duidelijk inferieur ten opzichte van impedantiemetingen. Bij gebruik van pH-dalingen groter dan 1, onafhankelijk bij welke pH, wordt het aantal reflux-episodes overschat. Analyse op basis van pH-dalingen die de pH 4 grens doorkruizen en groter zijn dan 0.5 maar kleiner dan 3.3 leveren de kleinste kans op overschatting van het aantal reflux-episodes op.

Hoofdstuk 3

De relatie tussen refluxsymptomen en reflux-episodes gemeten tijdens een ambulante refluxmeting kan het best bestudeerd worden met een symptoom-associatie analyse. De symptoomindex (SI) vertegenwoordigt het percentage reflux-episoden dat geassocieerd is met symptomen en de symptoomsensitiviteit index (SSI) vertegenwoordigt het percentage symptomen dat geassocieerd is met reflux-episoden De symptoom associatie probabiliteit (SAP) combineert beide parameters tot een index die de statistische relatie tussen het voorkomen van symptomen en reflux-episoden berekent met behulp van de Fisher's exact test.

In dit hoofdstuk werd de reproduceerbaarheid van deze indices bestudeerd bij 21 patiënten die zich presenteerden met typische refluxsymptomen en die, na staken van de zuurremmende medicatie, twee maal een 24-uurs pH-impedantie meting ondergingen met een minimale tussenpoos van 1 tot 4 weken. De SAP, SI en SSI werden voor elke meting berekend en de reproduceerbaarheid van deze indices werd vastgesteld met de "Kendall's coefficient of concordance". Voor de 24-uurs pH-impedantiemetingen was er geen reproduceerbaarheid van het aantal refluxsymptomen gevonden, terwijl de reflux-episoden en het aantal reflux-gerelateerde symptomen sterk reproduceerbaar waren. De SI was in vergelijking met de SAP en de SSI het minst reproduceerbaar. Over het algemeen was de SAP index het meest consistent reproduceerbaar, onafhankelijk van welke refluxdetectiemethode gebruikt werd. Wij adviseren voor het uitdrukken van de relatie tussen symptomen en reflux-episoden de SAP te gebruiken in de klinische setting.

Hoofdstuk 4

Gastro-oesofageale refluxpatiënten tonen een verschil in pathofysiologische achtergrond. Hierdoor kan ook een heterogene respons worden verwacht op een behandeling met een proton pomp remmer (PPI). In dit hoofdstuk wordt het effect van een kortdurende PPI behandeling in de huisartsenpraktijk onderzocht op de symptomen en de kwaliteit van leven van patiënten enerzijds met en zonder pathologische oesophageale zuurexpositie enerzijds en met of zonder een positieve associatie tussen de symptomen en reflux–episoden anderzijds. De onderzochte populatie bestond uit 74 patiënten met zuurbranden en deze werden gecategoriseerd in 4 groepen gebaseerd op de aanwezigheid van positieve of negatieve symptoom-reflux associatie zoals SAP, SI of SSI en de aan- of afwezigheid van pathologische reflux. Algemene en specifieke refluxsymptomen werden geïnventariseerd gedurende 1 week voor en de laatste week van een 2-weken durende kuur van eenmaal daags 40 mg esomeprazol. De kwaliteit van leven werd gescoord met behulp van de QOLRAD vragenlijst die 2 weken voor de start van de behandeling en direct na de behandeling ingevuld werd. De resultaten toonden dat de symptomatische refluxpatiënten die geen tekenen hadden van refluxziekte bij 24-uurs pH meting minder reageerden op een PPI kuur dan patiënten met een positieve symptoom-reflux associatie, of patiënten met een pathologische zuurexpositie. De slechte respons gold voor zowel symptomen als kwaliteit van leven.

Hoofdstuk 5

In de huisartsenpraktijk wordt gebruik gemaakt van de Proton Pomp Inhibitor test (PPI-test) waarmee aan de hand van de reactie op een kortdurende behandeling met een zuurremmer wordt gekeken of patiënten met klachten van zuurbranden gastro-oesofageale refluxziekte hebben. In dit hoofdstuk wordt de diagnostische waarde van de PPI-test alswel de toegevoegde waarde van deze test naast een reflux-anamnese in de huisartsenpraktijk onderzocht aan de hand van de symptoom associatie probabiliteit (SAP) uitkomst van een 24-uurs pH meting. Eerstelijns patiënten met reflux-suggestieve klachten ondergingen een 24-uurs pH meting waarna de SAP werd berekend. Vervolgens startten de reflux patiënten met een PPI gedurende 13 dagen. De PPI-test was positief, ofwel suggestief voor de diagnose gastro-oesofageale reflux, wanneer de symptomen adequaat onderdrukt waren. In de huisartsenpraktijkpopulatie bleek dat 70% van de geïncludeerde patiënten een positieve SAP hadden. De PPI-test had een hoge sensitiviteit en een lage specificiteit. De ambivalentie van de PPI-test wordt duidelijk aan de hand van de gevonden “likelihood ratios” die gedurende de 13 testdagen rond de 1.2 (CL 0.9-1.6) waren. Concluderend kon gesteld worden dat door het frequent voorkomen van de gastro-oesofageale refluxziekte de additionele waarde van de PPI-test in de huisartsenpraktijk beperkt is.

Hoofdstuk 6

Het gebruik van een specifieke gastro-oesofageale refluxziekte-vragenlijst biedt een mogelijkheid tot eenduidigheid in het diagnosticeren van gastro-oesofageale refluxziekte, plus de optie tot het kwantificeren van het effect van behandeling. In dit hoofdstuk werd de diagnostische en therapeutische respons van de “Reflux Disease Questionnaire” (RDQ) vragenlijst bepaald aan de hand van de SAP-uitkomst. Secundair werd de constructievaliditeit met behulp van de GSRS vragenlijst bepaald en de relatie met kwaliteit van leven aan de hand van de QOLRAD vragenlijst vastgesteld. In totaal vulden 74 huisartspatiënten met gastro-oesofageale refluxklachten de RDQ, GSRS en de QOLRAD vragenlijsten in een week voor en twee weken na gebruik van esomeprazol 40 mg gedurende twee weken. De SAP werd bepaald aan de hand van 24-uurs pH-meting voor de behandeling met esomeprazol. De diagnostische waarde van de RDQ (totale score en de 4 dimensie scores) werd bepaald aan de hand van de ‘area under the curve’ (AUC) van een “receiver operating curve”. Met behulp van multipele lineaire regressies werd de constructievaliditeit en de relatie tot kwaliteit van leven bepaald van de RDQ. De RDQ bleek een valide en betrouwbare vragenlijst met een goede constructievaliditeit en met een duidelijke weergave van de kwaliteit van leven. De diagnostische waarde van de RDQ bleek echter beperkt. Wellicht zou de RDQ vragenlijst in combinatie met een PPI-behandeling gastro-oesfageale refluxpatiënten kunnen onderscheiden volgens de SAP uitkomst.

Hoofdstuk 7

In de literatuur is gesuggereerd dat een hoge zoutconsumptie geassocieerd is met refluxsymptomen. In dit hoofdstuk werd onderzocht wat het effect is van een hoge zoutinname op gastro-oeosofageale reflux en refluxmechanismen. Een dubbel-blinde, placebo-gecontroleerde, cross-over studie werd uitgevoerd bij 10 gezonde mannen die gedurende een week 5 gram NaCl of een placebo in capsules innamen, waarna een manometrie en pH-impedantie-meting volgde gedurende 4.5 uur. Dit onderzoek liet zien dat een hoge zoutinname bij gezonde mannelijke vrijwilligers niet leidt tot een toename van gastro-oesofageale reflux, ondanks een verlaging van de onderste slokdarmsfincterdruk.

Antwoorden op de aan het eind van de introductie geformuleerde vragen.

1. Is het manometrische "common cavity" fenomeen specifiek voor een bepaald type reflux?
Het "common cavity" fenomeen is zeer specifiek maar niet sensitief voor detectie van reflux. Het is aspecifiek voor het type reflux. Een "common cavity" fenomeen komt het meest voor bij zure, vloeibare reflux maar wordt ook bij matige zure reflux en gas reflux gezien.

2. Kan een oesofageale pH-meting nog steeds gebruikt worden in de kliniek voor het diagnosticeren van gastro-oesofageale refluxziekte?
De oesofageale pH-meting is inferieur in vergelijking met impedantie voor de detectie van reflux en kan leiden tot een overschatting van het aantal reflux-episodes. De SAP is minder gevoelig voor overschatting van het aantal reflux-episodes. Bij het diagnosticeren van gastro-oesofageale refluxziekte met behulp van oesofageale pH-meting kan het beste de SAP gebruikt worden.

3. Zijn de symptoom associatie analyse indices reproduceerbaar?
Symptomen gerelateerd aan reflux-episodes en gedetecteerde reflux-episodes zijn goed reproduceerbaar. De SAP en SSI zijn ook goed reproduceerbaar, terwijl de SI minder goed reproduceerbaar is.

4. Welke groepen patiënten profiteren het meest van PPI-behandeling?
Patiënten met of een positieve SAP of een pathologisch percentage zure reflux, of beide, hebben de beste reactie op een PPI-behandeling. Symptomatische patiënten zonder duidelijk bewijs van gastro-oesofageale refluxziekte reageren het minst op de behandeling.

5. Voegt de PPI test iets toe aan een refluxanamese?
In een huisartsenpopulatie blijkt gastro-oesofageale refluxziekte veelvuldig voor te komen bij patiënten met gastro-oesofageale refluxsymptomen. Onder deze omstandigheden is de additionele waarde van een PPI test beperkt.

6. Is de RDQ een bruikbaar diagnostisch instrument in de huisartsenpraktijk?
Met de RDQ vragenlijst is het niet mogelijk om onderscheid te maken tussen patiënten met en patiënten zonder gastro-oesofageale refluxziekte volgens de SAP uitkomst, ondanks de uitstekende constructievaliditeit van deze vragenlijst. De RDQ is dus niet geschikt als diagnosticum. Het discriminerende vermogen van deze potentiële diagnostische vragenlijst zou mogelijk verbeterd kunnen worden door uitkomsten voor en na een PPI-behandeling te vergelijken.

7. Bestaat er een direct causaal veband tussen verhoogde zoutinname en gastro-oesofageale reflux?
Bij gezonde vrijwilligers leidt een verhoogde zoutinname tot een verlaging van de druk in de onderste slokdarmsfincter, maar niet tot een toename van gastro-oesofageale reflux. Desalniettemin zou een verhoogde zoutinname via een toegenomen perceptie in de oesofagus alsnog kunnen leiden tot een toename van gastro-oesofageale refluxsymptomen.

List of Publications

List of Publications

Aanen MC, de Waart DR, Williams PF, Out TA, Zweers MM, Krediet RT. Dextran antibodies in peritoneal dialysis patients treated with icodextrin. Perit Dial Int 2002; 22(4):513-515.

Aanen MC, Venturoli D, Davies SJ. A detailed analysis of sodium removal by peritoneal dialysis: comparison with predictions from the three-pore model of membrane function. Nephrol Dial Transplant 2005; 20(6):1192-1200.

Aanen MC, Bredenoord AJ, Smout AJ. Effect of dietary sodium chloride on gastro-oesophageal reflux: a randomized controlled trial. Scand J Gastroenterol 2006; 41(10):1141-1146.

Aanen MC, Weusten BL, Numans ME, de Wit NJ, Baron A, Smout AJ. Diagnostic value of the proton pump inhibitor test for gastro-oesophageal reflux disease in primary care. Aliment Pharmacol Ther 2006; 24(9):1377-1384.

Aanen MC, Bredenoord AJ, Samsom M, Smout AJ. The gastro-oesophageal common cavity revisited. Neurogastroenterol Motil 2006; 18(12):1056-1061.

Aanen MC, Numans ME, Weusten BL, Smout AJ. Diagnostic value of the Reflux Disease Questionnaire in general practice. Digestion 2006; 74(3-4):162-168.

Aanen MC, Weusten BL, Numans ME, de Wit NJ, Samsom M, Smout AJ. Effect of Proton-Pump Inhibitor Treatment on Symptoms and Quality of Life in GERD Patients Depends on the Symptom-reflux Association. J Clin Gastroenterol 2008; 42(5):441-447

Aanen MC, Bredenoord AJ, Weusten BL, Samsom M, Smout AJ. Reproducibility of Symptom Association Analysis in Ambulatory Reflux Monitoring. Am J Gastroenterol; accepted

Dankwoord

Dankwoord

Ik wil graag iedereen bedanken die een bijdrage heeft geleverd aan het tot stand komen van dit proefschrift!

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Familie en schoonfamilie

Ping

Curriculum Vitae

Curriculum Vitae

Marissa Celia Aanen werd geboren op 1 februari 1980 te Gouda. Na het behalen van haar VWO diploma is zij geneeskunde gaan studeren aan de Universiteit van Amsterdam. Zij heeft toen een stage kunnen lopen in Diakonessen Ziekenhuis te Paramaribo in Suriname. Tijdens de studie geneeskunde heeft zij de grondbeginselen van het onderzoek geleerd bij Professor Krediet aan de afdeling Nefrologie in het AMC waar zij onderzoek deed naar icodextrin-geïnduceerde peritonitis. Zij heeft vervolgens met een beurs van de Nierstichting kunnen werken als Elective Reseach Student in Stoke-On-Trent te Engeland. Het onderzoek ging over de mogelijkheden om zouten te verwijderen tijdens peritoneale dialyse bij nierpatiënten. Tijdens haar co-schappen heeft zij nog een periode kunstgeschiedenis gestudeerd. Na afronding van de studie geneeskunde is zij aan de slag gegaan als arts onderzoeker op de afdeling Maag-, Darm-, en Leverziekten in het UMC Utrecht bij haar promotor Professor Smout. Na het afronden van deze promotie over gastro-oesofageale reflux ziekten heeft zij een wereldreis gemaakt in Azië alwaar zij aan de BCLU University Beijing China, Mandarijns Chinees heeft gestudeerd. Op dit moment is zij werkzaam in het Tergooiziekenhuizen, locatie Hilversum als arts assistent interne geneeskunde.