Gastro-oesophageal reflux and belching revisited

A.J. Bredenoord

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Bredenoord, Albert Jan

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Gastro-oesophageal reflux and belching revisited

Gastro-oesofageale reflux en boeren herbezien

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. W.H. Gispen, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op vrijdag 22 september 2006 des middags om 12.45 uur

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Albert Jan Bredenoord
geboren op 9 november 1977 te Utrecht

Promotor:	Prof. dr. A.J.P.M. Smout
Co-promotoren:	Dr. B.L.A.M. Weusten Dr. R. Timmer

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1

General introduction

Both gastro-oesophageal reflux and belching are physiological phenomena. Gastro-oesophageal reflux is the backward flow of gastric contents into the oesophagus. Belching or eructation is the voiding of gas from the stomach to the mouth. When gastro-oesophageal reflux or belching occurs in high frequencies this becomes abnormal. Excessive gastro-oesophageal reflux results in gastro-oesophageal reflux disease (GORD) and excessive belching is referred to as aerophagia.

GORD

GORD is a disorder in which symptoms or lesions occur as a consequence of reflux of gastric contents into the oesophagus. GORD is a very common disorder; between 15 and 20 percent of the general population suffers at least weakly from reflux symptoms and oesophageal lesions are found in up to 15 percent of the general population.[1,2]

Pathophysiology of GORD

The etiology of gastro-oesophageal reflux disease is multifactorial. Conceptually, it arises as a result of an imbalance between the aggressive forces within the refluxate and the defensive forces that protect the oesophagus. The main defence of the oesophagus is the anti-reflux barrier at the oesophago-gastric junction. The antireflux barrier consists of two elements, the intrinsic and extrinsic sphincter.[3] The intrinsic sphincter or lower esophageal sphincter (LOS) can be regarded as a specialized part of the circular muscle layer of the oesophagus. The extrinsic sphincter is formed by a part of the crural diaphragm. Normally these two components of the anti-reflux barrier form a functional entity and act in concert to prevent the occurrence of gastro-oesophageal reflux. When a hiatal hernia is present a spatial dissociation of the LOS and diaphragmatic sphincter exists, which compromises the function of the anti-reflux barrier. In addition, material trapped in the space between the two sphincters, the hernia sac, can reflux readily during swallowing.[4]

In the early 1970s the presence of a hiatal hernia was synonymous with GORD. It was believed that a low LOS pressure, caused by a hiatal hernia, was the most important cause of gastro-oesophageal reflux.[5-7] It was observed that a low LOS pressure correlated with oesophageal acid exposure and oesophagitis.[8-11] The introduction of the sleeve sensor at the end of that decade directed most attention towards transient relaxations of the LOS (TLOSR).[12]

With the sleeve sensor it became possible to reliably detect LOS relaxations, which was not possible with a sidehole positioned in the LOS. Axial movements of the oesophagus, for example during peristalsis, would move the sphincter away from the sidehole resulting in a pressure decrease at the level of the sidehole.[13] The sleeve sensor instead measures the highest pressure exerted along a 6-cm long membrane, and can therefore measure relaxations, even during movement of the sphincter. The sleeve straddles the entire gastro-oesophageal junction and only measures the highest pressure in this area, the presence of a double pressure zone configuration as present in patients with a hiatal hernia can thus not be detected with this device.[14] In the early 80's studies showed that TLOSRs were the most important mechanism through which acid gastric contents can enter the oesophagus in asymptomatic subjects and also in patients with GORD.[15,16] Research interests had now completely moved from the studies on the anatomy of hiatal hernia to investigation of the motility and TLOSRs. Hiatal hernia and low LOS pressure were elbowed out of prominence.[17]
New technical developments have recently led to the introduction of high-resolution manometry.[18] With high-resolution manometry pressures are recorded with an array of sideholes spaced at small distances, mostly at 1 cm.[19] High-resolution manometry or micromanometry makes it possible to measure pressures during prolonged periods of time. In the original studies described in this thesis both hiatal hernias and TLOSRs were investigated with this technique.

Reflux symptoms
The most typical symptoms that are associated with gastro-oesophageal reflux are heartburn and regurgitation.[20] GORD can also manifest itself by atypical symptoms, including dysphagia, coughing, hoarseness, globus sensation and belching.[20] Furthermore, in a substantial part of the patients with non-cardiac chest pain, reflux is responsible for patients symptoms.[21,22] Current standard therapy for reflux symptoms is treatment with gastric acid-secretion inhibiting drugs such as proton pump inhibitors.
Endoscopic studies showed that the majority of patients with reflux symptoms had no signs of reflux-induced oesophageal mucosal damage; this is sometimes called endoscopy-negative reflux disease.[23] Endoscopy is thus not a very sensitive tool to investigate whether symptoms are related to reflux episodes. The current gold standard to investigate whether a patient's symptoms are caused by gastro-oesophageal reflux is ambulatory 24-hour pH monitoring with symptoms association analysis.[24,25] However, ambulatory 24-hour pH monitoring is limited by the fact that only acid reflux episodes can be measured with this technique.

Recently intraluminal impedance measurement was introduced as a new technique to monitor movements of gas and liquid in the oesophagus.[26,27] Reflux detection with impedance monitoring is independent of the acidity of the refluxate and with this technique it is therefore possible to detect all reflux episodes, both acid, weakly acidic and weakly alkaline.[28] Using impedance monitoring it has been shown that proton pump inhibitors do not reduce the total number of reflux episodes, but only reduce the acidity of the refluxate.[29] It has furthermore been suggested that not only acid reflux episodes, but also weakly acidic reflux can induce symptoms of heartburn and regurgitation.[29] In this thesis we describe a number of studies in which we aimed to clarify the determinants of perception of gastroesophageal reflux, using oesophageal pH and impedance monitoring. We furthermore investigated the diagnostic yield of the new impedance technique.

Aerophagia

Postprandial belching is normal, with 3-4 belches per hour, and results from the ingestion of air with swallowing. Belching is a common symptom in patients with gastro-oesophageal reflux disease and functional dyspepsia but can also occur as an isolated symptom.[30,31] When belching becomes troublesome and repetitive it is sometimes referred to as aerophagia.[32,33] A high prevalence of psychological and psychiatric disorders has been described in patients with excessive belching.[33-37] Until recently, technical limitations stood in the way of an adequate analysis of the events associated with belching and aerophagia. By counting the number of swallows, it has been concluded that aerophagia results from a stress-induced increase in swallow frequency.[38,39] It has also been stated that emotional arousal increases the frequency of swallowing.[40] The hypothesis of these studies was thus that with swallowing a high quantity of air is transported to the stomach and is subsequently belched out. Hence, the name for this disorder “aerophagia”, which is Greek for air-eating. As mentioned above, the advent of the intraluminal impedance recording technique makes it possible to monitor the passage of air through the oesophagus, either in aboral or oral direction. In this thesis we describe our efforts to elucidate the air transport patterns that result in repetitive belching.

The following questions will be addressed in this thesis:

1 What is the optimal sample frequency for intraluminal impedance monitoring? (Part I)
2 Is detection of gastro-oesophageal reflux with intraluminal impedance monitoring as reproducible as reflux detection using pH monitoring? (Part I)
3 Can high-resolution manometry be used to study the extrinsic and intrinsic component of the anti-reflux barrier and to detect TLOSRs? (Part II)
4 What is the role of intermittent spatial separation of LOS and diaphragm on the prevalence of gastro-oesophageal reflux? (Part II)
5 What are the determinants of perception of heartburn and regurgitation? (Part III)
6 Is there an additional diagnostic yield of combined impedance-pH monitoring compared to pH monitoring alone in patients off anti-secretory therapy? (Part III)
7 Which air transport pattern is responsible for excessive belching in patients with aerophagia? (Part IV)
8 What is the effect of distraction and attention on the frequency of belching in aerophagia? (Part IV)
9 Is liquid gastro-oesophageal reflux related to excessive air swallowing, intragastric air and belching? (Part IV)

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Part I

Impedance monitoring

2

Mimimum sample frequency for intraluminal impedance measurement of the oesophagus

A.J. Bredenoord
B.L.A.M. Weusten
R. Timmer
A.J.P.M. Smout

Dept. of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands
Gastrointestinal Research Unit, University Medical Center, Utrecht, The Netherlands

Neurogastroenterol Motil 2004;16:713–9.

Abstract

In all systems for impedance monitoring signals are stored in digital format after analog-to-digital conversion at a predefined rate, the sample frequency. We aimed to find the minimum sample frequency required to evaluate oesophageal transit and gastro-oesophageal reflux studies using impedance monitoring. In 10 healthy subjects and five patients with gastro-oesophageal reflux disease impedance signals were acquired during a 90-min postprandial period, using a sample frequency of 1000 Hz. Additionally, 10 liquid swallows were recorded in the healthy subjects. A dedicated computer program was used to derive, from the original 1000-Hz files, series of new data files with sample frequencies of 500, 200, 100, 50, 20, 10, 8, 5 and 4 Hz. In all of these files, liquid and gas reflux events were identified. In the analysis of the swallows, bolus head advance time (BHAT) and total bolus transit time were measured. Reflux events were detectable down to a sample frequency of 50 Hz. In transit analysis errors for BHAT at frequencies below 8 Hz errors exceeded 2.5 %. Therefore, in impedance monitoring the minimum sample frequency is 50 Hz for the detection of reflux and 8 Hz for the evaluation of oesophageal transit.

Introduction

Recently, intraluminal electrical impedance monitoring was introduced as a novel method to study bolus transport in oral and aboral direction in luminal organs.[1,2] Impedance measurement provides information about bolus transport during oesophageal peristalsis and has already been incorporated in routine function testing in some tertiary medical centres.[3,4] Studies combining impedance measurements with pH-metry provide new insights into pathophysiology of gastro-oesophageal reflux disease (GORD) and oesophageal acid clearance.[5-7] Furthermore, intraluminal impedance can be used to study aerophagia and belching.[8] Impedance measurements are also promising in the evaluation of reflux and regurgitation in paediatric practice.[9,10]

In all systems for intraluminal impedance monitoring the signals are stored in digital format after analog-to-digital (A/D) conversion. A/D conversion is done at a predefined rate, the sample frequency.

In order to be able to recognize events like bolus transit, liquid reflux, gas reflux and belches in intraluminal impedance signals a sufficiently high sample frequency is necessary. The disadvantage of a high sample frequency is that the size of the data files becomes huge, especially when measuring for 24-hour. In previous studies using oesophageal impedance monitoring sample frequencies ranging from 30 to 1000 Hz were used, as no systematic study has been done to investigate the minimum sample frequency.[8,11,12] In this study, we aimed to find the minimum sample frequency required to evaluate oesophageal transit, gastro-oesophageal reflux and belching using oesophageal impedance monitoring.

Methods

Subjects

We recorded oesophageal intraluminal impedance in 10 healthy volunteers (four males and six females; mean age: 24 years; range: 22–33 years), five patients with GORD (four males and one female; mean age: 35 years; range: 26–53 years) and five patients with frequent belching (two males and three females; mean age: 48; range: 28–58 years). The GORD patients had symptoms of heartburn and regurgitation as well as a pathological 24-hour pH-metric study (time with pH < 4 of more than 4.2 % of total time). The patients with excessive belching fulfilled Rome II criteria for aerophagia and had a history of repetitive, troublesome belching without any organic disorder of the oesophagus or stomach.[13] Healthy

subjects were free of any gastrointestinal symptoms and were not taking any medication. Written informed consent was obtained from all subjects and the protocol was approved by the Medical Ethics Committee of the University Medical Center, Utrecht.

Study protocol

A routine oesophageal manometry was performed to determine the distance from nostrils to lower oesophageal sphincter (LOS). Thereafter the impedance catheter was introduced transnasally and positioned with its distal electrode at the upper border of the LOS. After an adaptation period of at least 10 min recording was started. Subjects remained seated during the course of the study and were asked to minimize head movements. In the healthy subjects, 10 swallows of 5 mL water each were given 30 s apart. A standardized meal was offered to all subjects consisting of one hamburger (McDonald's Quarter Pounder), 20 g of fresh onions, 44 g of potato chips and 475 mL of orange juice (in total 967 kCal). This meal was used to elicit reflux in a previous study by our group.[14] Recordings were continued until 90 min after the meal.

Intraluminal electrical impedance assembly

A 7-channel impedance system was used (Aachen University of Technology, FEMU, Aachen, Germany).[2,3] The catheter (diameter 2.3 mm) contained 11 ring electrodes. From these 11 electrodes, seven impedance signals were recorded. The 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 LOS (Figure 1). Impedance signals were sampled at 1000 Hz.

Data analysis

Previously established criteria were used to analyze bolus transit events following the wet swallows in the healthy subjects before the meal and to identify gas reflux and liquid reflux during the postprandial recording period in the healthy volunteers and the GORD patients.[12,15,16] Regular gastric belches were identified as gas reflux from the stomach to the oesophagus and up to the pharynx. We furthermore identified 10 "supragastric belches" in each of the patients with excessive belching. In contrast to regular belches (gas reflux), these supragastric belches are immediately preceded by a rapid antegrade flow of air in the oesophagus that does not reach the stomach.[8] Supragastric belches were found to be the predominant mechanism of excessive belching in patients with aerophagia.[8]

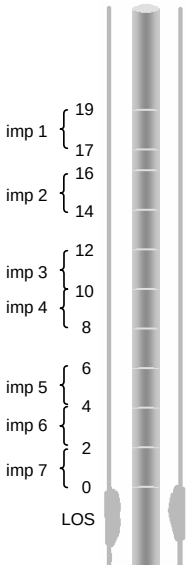

Figure 1. Position of the impedance catheter in the esophagus with respect to the manometric upper border of the lower oesophageal sphincter.

A specially designed computer program was used to derive, from each of the digital 1000-Hz impedance data files, new data files with sample frequencies of 500, 200, 100, 50, 20, 10, 8, 5 and 4 Hz. This was accomplished by copying every first sample out of every n samples of the 1000-Hz file to the new file (n=1000/new sample frequency).

In the analysis of the readings of the wet swallows, bolus head advance time (BHAT) along the catheter and total bolus transit time (TBTT) along the catheter were measured for all frequencies. Definitions for these parameters were adopted from Tutuian et al. (Figure 2).[4] Time of bolus entry was defined as the point at which impedance had fallen to a value below 50 % of the 3 s baseline level before initiation of the swallow. Bolus exit was determined as return to this 50 % point on the impedance recovery curve.

The amplitudes of the swallow-associated impedance events at channel 5 (5 cm above the LOS) were measured as the difference in impedance value between baseline and nadir impedance. This was performed for all of the different frequencies.

In the analysis of the liquid and gas reflux episodes, the amplitude of the impedance events (difference between baseline and lowest value for liquid, difference between baseline and highest value for gas) was measured in impedance channel 5 (5 cm above the LOS) (Figure 2). For each impedance event it was determined whether the propagation direction observed in the 1000-Hz signals could also be observed in the reduced frequency signals. Furthermore, for

reflux events and belches the propagating velocity of these events was calculated for all frequencies. This was done by dividing the distance along the catheter over which the liquid (liquid reflux) or gas (gas reflux and belches) bolus front travelled by the time.
Errors in the measurement of propagating velocity, BHAT and TBTT were calculated by comparing values at all the different sample frequencies with the value for these parameters calculated at 1000 Hz. The cut-off level for maximal acceptable error in BHAT and TBTT was arbitrarily set to 2.5 %.

Statistical analysis and presentation of data
Throughout the manuscript data are presented as mean ± SEM. The Student's t-test was used to assess differences between GORD patients and healthy volunteers. Differences were considered to be statistically significant when $p \leq 0.05$.

Results

In the healthy volunteers 33 liquid reflux and 30 gas reflux episodes were identified. Mean propagation velocities of liquid and gas reflux, when measured at 1000 Hz, were 0.71 ± 0.07 and 1.15 ± 0.14 m/s, respectively. In the GORD patients 17 liquid reflux and 12 gas reflux episodes were observed. Mean propagation velocities of liquid and gas reflux, when measured at 1000 Hz, were 0.58 ± 0.16 and 1.02 ± 0.31 m/s, respectively. As these were not significantly different from values in the healthy volunteers, we pooled data from these two groups for the determination of minimum sample frequency. The percentage of gas and liquid reflux that extended to the most proximal impedance segment was 76.0 and 23.8 %, respectively. As shown in Table 1, the detection of propagation of gaseous and liquid reflux events remained possible down to a sample frequency of 50 Hz. At lower frequencies reflux could not always be recognized as moving in oral direction because the impedance change in the most distal and the most proximal impedance channel reached by the reflux started at the same data sample (Figure 3). The increasing loss in detail in gas and liquid reflux events that occurs at lower sample frequencies is illustrated in figure 4. Table 1 at the other frequencies. Whereas the errors in amplitude measurement remained small for liquid reflux events, the errors for gas reflux events exceeded 10 % when frequencies were reduced below 50 Hz. Error in amplitudes did not impair detection of reflux events.

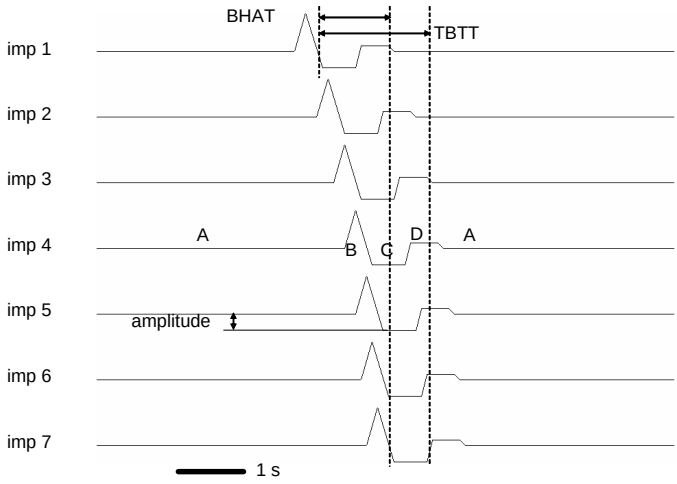

Figure 2 (A). Determination of total bolus transit time (TBTT) and bolus head advance time (BHAT). TBTT is defined as the elapsed time from bolus entry in the most proximal segment to bolus clearance in the most distal segment. BHAT is defined as the elapsed time from bolus entry in the most proximal segment to bolus entry in the most distal segment. (A) Baseline impedance. (B) Gas, pushed in front of the bolus and recognized by an increase in impedance. (C) Decrease in impedance representing liquid bolus. (D) Increase in impedance after the bolus, representing a contraction wave.

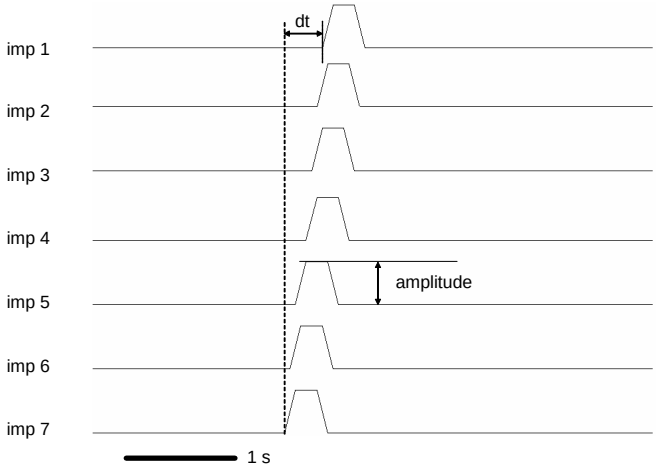

Figure 2 (B). Determination of gas reflux propagation velocity. Gas reflux is characterized by an increase in impedance that moves in oral direction. The dotted lines represent the onset of the increase in impedance in the most distal and most proximal measuring segment, indicating gas entry. Propagation velocity is calculated as v = dx/dt with dx as the distance between impedance segment 7 and the most proximal measuring segment reached by the reflux.

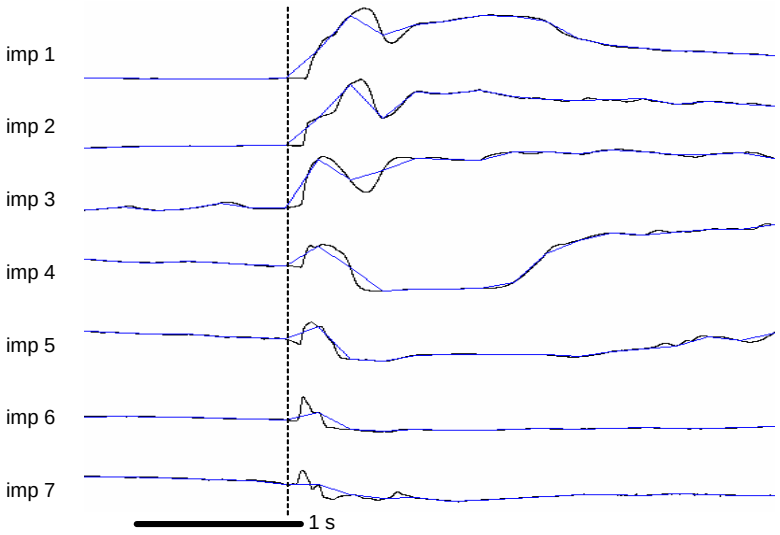

Figure 3. Example of a gas reflux episode, recognizable by an increase in impedance that propagates in oral direction, displayed at 1000 and at 5 Hz. At 1000 Hz the gas reflux event is clearly propagating from distal to proximal. In the 5-Hz tracing, the increase in impedance is simultaneous in all channels (dotted line). This makes it impossible to determine the direction of the movement of the gas bolus.

	Liquid reflux			Gaseous reflux			Supragastric belch		
Sample frequency	Propagation undetectable (%)	Error velocity (%)	Error amplitude (%)	Propagation undetectable (%)	Error velocity (%)	Error amplitude (%)	Propagation undetectable (%)	Error velocity (%)	Error amplitude (%)
500	0.0	0.5	0.0	0.0	1.2	0.1	0.0	3.4	0.0
200	0.0	5.2	0.0	0.0	4.3	0.3	0.0	11.3	0.1
100	0.0	8.3	0.0	0.0	11.9	0.4	0.0	14.2	0.0
50	0.0	10.5	0.0	0.0	19.6	2.2	0.0	17.4	0.4
20	0.0	30.5	0.1	9.5	32.3	12.6	18.0	40.9	1.9
10	0.0	24.9	0.1	35.7	34.5	24.9	48.0	42.4	14.2
8	0.0	47.2	0.5	38.1	39.3	24.1	54.0	45.7	14.3
5	2.0	32.1	14.9	59.5	53.1	25.3	80.0	59.8	19.8
4	5.0	47.3	13.8	61.9	79.0	27.0	100.0	-	17.2

Table 1. Failure to determine propagation direction (%) and error (%) in measurement of propagation velocity and amplitude of liquid and gas reflux events and supragastric belches at different sample frequencies, as compared to 1000 Hz

The impact of reduction of sample frequency was most pronounced for the supragastric belches (Table 1). None of these belches could be recognized at 4 Hz. The mean propagation velocity of the supragastric belches was 2.33 ± 0.13 m/s, i.e. even faster than that of gas reflux.

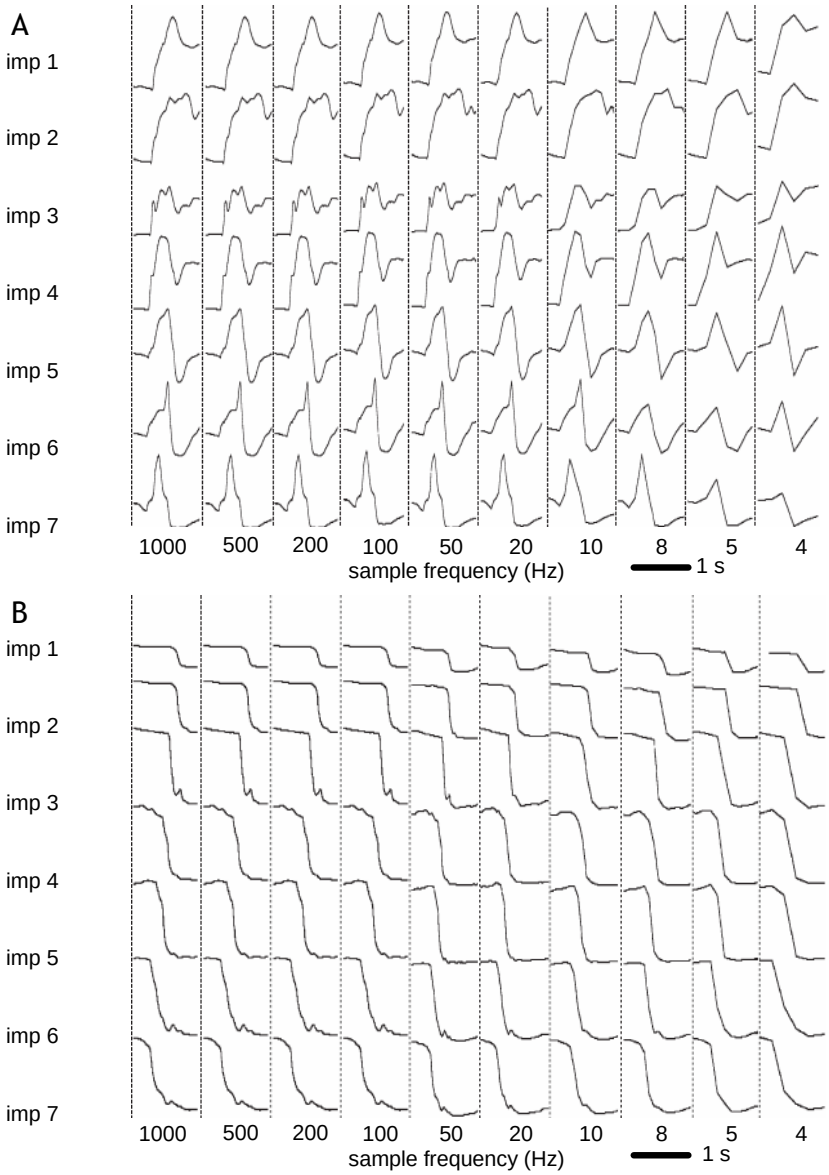

Figure 4 (A). Example of a gas reflux episode at different sample frequencies. With the reduction of the sample frequency, an increasing loss is seen in detail. At 8 Hz the direction is still recognizable, at 5 Hz the impedance rise of the reflux event at the proximal and distal channel appears simultaneous, making the direction of the propagation indeterminable. (B) Example of a liquid reflux episode at different sample frequencies. While an increasing loss in detail is obtained with reduction of sample frequency, the oral propagation direction is recognizable at all sample frequencies.

At a sample frequency of 1000 Hz the transit parameters BHAT and TBTT were 2.47 ± 0.13 and 7.09 ± 0.32 s, respectively. As shown in Table 2, the errors made in the measurements of these parameters remained less than 2.5 % when sample frequencies were reduced as far as to 8 Hz. Likewise, the error made in measurement of the amplitude of liquid transit-associated impedance drops was small (4.9 % at 4 Hz). As a result, all swallows could be clearly recognized, even when the sample frequency was reduced to 4 Hz (Figure 5).

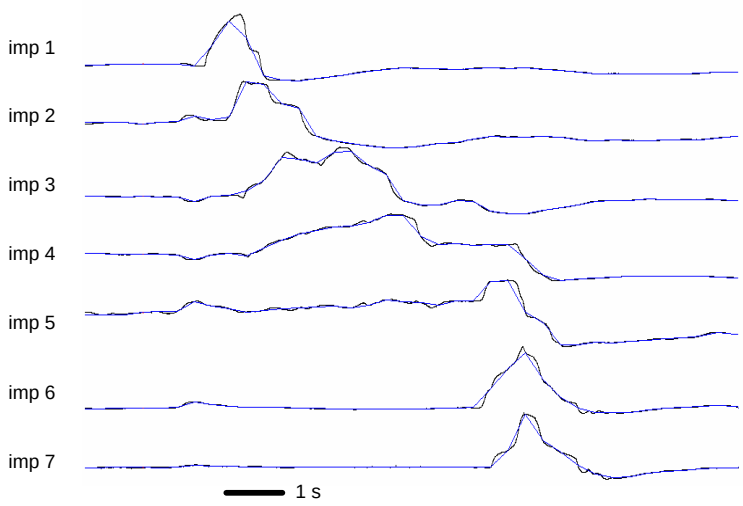

Figure 5. Example of peristalsis after a liquid swallow, displayed at 1000 and 5 Hz. In a relatively slow event as a swallow, differences between recordings at 1000 Hz and 5 Hz are small.

Sample frequency	TBTT error (%)	BHAT error (%)	Amplitude error (%)
500	0.1	0.1	0.0
200	0.4	0.8	0.0
100	0.4	1.9	0.0
50	0.7	1.1	0.2
20	0.8	2.0	0.1
10	1.1	1.6	2.2
8	2.3	1.9	2.0
5	2.1	3.3	2.4
4	2.7	10.7	4.9

Table 2. Error in measurement of total bolus transit time (TBTT), bolus head advance time (BHAT) and amplitude of the liquid bolus at different sample frequencies as compared to values at 1000 Hz

Discussion

This is the first paper addressing the minimally required sample frequency for intraluminal electrical impedance measurement of the oesophagus. Using specially designed software we were able to show that a reduction in sample frequency results in an increasing loss in detail of impedance tracings. The error at lower sample frequencies is larger for events with a high propagation velocity, such as gas reflux and supragastric belches. While at 20 Hz propagation direction is undeterminable in as many as 9.5 % of gas reflux events, all of the slower propagating liquid reflux events are still recognizable. The magnitude of the error at the lower sample frequencies is much larger for reflux events and for supragastric belches than for the bolus transit parameters TBTT and BHAT. This implies that it is justifiable to use a lower sample frequency for oesophageal transit tests than for reflux testing. If an appropriate sample frequency is defined as one at which the direction of propagation of the refluxate is distinguishable in 100 % of the cases, a sample frequency of at least 50 Hz is required for monitoring of gastro-oesophageal reflux. This finding justifies a considerable reduction in data file size compared to the currently used sample frequencies. Recording for 24-hour of seven impedance signals with a sample frequency of 1000 Hz, requires a storage capacity in the order of 900 megabyte. A 20-fold reduction of sample frequency, from 1000 to 50 Hz, will be associated with a similar reduction in data file size (to 45 Mb) and processing time. As the errors in amplitude of the impedancometric events are smaller at the given frequencies than the errors in propagation velocity, we do not consider this parameter to be a limiting factor. It might be useful to use a higher sample frequency for specific research purposes. When one uses a sample frequency of 50 Hz for gas reflux studies, all events are recognized, but an error in the measured propagation velocity of almost 20 % is found. Increasing the sample frequency will result in a more precise estimation of this parameter. We also tested minimum sample frequency for detection of supragastric belches as these events propagate even more rapid than gas reflux and would therefore possibly require a higher sample frequency.[8] It was found that aerophagia and supragastric belches can be studied at 50 Hz as all events are recognized but, given the large error in propagation velocity, a higher sample frequency might be useful in scientific studies. Mixed reflux is defined as the simultaneous occurrence of both liquid and gas reflux. To recognize this correctly, both components have to be identified. Therefore, we did not feel the need to distinguish mixed reflux as a separate category. As gas

reflux propagates much faster, recognition of mixed reflux events at lower sample frequencies depends on identification of the gas reflux component.
A sample frequency of 50 Hz for impedance monitoring contrasts to the sample frequency of 1 or 2 Hz that is mostly used for pH-metric studies. The low response rate of both glass and antimony pH electrodes makes that higher sample frequencies are not contributory. Furthermore, in most studies with pH monitoring, one sensor is used and reflux is recognized when pH falls below 4. For recognition of reflux with intraluminal electrical impedance both information about the change in impedance in several adjacent channels and information about the sequence of the channels in which this change occurs are required. For this, a higher time resolution is needed compared to pH monitoring.
The mean values of the parameters BHAT and TBTT, used for testing of swallowing and oesophageal peristalsis, are 2.47 ± 0.13 and 7.09 ± 0.32 s, respectively, well within the normal range of liquid bolus transport given by a multicenter report.[4] These events are relatively slow, compared to liquid and gas reflux events and supragastric belches, and errors from values at 1000 Hz at lower frequencies are much smaller. Even at 8 Hz, a relatively accurate estimation of BHAT, TBTT and the amplitude of impedance change can be made. Our recommendation of the use of a sample frequency of 8 Hz is less strict than the use of 50 Hz for reflux monitoring, as swallow parameters are still recognizable and interpretable at lower frequencies than 8 Hz.
Determination of the optimal sample frequency in this study was based on a seven-segment catheter with 17 cm between the most proximal and most distal measuring segment. A substantial part of reflux does not reach the most proximal impedance segment. Such events are harder to recognize with a low sample frequency as propagation distance is shorter and, therefore, the likelihood that they occur in the same sample is higher. The aim of this study was to find the sample frequency at which all reflux events could be detected and therefore we used all reflux episodes for analysis. This makes that our conclusions are valid for both limited gastro-oesophageal reflux as for reflux that extends to the proximal oesophagus.
In conclusion, using stepwise reduction of the sample frequency from 1000 to 4 Hz we determined the minimum sample frequencies required for oesophageal impedance measurements. The results indicate that the minimum frequency is 50 Hz for reflux monitoring and 8 Hz for oesophageal transit testing.

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Reproducibility of multichannel intraluminal electrical impedance monitoring of gastroesophageal reflux

A.J. Bredenoord
B.L.A.M. Weusten
R. Timmer
A.J.P.M. Smout

Dept. of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands
Gastrointestinal Research Unit, University Medical Center, Utrecht, The Netherlands

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Abstract

Objective: Esophageal impedance measurement is a novel method for gastroesophageal reflux monitoring. Reproducibility is an important aspect of every biomedical test. The aim of this study was therefore to asses the reproducibility of gastroesophageal reflux monitoring using impedance measurements. Methods: Impedance and pH signals were recorded in 20 healthy volunteers during 90-min postprandial periods on two separate days. Hourly rates of gas, liquid, and mixed gas-liquid reflux episodes were measured in each recording period as well as percentage of time with pH < 4 and rate of acid reflux episodes. As a quantitative description of inter- and intra-individual variation for each variable, the mean percentage of covariation (100 × SD/mean: %COV) was calculated. As a second measure for reproducibility, Kendall's coefficients of concordance (W values) were calculated. Results: For all variables, inter-individual %COV was at least 50 % higher than intra-individual %COV. Statistically significant concordances were found for gas reflux (W=0.81, p=0.04) and mixed reflux (W=0.85, p=0.03) while concordance for liquid reflux tended to be significant (W=0.75, p=0.08). This was comparable to the reproducibility of the number of acid reflux episodes and percentage of time with pH < 4 (W=0.78, p=0.05 and W=0.88, p=0.02, respectively). Conclusion: Postprandial gastroesophageal reflux data assessed with impedance monitoring are as reproducible as assessed with pH monitoring.

Introduction

Patients with symptoms of heartburn and regurgitation often suffer from reflux of acidic gastric contents into the esophagus. This can be shown with a pH study. However, there is evidence that reflux symptoms may also occur in association with non-acid reflux.[1] Furthermore, a subset of patients with reflux disease experiences no relief after effective acid suppression. It has been suggested that reflux of non-acid substances such as pepsin and bile acids may play a role in the genesis of reflux symptoms.[2] Furthermore, it has been shown that non-acid components of the refluxate also play a role in the genesis of Barrett's epithelium.[3]

Multichannel intraluminal electrical impedance monitoring makes it possible to detect non-acid liquid and gas flow through the esophagus.[4] Recent studies have shown that combined pH and impedance monitoring provide additional information compared to pH measurements alone.[5-7] The fact that impedance monitoring can also detect gas transport through the esophagus makes it a useful tool to study air swallowing and excessive belching as well.[8]

Currently, pH monitoring is a generally accepted test for the quantification of gastroesophageal reflux, and various studies have shown that reproducibility of pH monitoring is good.[9-15] The aim of this study was to investigate the reproducibility of esophageal electrical impedance monitoring and to compare this with the reproducibility of acid reflux measurements.

Methods

Patients

Twenty healthy volunteers (14 males and 6 females: mean age 28 yr, range 19–46 yr) underwent two separate recordings of esophageal impedance and pH within an interval of 1–2 wk. Patients were free of any gastrointestinal symptoms and were not taking any medication. 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 routine esophageal manometry was performed to determine the distance from the nostrils to the lower esophageal sphincter (LES). Thereafter, the impedance and the pH catheters were introduced transnasally

and positioned based on the manometric findings (see below). A standardized meal was offered consisting of one hamburger McDonald's Quarter Pounder), 20 g of fresh onions, 44 g of potato chips, and 475 ml of orange juice (in total 967 kcal). This meal was used to provoke reflux in a previous study of our group.[16] The meal had to be finished in 30 min. After the meal, impedance and pH signals were recorded for 90 min. Patients remained seated for the duration of the study.

Impedance and pH Monitoring

For impedance monitoring a 7-channel impedance catheter was used (Aachen University of Technology,FEMU, Aachen, Germany). This catheter (outer diameter 2.3 mm) enabled recording from seven segments, each recording segment being 2-cm long. The 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 localized LES. Impedance signals were stored in a digital system (Aachen University of Technology, FEMU, Aachen, Germany) using a sample frequency of 1000 Hz. Intraluminal pH monitoring was performed with a glass pH electrode (Ingold A.G., Urdorf, Switzerland) and data were stored in a digital datalogger (Orion, MMS, Enschede, the Netherlands) using a sampling frequency of 2 Hz. The pH glass catheter was positioned 5 cm above the upper border of the LES. Using a cable that connected the pH datalogger with the impedance datalogger the pH signals were stored on both dataloggers enabling synchronization.

Data Analysis

Previously established criteria were used to identify swallows, gas reflux, liquid reflux, and mixed gas-liquid reflux.[5,17,18] Furthermore, using the pH tracings, liquid reflux, mixed gas-liquid reflux, and gas reflux were classified as acidic or non-acidic, using a threshold of pH < 4. Percentage of time with pH < 4 was also assessed. Analysis was performed manually by two physicians with experience in this area; disagreement was solved by consensus. These observers were blinded to the outcome of the other measurement.

"Air swallows" were defined as swallows in which the liquid bolus, identifiable by a decrease in impedance, was preceded by an increase in impedance of at least 1000 Ω above baseline. A threshold of 1000 Ω was chosen because this was found to be well above the amplitude of baseline noise. The number of regular swallows as well as the number of "air swallows" were counted.

Evaluation of Reproducibility

Standard deviations (SD) and percentage coefficient of variation (100×SD/mean:%COV) were calculated for impedance and pH data. The mean %COV of the 20 values of the first measurement and the mean %COV of the 20 values of the second measurement were calculated. An overall mean %COV was derived as a measure of inter-individual variation. Furthermore, the mean %COV of the first and the second measurement in the 20 volunteers was calculated. This value, calculated from the values of the 20 individuals, was used as a measure of intra-individual reproducibility.[19]

Table 1. Intra-individual and inter-individual reproducibility of measurements of mixed gas-liquid reflux

	day		intra-individual		
volunteer	1	2	mean	SD	%COV
1	1.30	4.20	2.75	2.05	74.57
2	7.10	10.80	8.95	2.62	29.23
3	7.90	4.60	6.25	2.33	37.34
4	6.00	3.80	4.90	1.56	31.75
5	1.30	2.00	1.65	0.49	30.00
6	2.00	2.00	2.00	0.00	0.00
7	2.60	3.30	2.95	0.49	16.78
8	3.30	1.30	2.30	1.41	61.49
9	6.70	4.50	5.60	1.56	27.78
10	7.30	5.30	6.30	1.41	22.45
11	6.50	6.00	6.25	0.35	5.66
12	0.00	0.00	0.00	0.00	0.00
13	2.70	4.00	3.35	0.92	27.44
14	3.30	3.30	3.30	0.00	0.00
15	5.30	5.50	5.40	0.14	2.62
16	3.40	1.30	2.35	1.48	63.19
17	4.00	6.00	5.00	1.41	28.28
18	4.70	4.90	4.80	0.14	2.95
19	2.60	2.60	2.60	0.00	0.00
20	3.30	4.00	3.65	0.49	13.56
inter-individual					
mean	4.07	3.97	4.02	0.94	23.75
SD	2.26	2.31	2.10		
%COV	55.69	58.13	52.24		

(Rates/h) SD=standard deviation; %COV=percentage of covariance. The mean SD and mean %COV for the two columns (day 1 and day 2) constitute an index of inter-individual variation, whereas the equivalent values for the 20 individual rows are an index of intra-individual variation.

As a second measure for reproducibility, Kendall's coefficients of concordance (W value) were calculated using the mean values for the named variables from individual recordings and tested for significance. An error probability of $p \leq 0.05$ was considered statistically significant. Throughout the manuscript data are presented as mean ± SEM.
Assessment of reproducibility was facilitated by presenting data in Bland-Altman plots. In these plots the difference between the first and second measurement is plotted against the mean value of the two measurements, which makes it possible to graphically compare these two values. When the difference between measurements on the first day and the second day 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.

Table 2. Reproducibility of swallow and reflux parameters

		Intra-individual		Inter-individual			
	Mean	SD	%COV	SD	%COV	Kendall's W	p value
Number of mixed reflux episodes / h	4.02	0.94	23.75	2.10	52.24	0.85	0.03
Number of liquid reflux episodes / h	1.47	0.87	59.01	1.30	88.30	0.75	0.08
Number of gas reflux episodes / h	2.74	0.92	56.15	2.34	85.65	0.81	0.04
Number of swallows / h	64.15	7.66	13.04	24.66	38.44	0.90	0.02
Number of air swallows / h	22.50	6.07	28.80	11.31	50.30	0.84	0.03
Number of mixed acid reflux episodes / h	2.85	1.20	51.37	1.97	69.27	0.78	0.06
Number of liquid acid reflux episodes / h	1.35	0.99	50.02	1.73	127.79	0.77	0.06
Number of episodes pH < 4	3.52	1.00	36.37	2.23	64.57	0.78	0.05
% time pH < 4	6.12	2.45	54.77	7.98	129.98	0.88	0.02

SD=standard deviation; %COV=percentage of covariance.

Results

As shown in Table 1 the mean rate at which mixed gas-liquid reflux episodes occurred was 4.0/h. As illustrated the variation between different patients was much larger than the variation occurring within the same patient (Figure 1). Scattering of the data points occurs close to the x-axis in a rather symmetrical way.

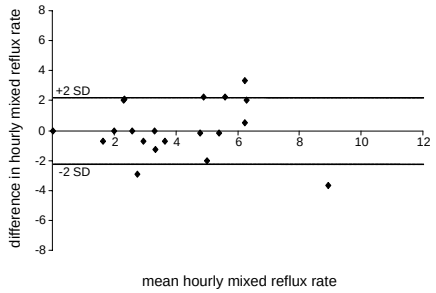

Figure 1. Reproducibility of mixed reflux rate (Bland-Altman plot)

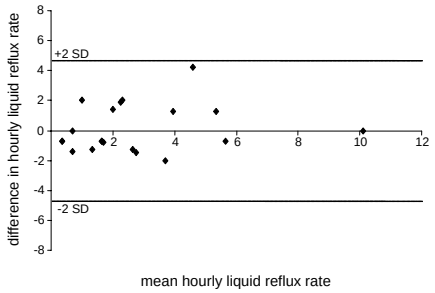

Figure 2. Reproducibility of liquid reflux rate (Bland-Altman plot)

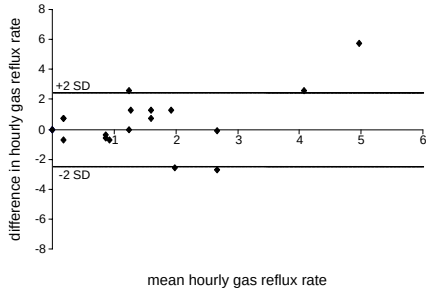

Figure 3. Reproducibility of gas reflux rate (Bland-Altman plot)

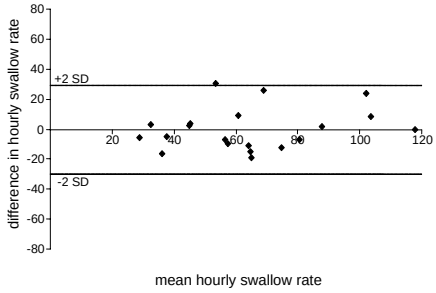

Figure 4. Reproducibility of swallow rate (Bland-Altman plot)

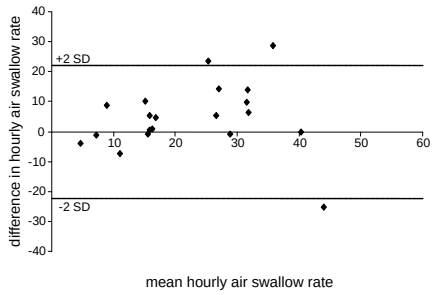

Figure 5. Reproducibility of air swallow rate (Bland-Altman plot)

As shown in Table 2 similar findings were made for the other reflux parameters, for swallowing rate, and for air swallowing. For virtually all parameters, the inter-individual %COV was considerably higher than the intra-individual %COV. Concordance between the measurements was substantial for all parameters with Kendall's W values varying between 0.75 and 0.90 (Table 2). Statistically significant concordance was reached for hourly rate of gas reflux episodes, mixed reflux episodes, acid reflux episodes, swallowing, air swallowing, and percentage of time with pH below 4. For three parameters the reproducibility was borderline significant: hourly rate of liquid reflux episodes, mixed acid reflux episodes, and liquid acid reflux episodes. The hourly rate of these three types of events was rather low, as can be seen in Table 2.
Figures 2–5 show Bland-Altman plots for hourly rates of liquid reflux episodes, gas reflux episodes, swallows, and air swallows. In these figures data points are closely scattered around the x-axis, indicating a relatively small difference between the two measurements as compared to the mean of the two measurements. Furthermore, the scattering around the x-axis is symmetrical, indicating that the values of the second measurement are randomly distributed around the mean of the two measurements and that no upward or downward trend exists.

Discussion

Previous studies showed that pH monitoring is a fairly reproducible method for detection of gastroesophageal reflux.[9-15] In a study by Wiener et al., in which a cutoff value of 4 % of the time with pH < 4 was used for the diagnosis of gastroesophageal reflux disease (GERD), reproducibility for this diagnosis was 80 %.[15] Most studies that investigated reproducibility of the percentage of time with pH < 4, reported a higher reproducibility.
We studied reproducibility of impedance monitoring for the detection of gastroesophageal reflux. As shown in Table 2, %COV is much larger between patients than it is within patients. Furthermore, testing for concordance using Kendall's W test showed that the concordance between the two measurements of gas and mixed reflux was statistically significant, while concordance between the two measurements of liquid reflux tended to be statistically significant.
Results from our pH studies confirmed those obtained in previous reports, and both percentage of time with pH < 4 and hourly rate of reflux episodes were found to be reproducible. Reproducibility of the rate of liquid reflux, mixed gas-

liquid acid reflux, and liquid gas-liquid acid reflux episodes were borderline significant. This is most likely due to a type 2 error, resulting from the rather lowrate of (acid) reflux episodes in these healthy volunteers as well as to the relatively short recording time (90 min). Others have shown that reproducibility increases with the length of the study, showing much higher intra-individual concordance in 24-hour measurements than in 3-hour measurements.[10] Since in our 90 min study standardized meals and position were used, the reproducibility found may theoretically differ from the reproducibility of 24-hour ambulatory impedance monitoring.

Reproducibility of a biomedical test is determined not only by patient-related factors, but also by technical factors. Differences in catheter position, data acquisition, and data analysis can influence the results of impedance monitoring. The degree of reproducibility is only acceptable when variations caused by technical factors are rather small. The fact that we found a good reproducibility of gastroesophageal reflux testing with intraluminal impedance monitoring can be considered as an important validation of this technique. Apart from reflux parameters, swallowing rate and air swallowing rate as determined with intraluminal impedance were also found to be reproducible in healthy volunteers. The frequencies found in this study were well within the reported range.[20]

The reproducibility of reflux monitoring using esophageal impedance measurement was found to be comparable to the reproducibility of reflux testing with pH monitoring. This indicates that esophageal impedance monitoring can be an important new tool for studying and diagnosing GERD.[10] The additional value of impedance measurements in conjugation with pH monitoring explains the increasing use of this technique. A recent publication of normal values and the consensus report concerning terminology have opened doors to more widespread clinical application.[21,22] Furthermore, the reproducibility of impedance measurements indicates that this technique might be suitable for investigation of the effects of new drugs and other treatment modalities on the occurrence of gastroesophageal reflux. However, one should take into account that, although intra-individual variations are small compared to inter-individual variations, a normal day to day variance within patients does occur and that this may limit the statistical power of studies with small sample sizes. In ambulatory studies physiological intra-individual variation could be larger than the variations found in this study, since in our setting patients were studied in the same position and used the same standardized meal during each of the two measurements.

The Porto consensus report introduced a new nomenclature for reflux monitoring.[22] In this nomenclature, definitions of reflux are based on the combined use of pH and impedance monitoring. Reflux is thus divided in acid reflux (fall of pH below 4), superimposed reflux (when pH is already below 4), weakly acidic reflux (when pH is between 4 and 7), and weakly alkaline reflux (pH above 7). Reproducibility of these four types of reflux depends on the combination of pH and impedance monitoring techniques. The aim of this study was to investigate reproducibility of impedance monitoring alone and therefore we did not investigate reproducibility of these four parameters.
In conclusion, we showed that intraluminal impedance measurement is a reproducible method for studying (air) swallowing, liquid reflux, gas reflux, and mixed gas-liquid reflux. The reproducibility of measurement of these reflux events is comparable to the reproducibility of acid reflux measurement by means of pH monitoring.

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Part II

The anti-reflux barrier

4

The gastro-oeophageal pressure inversion point revisited

A.J. Bredenoord
B.L.A.M. Weusten
J.M.M. Roelofs
A.J.P.M. Smout

Dept. of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands
Gastrointestinal Research Unit, University Medical Center, Utrecht, The Netherlands

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Abstract

Background: The pressure inversion point (PIP) is defined as the point at which, during stationary pullthrough manometry of the oesophago-gastric junction, the polarity of the respiratory-associated pressure variations changes. Traditionally, the PIP is ascribed to transition of the pressure sensor from the abdominal to the thoracic cavity. We used high-resolution manometry to investigate the validity of this concept in six healthy volunteers and six patients with a sliding hiatus hernia. Methods: In the analysis, the position of the PIP was identified. When there was a second, more distal, PIP, its position was also noted. The amplitude of the respiratory-associated pressure variations, defined as the difference between end-expiratory and end-inspiratory pressure, was measured. Results: Double PIPs were found both in healthy controls (23 ± 8 % of time) and in patients (38 ± 9 % of time). Amplitudes of the respiratory-associated pressure variations were significantly higher at the proximal and distal border of the PIP (3.36 ± 0.2 kPa and 2.29 ± 0.2 kPa) than in the oesophageal body (0.54 ± 0.03 kPa, $p<0.001$) and in the stomach (0.54 ± 0.03 kPa, $p<0.001$). We also observed a relationship between the localization of the highest end-expiratory pressure and the position of the PIP. During TLOSRs respiratory variation amplitudes at the proximal and distal border of the PIP decreased to 0.61 ± 0.02 kPa and 0.29 ± 0.01 kPa, approximating respiratory pressure variation in oesophagus and stomach. Conclusion: Our findings suggest that the PIP is caused by sliding of the high-pressure zone along pressure sensors rather than by the transition from the thoracic to the abdominal compartment.

Introduction

From the earliest days of oesophageal manometry onwards, the so-called pressure inversion point (PIP) or point of respiratory reversal was recognized. The PIP is defined as the site at which, during a stationary pull-through manoeuvre, the polarity of the respiration-associated pressure variations changes. The PIP is usually considered to be the result of the transition from the abdominal pressure compartment into the thoracic pressure compartment at the level of the diaphragmatic hiatus. The PIP has been used to measure the proportion of the LOS that is positioned in the abdomen. A short abdominal part of the sphincter has been associated with poor sphincter function.[1] However, others have explained the PIP as a manometric artifact, caused by sliding of a high-pressure zone along the manometric sensors.[2]

Our thoughts about the PIP are likely to be affected by the techniques for manometry of the oesophago-gastric junction. Since the advent of the sleeve sensor in 1976 the interest in the PIP seems to have faded away.[3] When a sleeve sensor is used, no PIP is to be found, because the sleeve straddles the entire gastro-oesophageal high-pressure zone and only measures the highest pressure in this area. In 1996, micromanometry, or high-resolution manometry, was introduced. Compared to conventional catheters, the micromanometric catheter contains smaller lumina, which are perfused at very low perfusion rates.[4,5] These developments enabled pressure monitoring with an array of sideholes spaced at 1 cm.

With the new possibilities offered by high-resolution manometry new questions about the nature of the PIP emerged. In this study we aimed to re-examine the two hypotheses about the origin of the PIP.

Methods

Subjects

We studied 6 healthy volunteers (3 men: mean age 37 years, range 23–58 years) and 6 gastro-oesophageal reflux patients (4 men: mean age 46 years, range 32–57 years) with a proven sliding hiatus hernia of 3 cm. All subjects recently underwent an upper endoscopy to rule out the presence of a hiatal hernia in the healthy volunteers and to confirm the presence of the sliding hernia in the other group. Severe oesophagitis (Savary Miller scale higher than 1) and Barrett epithelium were exclusion criteria. All subjects gave written informed consent

and the protocol was approved by the medical ethics committee of the University Medical Center Utrecht.

Study protocol

The use of gastric acid-inhibitory drugs and drugs that influence gastrointestinal motility was discontinued 3 days before the study. After an overnight fast the manometry catheter was introduced transnasally. The catheter was positioned such that at least one distal sidehole recorded gastric pressure and that the distal high-resolution area of the catheter straddled both high-pressure zones. Subjects were in a supine position and after an adaptation period of at least 10 min the experiment was started and patients were asked to breathe normally and minimize head movements. After 2 h of continuous recording in the fasting state, the subjects consumed a standardized liquid meal of 300 ml (Nutridrink, Nutricia, 150 kCal/100 mL) and the study was continued for another 2.5 h.

Manometric assembly

An 18-channel water-perfused silicone rubber catheter (outer diameter 4.0 mm, length 75 cm, channel diameter 0.4 mm) was used for manometric recordings (Figure 1). The assembly incorporated five proximal sideholes. The sidehole most clearly showing swallow-induced pharyngeal contractions was selected for recording swallows during the measurement. There were 4 oesophageal sideholes at 5-cm intervals and 7 sideholes at 1-cm intervals at the distal end of the catheter. The sideholes are numbered with respect to sidehole 0, which is the sidehole that is positioned at the squamocolumnar junction. All sideholes, except for those at 1 cm and -1 cm from sidehole 0, were perfused at a rate of 0.08 mL/min with degassed water using a pneumohydraulic perfusion system (Dentsleeve Pty Ltd, Wayville, South Australia).

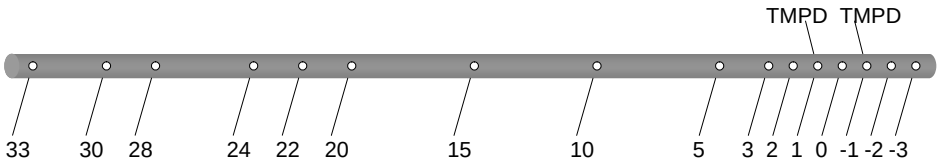

Figure 1. The catheter used in this study. All distances (in cm) are measured from the distal (gastric) end of the catheter (sidehole 0). TMPD was measured at sideholes -1 and 1.

In order to monitor the movements of the squamocolumnar junction along the transducers, measurement of the transmucosal potential difference (TMPD) in

oesophagus and stomach was performed using the sideholes at -1 and 1 cm. This technique makes use of the fact that TMPD across oesophageal mucosa is less negative (around -5 mV) than the TMPD across gastric mucosa (-20 to -30 mV) and movement of the squamocolumnar junction relative to the catheter will give a change in TMPD value. TMPD is of proven value in positioning antroduodenal catheters.[6] The two TMPD channels were perfused with degassed 0.9 % saline from separate reservoirs, also at a rate of 0.08 mL/min. An Ag/AgCl disposable ECG electrode placed on the upper part of the chest was used as reference electrode.
Pressures were recorded with external pressure transducers (Abbott, Sligo, Ireland). Pressure and TMPD data were stored in digital format in two 12-channel dataloggers (Medical Measurement Systems, Enschede, The Netherlands), using a sample frequency of 8 Hz for both pressure and TMPD. At the end of the study all data were transferred to the hard disc of the computer.

Data analysis
In the analysis, pressure readings were divided into 1-min segments. For each of these segments the position of the PIP was identified. When there was a second, more distal, PIP, this was noted in the same way. In addition, the sideholes were identified which measured the highest end-expiratory pressure and the largest respiratory variation in pressure (difference between the expiratory and inspiratory pressure). The respiratory pressure variations recorded above the PIP (maximum at expiration, minimum at inspiration) and below the PIP (maximum at inspiration, minimum at expiration) were measured in all channels. The most proximal sidehole measuring gastric pressure was identified, as was the most proximal sidehole where the pressure remained unchanged during contraction of the LOS or diaphragm. In the analysis described above, episodes with LOS relaxations (either swallow-associated or spontaneous) and episodes with straining were not taken into account.
LOS pressure was calculated using the intragastric pressure as reference. A transient LOS relaxation (TLOSR) was defined as a drop in LOS pressure with a velocity > 0.4 kPa/3 s, a duration > 10 s, a nadir pressure < 0.4 kPa, and absence of a swallow in the time window from 5 s before to 2 s after the start of the relaxation.[7]
For each of the TLOSRs identified, the amplitude of the remaining respiratory pressure variation and the end-expiratory pressure were measured in the different channels. For each of the 1-min periods, TMPD in both channels (1 cm and -1 cm) was measured both during inspiration and during end-expiration. In

the first two healthy subjects studied, TMPD was not measured and thus these two subjects were not taken into account for analysis of TMPD signals.

Statistical analysis and presentation of data

Data were analysed using Student's *t* test when the data were parametric and using the Wilcoxon signed-rank test when data were non-parametric and the differences were considered statistically significant when $p<0.05$. throughout the manuscript dates are presented as mean ± sem (standard error of the mean) and pressures are expressed in kPa (1 kPa=7.5 mmHg).

Results

Pressure patterns in relation to the PIP

Figure 2 is an example of the characteristic pressure variations observed in the presence of a single PIP. The highest endexpiratory pressure was usually measured at the sidehole directly proximal to the PIP, and the largest respiratory pressure variations were typically found immediately distal to the PIP. As shown in figure 3, this was the case both in healthy volunteers and in patients with hiatus hernia, provided a single PIP was present.

Table 1. Respiratory pressure variations (kPa) and end-expiratory pressure at different positions with respect to the PIP under normal circumstances and during TLOSR.

Distance to PIP (cm)	Respiratory pressure variation (kPa)	Respiratory pressure variation during TLOSR (kPa)	End-expiratory pressure (kPa)	End-expiratory pressure during TLOSR (kPa)
4.5+	0.54 ± 0.03*	0.61 ± 0.02*	-0.38 ± 0.20	0.17 ± 0.04#
3.5+	0.55 ± 0.03*	0.60 ± 0.02*	-0.40 ± 0.21	0.10 ± 0.05#
2.5+	0.57 ± 0.05*	0.58 ± 0.02*	3.70 ± 0.39	0.04 ± 0.04#
1.5+	0.84 ± 0.03*	0.59 ± 0.02*	2.29 ± 0.41	0.05 ± 0.04#
0.5-	3.36 ± 0.23	0.61 ± 0.02*	3.01 ± 0.52	0.08 ± 0.09#
0.5-	2.29 ± 0.19	0.29 ± 0.01*	2.50 ± 0.51	0.06 ± 0.05#
1.5-	0.82 ± 0.11*	0.30 ± 0.01*	1.09 ± 0.38	0.08 ± 0.04#
2.5-	0.31 ± 0.01*	0.29 ± 0.01*	0.08 ± 0.09	0.06 ± 0.03
3.5-	0.29 ± 0.01*	0.29 ± 0.01*	0.03 ± 0.06	0.03 ± 0.04

*$p<0.001$ compared to respiratory pressure variation adjacent to PIP (0.5 and -0.5 cm); #$p<0.001$ compared to mean end-expiratory pressure

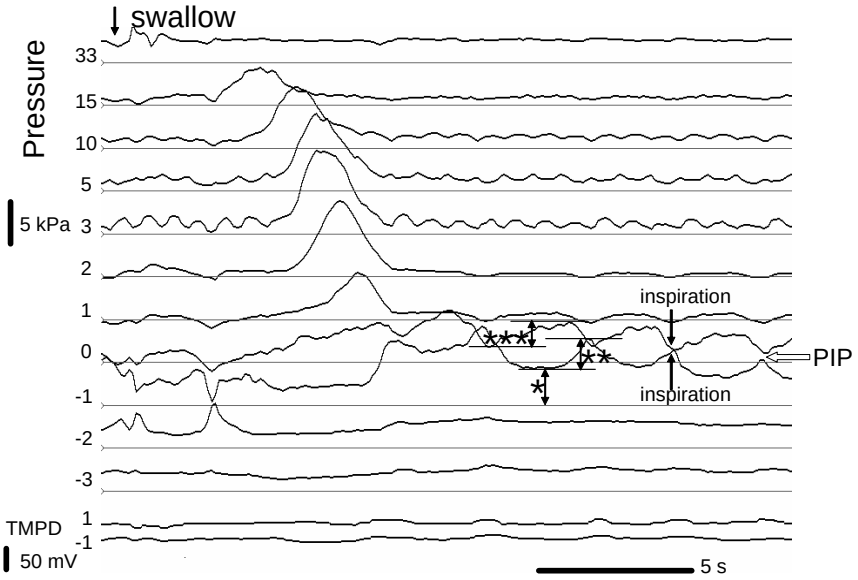

Figure 2. Manometric recording of the oesophagus with high-resolution manometry. The tracing starts with a swallow: a relaxation of the UOS at sidehole 33 is followed by a peristaltic contraction wave in the body of the oesophagus (15, 10, 5, 3, 2 cm) and a relaxation of the LOS (1, 0, -1, -2). In the second half of the figure the PIP is recognizable between 0 and -1. The high-frequent pressure variations in channels 10, 5 and 3 are of vascular origin. The two lower channels show the TMPD signals. In this example, channel -1 measured the highest endexpiratory pressure (*) and also the largest respiration-associated pressure were also seen in channel -1 (**). The respiration-associated pressure variations in channel 0 (***), proximal to the PIP, are slightly lower than those in channel -1.

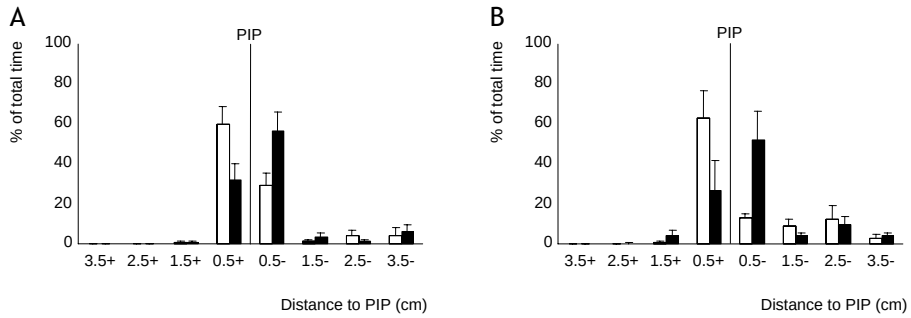

Figure 3. Distribution (in % of total time) of the location of the highest end-expiratory pressure (hatched bars) and largest respirationassociated pressure variations (black bars) with respect to a single PIP in healthy volunteers (left) and patients with a hiatal hernia (right). The PIP is mostly bordered proximally by the highest end-expiratory pressure and distally by the largest respiration-associated pressure variations.

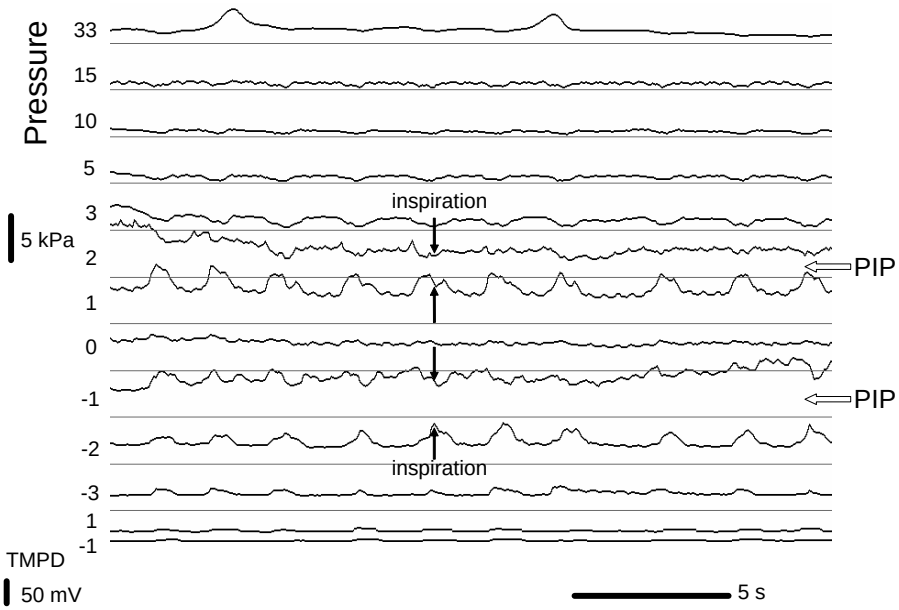

Figure 4. Example of a double PIP. The proximal PIP is located between the sideholes at 1 and 2. The distal PIP is found between the sideholes at -1 and -2.

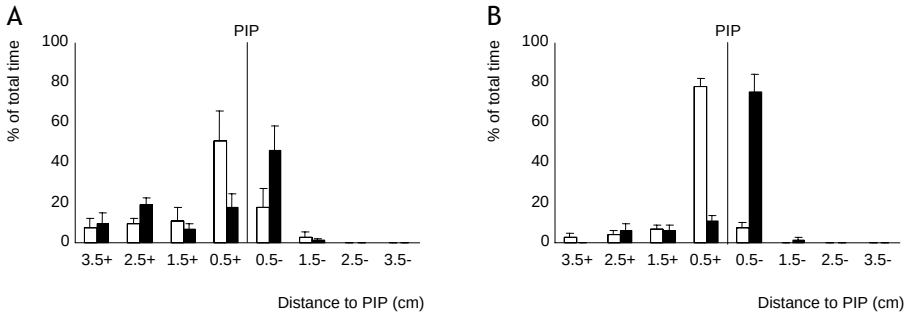

Figure 5. Distribution (in % of total time) of the location of the highest end-expiratory pressure (hatched bars) and largest respiration-associated pressure variations (black bars) with respect to distal PIP, when present, in healthy volunteers (panel A) and in patients with a hiatal hernia (panel B). The PIP is mostly bordered proximally by the highest pressure and distally by the largest respiration-associated pressure variations.

The amplitude of the respiratory pressure variations measured by the sidehole directly proximal to the PIP was significantly higher than the amplitude of the respiratory pressure variation measured by the sideholes in the body of the oesophagus (Table 1). Likewise, the amplitude of the respiratory pressure variations measured by the sidehole directly distal to the PIP was significantly higher than the amplitude of the respiratory pressure variations measured by the sideholes more distally (Table 1). During TLOSRs the respiratory pressure variations decreased amplitudes comparable to the amplitudes of respiratory pressure variations in oesophagus and stomach (Table 1).

Double PIP

A typical example of pressure tracings recorded during presence of a double PIP is shown in figure 4. A double PIP was present during 23 ± 8 % of the time in healthy controls and during 38 ± 9 % of the time in hiatal hernia patients. The difference was not significant. Only two healthy controls showed no double PIP at all. All hiatal hernia patients had periods with a double PIP. When a second PIP was present, the highest end-expiratory pressure was found adjacent to the distal PIP in 69 ± 6 % of the time in the healthy controls and in 87 ± 2 % of the time in the hiatal hernia patients. The maximal respiration-associated pressure variations were found in 64 ± 9 % of the time adjacent to the distal PIP in healthy controls and in 86 ± 6 % of the time in hiatal hernia patients (Figure 5).

In case of a double PIP, the distal PIP was located immediately proximal to the intragastric sidehole in 73 ± 9 % of total time. The average distance between the two PIPs was 2.5 ± 0.2 cm in healthy controls and 2.6 ± 0.2 cm in hiatal hernia patients (NS). The distance between the proximal PIP and the most proximal intragastric sidehole was significantly larger in periods when a double PIP was present (4.4 ± 0.6 cm) than in periods with only one PIP (3.9 ± 0.2 cm, $p<0.05$).

TMPD signals

Mean TMPD measured at the sidehole at 4 cm proximal to the distal end of the catheter was -7.8 ± 5.6 mV during inspiration and -9.5 ± 6.0 mV during expiration ($p<0.05$). The TMPD in the sidehole at 2 cm proximal to the distal end of the catheter was also significantly less negative at inspiration than at expiration (-19.7 ± 4.0 mV and -21.4 ± 3.9 mV, respectively, $p<0.05$).

Discussion

Our results strongly support the hypothesis of Harris et al., namely that the PIP is the result of sliding of a high-pressure zone along manometric sensors.[2,8] The following arguments favour this hypothesis.

Firstly, we observed a strong relationship between the position of the PIP, the highest end-expiratory pressure and the highest respiratory pressure variation. This observation can be explained as follows. During expiration the LOS moves proximally and during inspiration the LOS moves distally with a total longitudinal excursion of approximately 1 cm.[9,10] The sidehole at the distal border of the LOS will record the highest pressure at inspiration; the sidehole at the proximal border will record the highest pressure at expiration (Figure 6).[11] This explains why we found the highest endexpiratory pressure most of the time in the sidehole immediately proximal to the PIP.

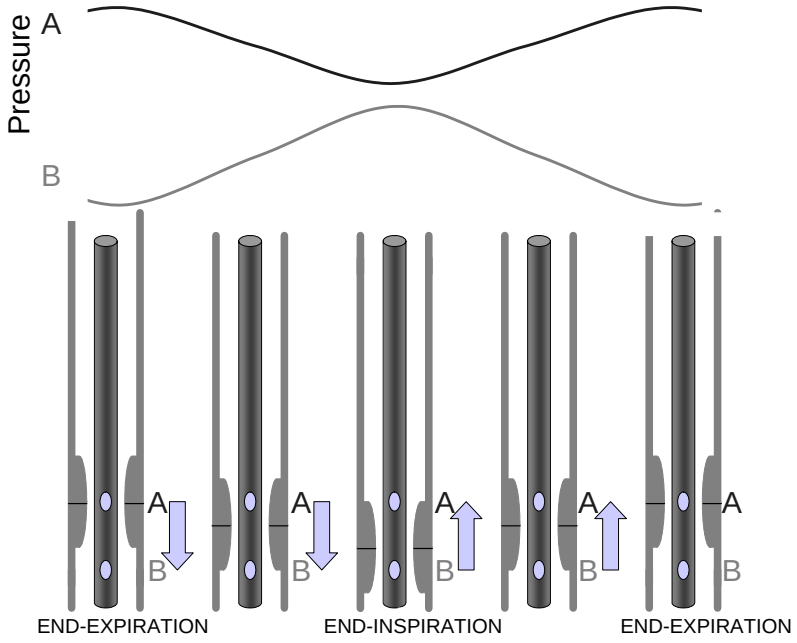

Figure 6. Sliding of the distal oesophagus along a catheter with two sideholes A and B. The figure above represents the recordings of the sideholes. The thickening of the oesophageal wall represents the LOS. The line in it is the mucosal transition. Movement with respiration of the distal oesophagus with regard to the sideholes creates the effect on oesophageal manometry that we recognize as the PIP. This figure also explains the high coincidence of the highest end-expiratory pressure and the position of the PIP.

Secondly, the respiratory pressure variations were significantly larger around the PIP than in the body of the oesophagus and in the stomach. The amplitude of the intra-oesophageal respiratory pressure variations is comparable to the amplitude of the pressure variations in the thoracic cavity that occur during breathing. Likewise, the pressure variations seen in the intragastric sidehole are comparable in size to the pressure changes that occur in the abdomen during breathing. The pressure variations that occur with breathing in the highpressure zone at the oesophago-gastric junction are much larger and, thus, are likely to have another origin. As mentioned above, the origin of the respiratory variations may lie in the fact that the LOS moves along the sideholes with respiration and measures different pressures in the different parts of the LOS.

The hypothesis that the PIP reflects the transition of thoracic oesophagus into the abdominal oesophagus does not explain why the respiratory pressure variations are much larger at the oesophago-gastric junction than in the body of the oesophagus and in the stomach. Usually it is assumed that these large pressure variations around the PIP are the result of the contraction of the diaphragm with inspiration. Although our observations do not rule out the possibility that diaphragmatic contractions contribute to the measured signal, contractions of the diaphragm cannot explain the large negative pressure deflections with inspiration that are observed a sidehole 1 cm more proximal (Figure 2).

Thirdly, during a TLOSR, when the LOS relaxes completely, the large respiratory pressure variations adjacent to the PIP disappear and the amplitude of the variations in the upper LOS segment becomes comparable to that in the oesophageal body, and the amplitude of the variations in the lower LOS segment becomes comparable to the pressure variations that occur with breathing in the stomach. Thus, when the LOS relaxes the PIP becomes hardly recognizable.

The recorded TMPD signals confirm that the mucosal transition moves up with expiration (mean oesophageal TMPD being more negative and measuring gastric TMPD during a greater part of time) and down with inspiration (mean baseline TMPD being less negative indicating that the gastric sidehole measures oesophageal TMPD during a greater proportion of the time).

In hiatal hernia patients a part of the gastric cardia is tented through the diaphragmatic sphincter. It has been reported that manometric recordings of the distal oesophagus in these patients may show two separate high-pressure zones and a double PIP, but this does not appear to be a consistent finding.[12-15]

Some reports hold that the PIP is always at the level of the diaphragmatic hiatus, whereas other studies have indicated that the PIP coincides with the LOS.[2,16-18]

Our data support the view that both concepts are correct in the case of a double PIP, since the PIP is a manometric artifact created by a pressure gradient. The proximal PIP coincides with the most proximal high-pressure zone, the LOS, and the distal PIP coincides with the second, more distal high-pressure zone, the diaphragmatic sphincter. Our finding that the distal PIP, when present, is found immediately proximal to the intragastric sidehole in 73 ± 9 % of cases supports this theory. In the case of a single PIP, this PIP lies well above the intragastric sidehole and seems to be the manometric manifestation of the LOS, as previously shown.[18] In the case of a double PIP, the distance between proximal PIP and intragastric sidehole is even larger.

Our results show that the phenomenon of a double PIP occurs both in healthy controls and in hiatal hernia patients. However, a double PIP was only seen in a small proportion of the time and this might explain why previous studies using pull-through techniques often not could demonstrate a double PIP. The difference in distance between the proximal and distal PIP was not statistically significant between the two groups, perhaps due to the fact that our patients only had a hiatal hernia of 3 cm.

Kahrilas et al. found that in the case of a hiatal hernia the distal high-pressure zone has a higher pressure than the proximal high-pressure zone.[13] In the case of a double PIP, we also found the highest end-expiratory pressure most of the time around the distal PIP, and this explains why the highest respiratory pressure variations are also found around the distal PIP.

When the dissociation between LOS and diaphragmatic hiatus is smaller than 2 cm this is called a physiologic herniation and the part between the two high-pressure zones is called the phrenic ampulla.[19] This physiologic herniation, resulting in a small dissociation between the LOS and the diaphragmatic hiatus, might be the explanation for the double PIP found in healthy volunteers.

The observations made in this study have implications for clinical practice, i.e. for routine oesophageal manometric studies. The PIP does not simply represent the oesophagogastric junction but the sliding of a high-pressure zone along a pressure sensor. To complicate matters further there can be two PIPs, even in healthy subjects. A first implication is that the PIP cannot be used to measure the length of the intrathoracic and abdominal parts of the LOS. A second implication is that if one uses the PIP for localization of the LOS, it is possible that a distal PIP, caused by the diaphragm is mistaken for the sphincter. These conclusions are valid for both stationary high-resolution manometry and for routine pull-through manometry.

In conclusion, our observations made with high-resolution manometry indicate that the PIP is a manometric artifact caused by sliding of one or two high-pressure zones at the oesophago-gastric junction along the catheter and does not reflect the transition from the thoracic to the abdominal compartment.

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5

Double-peaked high-pressure zone at the esophagogastric junction in controls and in patients with a hiatal hernia: A study using high-resolution manometry

A.J. Bredenoord
B.L.A.M. Weusten
S. Carmagnola
A.J.P.M. Smout

Dept. of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands
Gastrointestinal Research Unit, University Medical Center, Utrecht, The Netherlands

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Abstract

The lower esophageal high-pressure zone (HPZ) consists of the intrinsic lower esophageal sphincter (LES) and the diaphragmatic sphincter. In patients with a hiatal hernia these constituents are separated. We performed high-resolution manometry of the esophagogastric HPZ in six controls, six patients with a small hernia, and six patients with a large hernia. Prevalence of a double-peak pressure profile of the HPZ was noted. Pressures and distances between the peaks were assessed. Prevalence of the double-peak profile was similar between patients with a small hernia and controls, but patients with a large hernia showed a higher prevalence with inspiration ($p<0.05$) than the others. The distance between the two peaks was larger in patients with a large hernia ($p<0.05$). In conclusion, high-resolution manometry makes it possible to distinguish the diaphragmatic pressure component from the LES. Two pressure peaks can be found both in hernia patients and in healthy volunteers.

Introduction

An intraluminal high-pressure zone (HPZ) between the esophagus and the stomach prevents reflux of gastric contents into the esophagus. Both the intrinsic lower esophageal sphincter (LES) and the right diaphragmatic crus are believed to contribute to this antireflux barrier.[1-3] In patients with a hiatal hernia, part of the gastric mucosa is tented through the diaphragmatic hiatus and the LES is separated from the diaphragmatic sphincter. This spatial separation can be identified with endoscopy, radiology, and, also, manometry.[4-8]

With pull-through manometry two distinct pressure zones can occasionally be identified in patients with a hiatal hernia, the proximal zone representing the LES and the distal the diaphragmatic sphincter. However, with these techniques, only a snapshot image of the esophagogastric HPZ is obtained. With sleeve sensor manometry the double-peaked HPZ morphology cannot be observed, because with this device only the highest pressure over the sleeve sensor membrane is registered. New technical developments have led to the introduction of micromanometry.[9] Micromanometry catheters contain smaller lumina compared to conventional manometry catheters and are perfused at very lowperfusion rates. This development has opened doors to the recording of pressures with an array of sideholes spaced at 1 cm without overloading the esophagus with large amounts of water.[10] High-resolution manometry or micromanometry makes it possible to measure pressure during prolonged periods of time. This could be useful, since sliding hiatal hernias are believed to have dynamic properties: Their size can change over time.[11]

The aim of this study was to investigate whether the contribution of the LES and the diaphragm to the HPZ at the esophagogastric junction can be distinguished using highresolution manometry and to assess dynamic changes in the HPZ over time, after a meal, and during the respiratory cycle.

Methods

Subjects

We studied six healthy volunteers (three men and three women; mean age, 37 years; range, 23–58 years), six gastroesophageal reflux disease patients (four men and two women; mean age, 46 years; range, 32–57 years) with a proven sliding hiatus hernia of approximately 3 cm, and six gastroesophageal reflux disease patients (four men and two woman; mean age, 59 years; range, 36–74 years) with

a proven sliding hiatus hernia of approximately 5 cm. All subjects recently underwent an upper endoscopy to rule out the presence of a hiatal hernia in the healthy volunteers and to confirm the presence of the sliding hernia in the patients. Erosive esophagitis (Los Angeles classification higher than A) and Barrett epithelium were exclusion criteria. All subjects gave written informed consent and the protocol was approved by the medical ethical committee of the University Medical Center Utrecht.

Study Protocol

The use of gastric acid-inhibitory drugs and drugs that influence gastrointestinal motility were discontinued 5 days before the study. After an overnight fast the manometry catheter was introduced transnasally. The catheter was positioned such that at least one distal sidehole recorded gastric pressure and that the distal high-resolution area of the catheter straddled both HPZs. Subjects were in a supine position and after an adaptation period of at least 10 min the experiment was started. Patients were asked to minimize head movements. After 2 hours of continuous recording in the fasting state, the subjects consumed a standardized liquid nutrient meal of 300 ml (150 kcal/100 ml; 13 % protein, 39 % carbohydrate, 48 % fat) (Nutridrink, Nutricia, The Netherlands) and the study was continued for another 2 hour.

Manometric Assembly

An 18-channel water-perfused silicone rubber catheter (outer diameter, 4.0 mm; length, 75 cm; channel diameter, 0.4 mm) was used for manometric recordings in controls and in patients with a small hiatal hernia (Figure 1A). The assembly incorporated five proximal sideholes. The sidehole most clearly showing swallow-induced pharyngeal contractions was selected for recording swallows during the measurement. There were four esophageal sideholes at 5-cm intervals and seven sideholes at 1-cm intervals at the distal end of the catheter. The sideholes are numbered with respect to sidehole 0, which is the sidehole that is positioned at the squamocolumnar junction. In the patients with a hiatal hernia of 5 cm a catheter with four additional sideholes at the distal end of the catheter was used (Figure 1B). This made it possible to position the catheter in such a way that the high-resolution area of the catheter straddled both LES and diaphragm in these patients. All sideholes were perfused at a rate of 0.08 ml/min using a pneumohydraulic perfusion system (Dentsleeve Pty Ltd., Wayville, South Australia).

Pressures were measured with external pressure transducers (Abbott, Sligo, Ireland). Pressure data were stored in digital format in two 12-channel dataloggers (Medical Measurement Systems, 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.

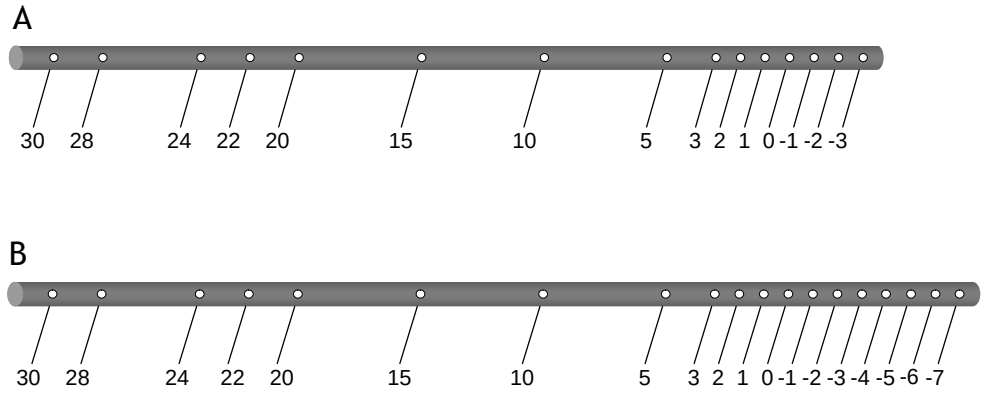

Figure 1. Schematic representation of the manometric catheter used in this study. (A) Catheter used in healthy volunteers and in patients with a small hiatal hernia. (B) Catheter used in patients with a large hiatal hernia. All distances (cm) are measured from the sidehole in the middle of the high-resolution area (sidehole 0).

Data Analysis

In the analysis, pressure readings were divided into 2-min segments. In these 2-min segments basal endexpiratory and basal end-inspiratory pressurewas determined for each of the channels 10 to −3, referenced to intragastric pressure. Determination of these pressures for the 2-min segments was performed at the first time point in each 2-min segment without LES relaxation (either swallow-associated or spontaneous), peristaltic contraction, or straining.

A pressure peak was identified when the pressure was above 1.5 kPa compared to the gastric baseline pressure. It was noted whether there were one or two separate pressure peaks within the HPZ. Based on the tracings in the distal esophagus, HPZs were categorized as having either one or two pressure peaks (Figure 2). A HPZ was regarded as double-peaked when at least one sidehole measured a pressure lower than 1.5 kPa between the two peaks. The distance between the two pressure peaks of the double-peaked shaped HPZ was determined by measuring the distance between the pressure channels that were

measuring these pressure peaks. In the analysis, the 2-min segments were grouped in a 2-hour preprandial period and four postprandial periods, each lasting 30 min.

Statistical Analysis and Presentation of Data
Parametric paired data were compared with ANOVA for repeated measures. Nonparametric paired data were compared with the Friedman test. Post hoc comparisons were performed using the Bonferroni test. Differences were considered statistically significant at $p \leq 0.05$. Throughout the manuscript data are presented as mean ± SEM and pressures are expressed as kilopascals (1 kPa=7.5 mm Hg).

Results

There was no significant difference in the prevalence of the double-peaked HPZ profile between healthy controls and patients with a small hiatal hernia, but the double-peaked profile was more prevalent in patients with a large hiatal hernia than it was in the other two groups (Figure 3). Even in patients with a large hiatal hernia a single-peaked HPZ was observed preprandially 26 % of the time during inspiration and 63 % of the time during expiration. After consumption of the liquid nutrient meal a pronounced decrease in the prevalence of the double-peaked HPZ profile was seen in all groups. After 60 to 90 min this effect of the meal faded away and the prevalence of the double-peaked profile increased to preprandial values.
Figure 4 shows the mean pressure of the distal and proximal component of the double-peaked HPZ during inspiration and expiration. In all groups the amplitude of the distal, diaphragmatic peak increased with inspiration. The amplitude of the proximal (LES) pressure peak increased with inspiration in the controls and the patients with a small hiatal hernia but not in the patients with a large hiatal hernia. During inspiration LES pressure was significantly lower in patients with a large hiatal hernia compared with the other two groups. Amplitude in the distal, diaphragmatic pressure peak was also lower in the patients with a large hiatal hernia, both in inspiration and in expiration.
When a double-peaked HPZ was present, the distance between the proximal and the distal pressure peaks was larger in the patients with a large hiatal hernia than the other two groups (Figure 5). There was no difference in distance between the pressure peaks in inspiration and those in expiration. Postprandially,

the distance between the two peaks of the HPZ shortened significantly in the patients with a large hiatal hernia, whereas in the other groups the distance between the peaks remained unchanged.

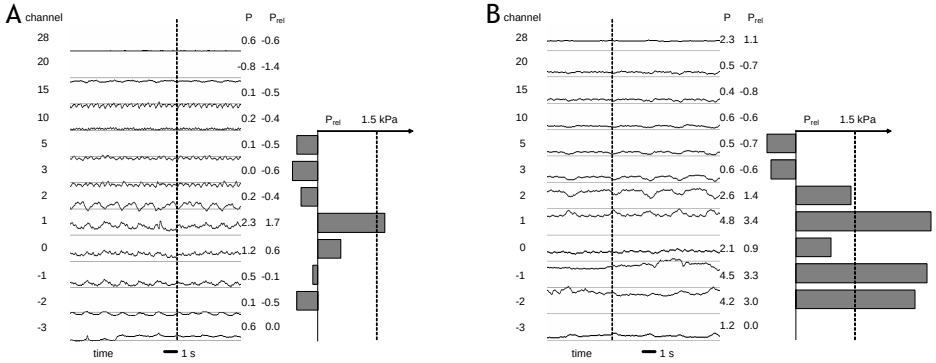

Figure 2. Manometric profiles of the lower esophageal HPZ. A pressure peak was defined to be present if the pressure in a channel was 1.5 kPa higher than the gastric baseline pressure. *P*rel is the pressure relative to the intragastric pressure. (Left) An example of a single-peak HPZ is shown. The panel on the right shows the pressure at the moment of the dashed line. A single-pressure peak profile is recognized. (Right) Example of a manometric tracing with a double-peaked pressure profile, the peaks being located at channels 1 and −1.

Transitions between the two different profiles from one 2-min segment to the next occurred frequently in all groups. For example, in the patients with a large hiatal hernia, the HPZ profile switched an average of 12.6 ± 2.0 times from the single- to the double-peak profile and back in the 2-hour preprandial period (Table 1). There were no significant differences between transition rates in the different groups, nor was there an effect of the meal.

Table 1. Numbers of transitions between the two profiles from one 2-min segment to the next, calculated as per hour values

	Controls	Patients with small hernia (3 cm)	Patients with large hernia (5 cm)
Preprandial	3.1 ± 1.1	4.9 ± 0.8	6.8 ± 1.0
0-30 min postprandial	1.7 ± 0.9	4.7 ± 1.4	5.3 ± 1.2
31-60 min postprandial	2.0 ± 1.0	4.7 ± 1.6	3.3 ± 1.1
61-90 min postprandial	2.7 ± 1.6	4.3 ± 0.9	2.0 ± 0.7
91-120 min postprandial	2.3 ± 1.2	4.7 ± 0.8	2.3 ± 1.1

Note. No statistically significant differences were found.

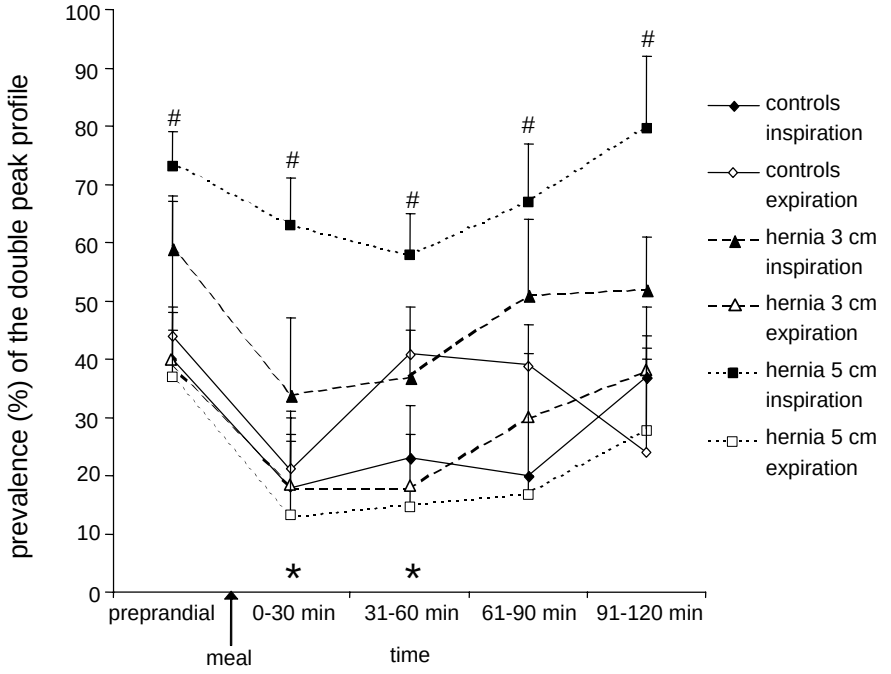

Figure 3. Prevalence of the double-peaked profile in healthy controls, patients with a small hiatal hernia, and patients with a large hiatal hernia in end-expiration and end-inspiration. Only in the group of patients with a large hiatal hernia is there a significant difference between inspiration and expiration. During inspiration the double-peaked profile was seen significantly more often in the patients with a large hiatal hernia than in the other groups. *p<0.05 compared to preprandial values. #p<0.05 compared to the other groups.

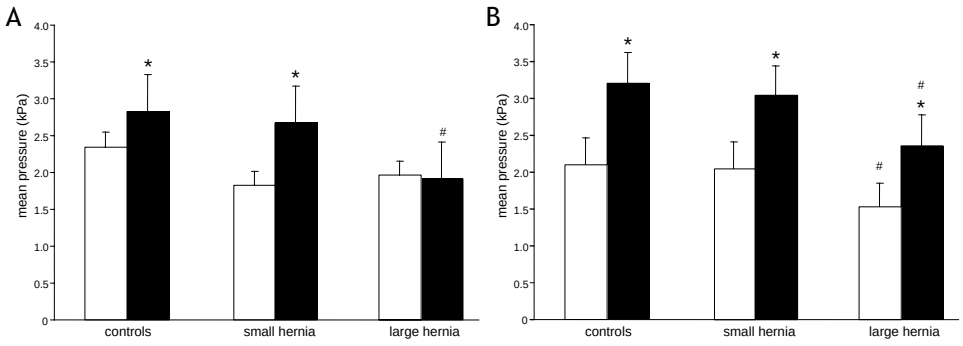

Figure 4. Mean pressures during expiration (white bars) and inspiration (black bars) in the proximal (LES) pressure peak (A) of the double-peaked profile and in the distal (diaphragm) pressure peak (B). *p<0.05 compared to expiratory values. #p<0.05 compared to the other groups.

Discussion

Although the double-peaked manometric morphology of hiatal hernias had already been described in 1962 and has received attention in some more recent studies, this is the first study in which prolonged manometry was used to study the manometric profiles of hernia patients and in which an effect of a meal on this profile was observed.[7,12-15] Our data suggest that a double-peaked morphology represents the two components of the lower esophageal HPZ: the LES and the diaphragmatic crus.

Our findings include a significant difference in the prevalence of the double-peaked pressure profile between healthy volunteers and patients with a small hiatal hernia, on the one hand, and patients with a large hiatal hernia, on the other. However, the double-peaked manometric morphology was also rather common in healthy volunteers. Recently, we found double pressure inversion points in hernia patients and also in healthy controls, suggesting that a double-pressure peak profile could exist in both.[16] In patients with a hiatal hernia both the double-peaked profile and the single-peak profile were present, illustrating the reducibility of sliding hernias. Furthermore, this implies that a single-peak profile does not exclude the presence of a hiatal hernia.

A small spatial separation of LES and diaphragm is considered normal and is sometimes referred to as the epiphrenic ampulla. The epiphrenic ampulla, which has been identified manometrically and radiographically in healthy volunteers, is hypothesized to be a potential hiatal hernia.[17] Our findings stress the artificial nature of the difference between a hiatal hernia and an epiphrenic ampulla: The first has a distance between diaphragm and LES of 3 cm or more and the latter has a dissociation between the two of less than 3 cm. Another study using stationary pull-through manometry reported that, although large hernias were easily recognized, the sensitivity for smaller hernias was poor.[13] With high-resolution manometry we were able to track the changes in manometric morphology of the lower esophageal HPZ during the course of the study and the transition between the two profiles in the same patient illustrated the dynamic features of the region and the reducibility of the hernia. Indeed, the manometric morphology in the same subject changed often during the course of the study. Others have shown this double-peaked structure in patients.[7,15,18] and even in healthy volunteers.[19] But using pull-through manometry one can only observe the lower esophageal HPZ in a snapshot, and it was hitherto unclear whether a double-peaked profile would be structural.

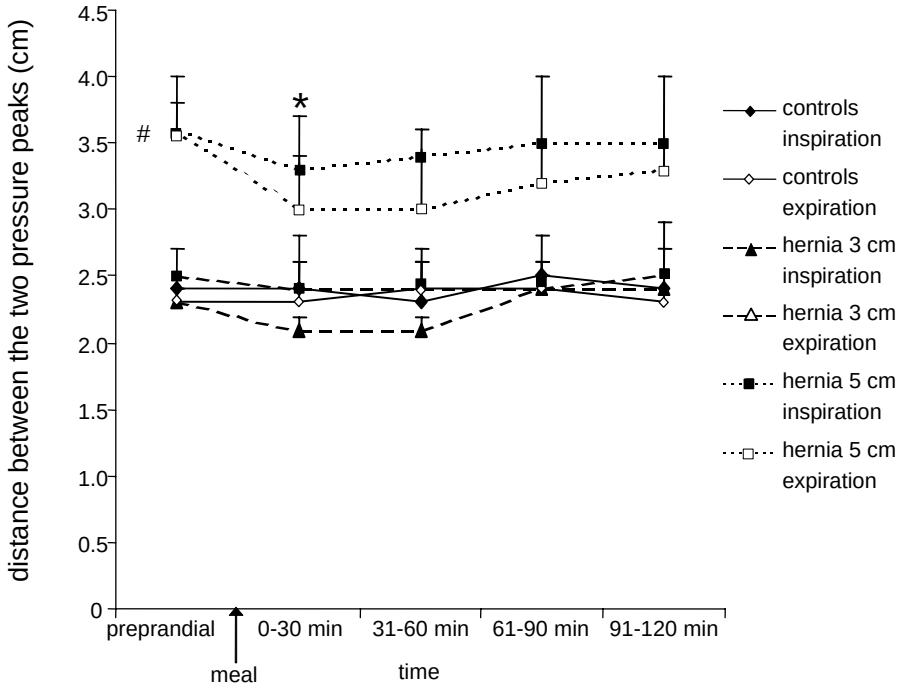

Figure 5. Distance between the two pressure peaks in the double-peaked profile. The distance was larger in the patients with a large hiatal hernia. There were no differences between end inspiration and end expiration. *p<0.05 compared to preprandial values. #p<0.05 compared to the other groups.

It is known that distal movement of the HPZ at the esophagogastric junction occurs with inspiration.[20] Since the distance between the two peaks of the HPZ was independent of the phase of the respiratory cycle, it can be concluded that both components of the HPZ move distally over the same distance with respiration in healthy controls and small hernias. The observation that the prevalence of the different profiles is similar in inspiration and expiration corroborates this conclusion. If, for example, the diaphragm moved more distally with inspiration than the LES, the distance between the two pressure peaks would increase with inspiration and a double-peaked profile would be recognized more easily. In patients with a large hiatal hernia, the double-peaked profile is less prevalent in expiration than in inspiration. Two factors could contribute to this observation: first, that the diaphragm moves more distally with inspiration than does the LES and, second, that the distally diaphragmatic pressure peak is not recognized because of a low tonic expiratory pressure, and as a result, a single-peak profile is found.

Although the results of this study suggest that the two HPZs we found with high-resolution manometry represent the diaphragm and the LES, we did not provide evidence as conclusive as Lin et al. did by using closely spaced sideholes and concomitant videofluoroscopy.[17] Theoretically, the two HPZs we found could be the result of asymmetry of the LES as well.

In our study, we found a striking effect of a meal on the prevalence of the double-peaked profile. Postprandially, the prevalence of the double-peaked profile was significantly reduced in all groups. After about 60 to 90 min a gradual return to fasting conditions was observed. Apparently, feeding reduces the hernia and decreases the distance between diaphragm and LES. The fact that the distance between the two pressure peaks of the HPZ in the hernia profile decreases after feeding is an additional argument for this conclusion. In a recent paper, the Chicago group observed a shortening of the HPZ after inflation of the stomach with air.[21] A likely explanation for the observed reduction is that upon filling of the stomach, part of the hernia or epiphrenic ampulla is pulled back from the thoracic into the abdominal cavity.

The dissociation between LES and diaphragm in the double-peaked profile made it possible to quantify the pressures of the LES and the diaphragm separately. The pressure of the diaphragmatic peak was higher in inspiration, as expected. Surprisingly, the pressure of the proximal peak also increased with inspiration in the healthy volunteers and in the patients with a small hiatal hernia. There are two possibilities to explain this: Either the intrinsic sphincter contracts with inspiration or part of the diaphragm surrounds the proximal HPZ and is responsible for this inspiratory pressure increase. The fact that we did not observe this inspiratory pressure increase in the LES in the patients with a large hiatal hernia favors the second explanation: The diaphragmatic fibers are located farther distally in these patients and do not influence LES pressure.

In a study by Kahrilas and coworkers, in which hiatal hernias were studied manometrically, the basal expiratory pressure was found to be lower in each of the two pressure peaks compared to the pressure of only one single pressure peak, however, this could not be confirmed by others.[15,18] In our study, the pressures of the diaphragmatic and LES peak in the double-peaked profile were not lower than the pressure of a single pressure peak, when present in the different groups. It is unclear whether this is due to methodological differences.

Opinions about the importance of hiatal hernia in the pathogenesis of gastroesophageal reflux disease differ, but more and more it becomes clear that patients with an irreducible hiatal hernia have more transient LES relaxations, more swallow-induced reflux, and more severe acid-induced mucosal

damage.[14,21,22] It is uncertain whether this is true for reducible hernias as well.[23] Furthermore, it was stated that future research on the pharmacological control of the gastroesophageal junction in hiatal hernia would seem promising. One might add that, since the difference between small reducible hiatal hernias and a normal epiphrenic ampulla appears to be artificial and the anatomy of the region is very dynamic, these future studies should pay particular attention to the definition of a hiatal hernia.[24] It is uncertain if the influence of a hiatal hernia on reflux depends on structural effects or on the temporal dissociation of LES and diaphragm. High-resolution manometry seems a suitable tool to investigate this.

In conclusion, this study shows that high-resolution manometry makes it possible to distinguish the diaphragmatic pressure component from the LES. A spatial dissociation between the two high-pressure peaks can be found not only in hiatal hernia patients but also in healthy volunteers. Manometric profiles of the lower esophagus fluctuate, and after a meal the hiatal hernia is reduced temporarily.

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6

Sleeve sensor versus high-resolution manometry for the detection of transient lower esophageal sphincter relaxations

A.J. Bredenoord
B.L.A.M. Weusten
R. Timmer
A.J.P.M. Smout

Dept. of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands
Gastrointestinal Research Unit, University Medical Center, Utrecht, The Netherlands

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Abstract

Transient lower esophageal sphincter relaxations (TLESRs) are the most important mechanism by which gastroesophageal reflux occurs, and sleeve sensor manometry is the gold standard for detection of TLESRs. The aim of this study was to evaluate manometry with closely spaced sideholes (high-resolution manometry) for the detection of TLESRs as an alternative. In 12 patients with gastroesophageal reflux disease, a 90-min postprandial manometry was performed by using a catheter incorporating both a sleeve sensor and closely spaced sideholes in the esophagogastric junction. TLESRs recorded with both techniques were scored. Reflux during TLESRs was detected by using manometry (common cavity), intraluminal impedance, and pH monitoring. A total of 145 TLESRs were detected by using both techniques, 117 with high-resolution manometry and 108 with sleeve sensor manometry [not significant (NS)]. Manometric signs of reflux during TLESRs detected with high-resolution and sleeve sensor manometry were found in 62.4 and 56.5 %, NS, respectively, versus 38.5 and 35.2 %, NS on pH-metry and 70.1 and 60.2 %, NS on impedance monitoring. TLESRs recognized only with high-resolution manometry were more often accompanied by reflux, as detected with manometry (59.5 %) and impedance monitoring (67.6 %), than TLESRs recognized only with sleeve sensor manometry (32.1 and 28.6 %). High-resolution manometry is at least as accurate as sleeve sensor manometry for the detection of TLESRs.

Introduction

Before the advent of the sleeve sensor, lower esophageal sphincter (LES) pressure was measured by using a single perfused sidehole or miniature pressure transducer positioned in the lumen of the sphincter. Because of axial movements of the distal esophagus with respect to the pressure sensor, it was difficult to ascertain that a drop in pressure was caused by an LES relaxation. The introduction of the perfused sleeve sensor by Dent in 1976 was an important step forward.[11] The sleeve sensor records the highest pressure along a membrane, thus reducing movement artifacts almost entirely. This technical improvement led to the discovery of relaxations of the LES not associated with swallowing, initially referred to as "inappropriate" LES relaxations, and their important role in the pathogenesis of gastroesophageal reflux disease (GERD) became clear.[1,13,17,22,24] Subsequent studies showed that these inappropriate or transient LES relaxations (TLESRs) are the result of a vagally mediated reflex, triggered by mechanoreceptors in the proximal stomach with the purpose of protecting the stomach against excessive gaseous dilatation.[14,15,21,23] TLESRs often facilitate acid reflux, which means that TLESRs are now considered to be a promising target for pharmacotherapy of GERD.[2,6,18,33,35]

New technical developments have led to the introduction of micromanometry.[8,20] Micromanometry catheters contain smaller lumina compared with conventional manometry catheters, and are perfused at very low perfusion rates. This development has made it possible to record pressures at 1-cm intervals without overloading the esophagus with a large quantity of water. This method, known as high-resolution manometry, offers the theoretical advantage above sleeve sensor manometry that more detailed information of the gastroesophageal junction can be obtained.[3,4,12] Until now it has not been clarified whether TLESRs can be adequately studied by using high-resolution manometry. Therefore, the aim of this study was to compare the detection of TLESRs using high-resolution manometry with the detection of TLESRs using sleeve sensor manometry.

Methods

Subjects

We studied 12 patients (5 men and 7 women, mean age: 50 yr, range: 18–81 yr) with an esophageal acid exposure time of >4.2 % of the total time during a recent 24-hour pH study. Written informed consent was obtained from all subjects, and

the protocol was approved by the medical ethics committee of the University Medical Center Utrecht.

Study protocol

The use of gastric acid inhibitory drugs and drugs that influence gastrointestinal motility was discontinued 5 days before the study. After an overnight fast, the manometry catheter was introduced transnasally. The catheter was positioned such that at least the most distal sidehole recorded gastric pressure and that the high-resolution area of the catheter and the sleeve sensor straddled the LES. After positioning of the manometry catheter, the impedance and the pH catheter were introduced transnasally and positioned based on the manometric findings (see below). Subjects were in an upright position, and after an adaptation period of at least 10 min, the experiment was started. Patients were asked to minimize head movements.

After 30 min of recording in the fasting state, the subjects consumed a standardized meal consisting of a hamburger (McDonald's Quarter Pounder consisting of a bun, sauce, meat, pickle and cheese), 20 g of fresh onions, 44 g of potato chips and 475 ml of orange juice (in total 967 kCal). The meal had to be finished in 30 min. After ingestion of the meal, recording was continued for another 90 min.

Manometric technique

An 18-channel water-perfused silicone rubber catheter (outer diameter: 4.0 mm, length: 75 cm, channel diameter: 0.4 mm) was used for manometric recording (Figure 1). The proximal part of the assembly incorporated five sideholes at 1-cm intervals. Of these, the sidehole most clearly showing swallow-induced pharyngeal contractions was selected for recording swallows. After selection of this sidehole, perfusion of the other four pharyngeal sideholes was discontinued because it has been suggested that pharyngeal stimulation with water may trigger TLESRs.[19] There were four esophageal sideholes at 5-cm intervals and seven sideholes at 1-cm intervals at the distal end of the catheter. In addition, the distal end of the catheter incorporated a 6-cm long reverse-perfused sleeve sensor. The sideholes in the manometry catheter were labeled according to their distance to the midsleeve channel (sidehole 0). All sideholes were perfused at a rate of 0.08 ml/min using a pneumohydraulic perfusion system (Dentsleeve, Wayville, South Australia). The sleeve sensor was perfused at a rate of 0.30 ml/min.

Pressures were measured with external pressure transducers (Abbott, Sligo, Ireland). Pressure data were stored in digital format in two 12-channel dataloggers (Medical Measurement Systems, Enschede, The Netherlands) using a sample frequency of 8 Hz. At the end of the study, all data were transferred to the hard disk of the computer.

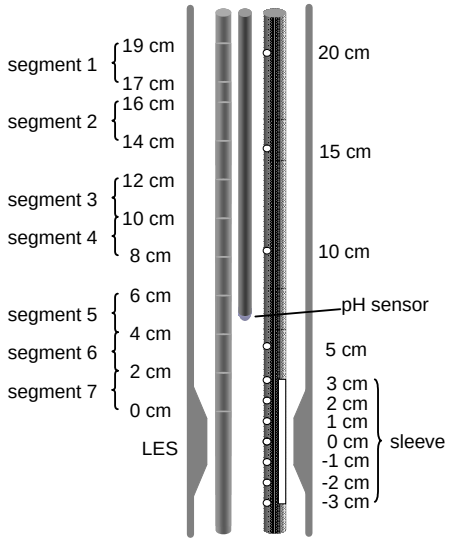

Figure 1. Impedance (left) and pH (middle) catheters were positioned with respect to the upper border of the lower esophageal sphincter (LES). The manometry catheter (right) was positioned in such a way that the most distal sidehole registered gastric pressure and the sleeve sensor straddled the LES. The sideholes on the manometry catheter were labeled according to their distance to midsleeve.

Intraluminal impedance and pH monitoring

For intraluminal impedance monitoring, a seven-channel impedance catheter was used [Aachen University of Technology, Forschungszentrum für Elektro-Magnetishe Umweltverträglichkeit (FEMU), Aachen, Germany]. This catheter (outer diameter: 2.3 mm) enabled recording from seven segments, each recording segment being 2 cm long. The 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 localized LES (Figure 1). Impedance signals were stored in a digital system (Aachen University of Technology, FEMU) using a sample frequency of 50 Hz.[5] Intraluminal pH monitoring was performed with a glass pH electrode (Ingold, Urdorf, Switzerland), and data were stored in a digital datalogger (Orion, Medical Measurement Systems) using a sampling frequency of 2 Hz. The pH glass catheter was positioned 5 cm above the upper border of the LES (Figure 1). With the use of a cable that connected the pH datalogger with the impedance datalogger, the pH signals were stored on both dataloggers enabling synchronization.

Data analysis

End-expiratory LES pressure was calculated by using the intragastric pressure as reference. Pressure tracings of the sideholes and sleeve sensor were analyzed on a computer screen. It was possible to obscure signals from individual pressure transducers to blind the observer for these signals. Analysis of TLESRs was thus performed separately with the observer blinded for either the tracings of the sideholes in the high-resolution area (signals of sideholes -2, -1, 0, 1, and 2 not shown on screen) or the sleeve sensor tracings.

In accordance with criteria developed by Holloway et al., a TLESR was defined as a drop in LES pressure with a velocity >0.4 kPa/3 s, time from onset to complete relaxation of <10 s, a nadir pressure of <0.26 kPa, and absence of a swallow in the time window from 4 s before to 2 s after the start of the relaxation.[16] Excluding multiple swallows, LES pressure falls that fulfill the first three criteria but have a duration of >10 s can also be classified as TLESRs regardless of the timing of LES relaxation to swallowing. In the analysis of TLESRs in the high-resolution manometry signals, the signals recorded from the two sideholes with the highest resting pressure had to fulfill the above criteria. An additional criterion was that pressure in adjacent sideholes should not increase simultaneously with the decrease in pressure in the other sideholes. This criterion was added to avoid movement artifacts.

For each TLESR identified, it was observed whether a common cavity phenomenon could be identified. A common cavity was defined as an abrupt increase in intraesophageal pressure to intragastric pressure in at least two distal esophageal recording sites.[36]

In the impedance tracings, gas reflux was defined as a rapid (>3000 Ω/s) and pronounced retrograde moving increase in impedance in two consecutive impedance sites.[29] Liquid reflux was defined as a retrograde moving 40 % fall in impedance in the two distal impedance sites. Mixed liquid-gas reflux was defined as gas reflux occurring during or immediately before liquid reflux.

In the pH tracings, a decrease in pH of ≥1 unit or a drop of pH below 4 was considered an indicator of reflux of acid gastric content into the esophagus.[34] Analysis of the impedance and pH signals was performed while the investigator was blinded for the results of the TLESR analysis.

Statistical analysis and presentation of data

The Chi^2 test was used to compare proportions. Mean TLESR duration was compared by using the Wilcoxon rank sum test. Numbers of TLESRs per subject were compared by using the Wilcoxon signed-rank test. Differences were

considered statistically significant when $p \leq 0.05$. Throughout the manuscript, parametric data are presented as means ± SE and nonparametric data as median (interquartile range). Pressures are expressed in kPa (1 kPa=7.5 mmHg).

Results

In total, 145 TLESRs were identified, either with the sleeve sensor or with high-resolution manometry or with both manometric techniques. The sleeve sensor identified 108 TLESRs; with high-resolution manometry 117 TLESRs could be identified. This implies that the sleeve sensor detected 74.5 % of all TLESRs,

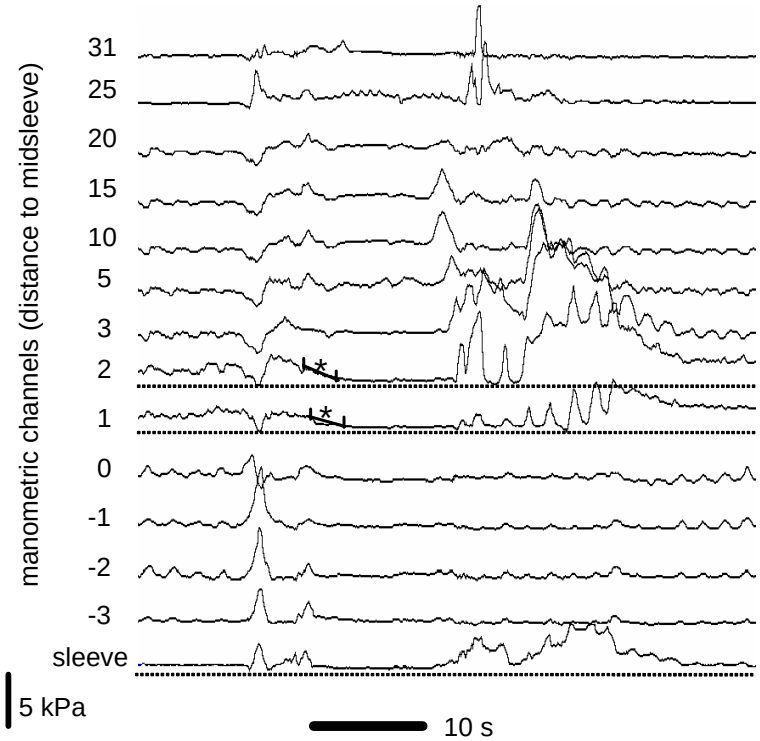

Figure 2. Transient lower esophageal sphincter relaxation (TLESR). Both the signals from the closely spaced sideholes and the sleeve sensor are shown in this figure. In channels 1 and 2, a simultaneous decrease in pressure (*) occurs, the relaxation rate being >0.4 kPa/3 s. In the sleeve sensor signal, a decrease in pressure can be noted, but the rate does not reach 0.4 kPa/3 s because of low baseline LES pressure. Channels -1 to -3 are located in the stomach. The dotted line indicates gastric pressure.

whereas high-resolution manometry detected 80.7 % (p=0.2). The median number of TLESRs per patient found with the sleeve sensor was 8 (range, 7–12) and with high-resolution manometry was 9 (range, 8–12), the difference being not statistically significant. High-resolution manometry detected more TLESRs in eight patients, whereas sleeve sensor manometry detected more TLESRs in three patients; in one patient an equal number of TLESRs was found with both techniques.
Median duration of the TLESRs was 17.0 (range, 14.0 – 22.0) s for sleeve sensor-detected and 18.5 (range, 14.0 – 22.8) s for high-resolution manometry-detected TLESRs, the difference also being not statistically significant. Proportions of all TLESRs found with either sleeve or high-resolution manometry accompanied by evidence of gastroesophageal reflux as detected by manometry, impedance, or pH monitoring were not significantly different (Table 1). Whereas 80 TLESRs fulfilled the criteria for TLESRs on both sleeve sensor and high-resolution manometry, 28 TLESRs were detected only with the sleeve sensor, and 37 TLESRs were exclusively found with high-resolution manometry (Figure 2). Significantly higher proportions of TLESRs detected with high-resolution manometry only were associated with reflux, compared with TLESRs only detected with the sleeve sensor ($p<0.05$).

Table 1. Percentage of TLESRs accompanied by evidence of gastroesophageal reflux

	TLESRs detected with both methods	all TLESRs detected with sleeve sensor	TLESRs detected with sleeve sensor only	All TLESRs detected with high-resolution	TLESRs detected with high-resolution only
Common cavity	65.00 %	56.48 %	32.14 %	62.39 %	59.46 %*
pH drop	40.00 %	35.19 %	21.43 %	38.46 %	35.14 %
Impedance, total	71.25 %	60.19 %	28.57 %	70.09 %	67.57 %*
Impedance, gas reflux	11.25 %	12.04 %	10.71 %	12.82 %	16.22 %
Impedance, mixed gas-liquid reflux	41.25 %	32.41 %	10.71 %	38.46 %	32.43 %*
Impedance, liquid reflux	18.75 %	15.74 %	3.57 %	18.80 %	18.92 %*

Values are percent. *p<0.05 compared with transient lower esophageal sphincter relaxations (TLESRs) only detected with sleeve sensor.

Several reasons were identified why TLESRs may fulfill the criteria with one of the two techniques and not with the other. TLESRs that fulfilled the Holloway criteria (16) in the sleeve sensor tracing but not in the high-resolution manometry tracings did not meet the criteria for maximum nadir pressure (11 cases), rate of decrease in pressure (6 cases), and relaxation duration (1 case).

Sometimes multiple criteria were not fulfilled (10 cases, of which 3 maximum nadir and rate of decrease, 1 maximum nadir and relaxation duration, and 6 all 3 above-mentioned criteria). The TLESRs that only fulfilled the criteria when measured with high-resolution manometry were not recognized in the sleeve sensor signal as a consequence of *1*) a low basal LES pressure (≤0.4 kPa) that was not high enough to detect the required rate of decrease in pressure (13 cases), *2*) a too-slow decrease in pressure (9 cases), *3*) a combination of too-high nadir LES pressure and a too-slow pressure decrease (6 cases), *4*) too-high nadir pressure (4 cases), or *5*) the combination of a swallow in the 4 s before and 2 s after the onset of the relaxation and a duration of relaxation shorter than 10 s because of an after-contraction in the distal esophagus that obscured the relaxation of the LES (4 cases) (Figure 3).

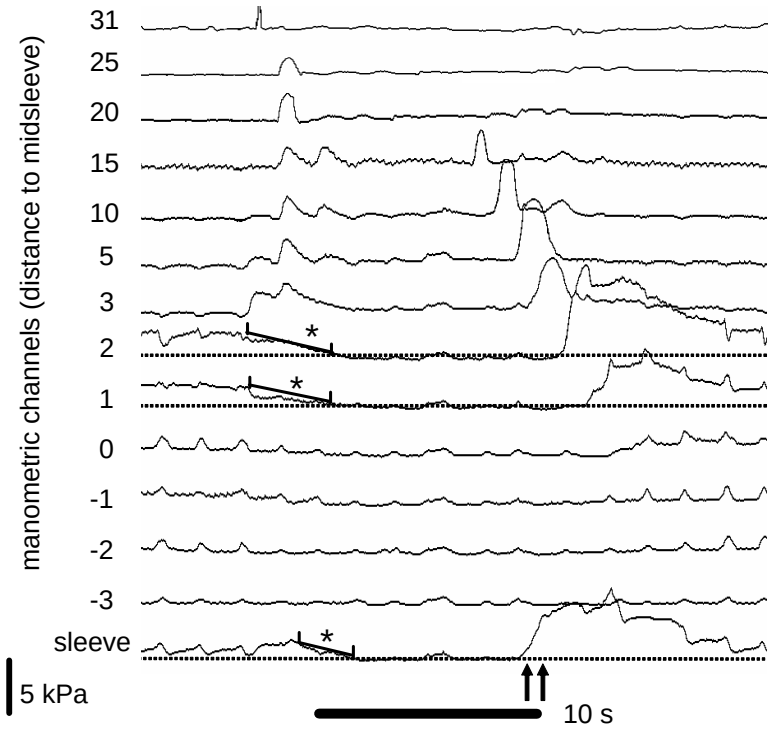

Figure 3. TLESR. Channels 1 and 2 and the sleeve show a relaxation to gastric pressure (*) with a relaxation rate of >0.4 kPa/3 s, followed by secondary peristalsis. The increase in pressure in the proximal end of the sleeve (arrows) induced by the peristaltic contraction makes the relaxation last shorter in the sleeve sensor. A swallow is observed in the window between 4 s before and 2 s after the onset of the relaxation, but the relaxation measured with the sideholes lasts longer than 10 s but not as measured with the sleeve sensor. The dotted line indicates gastric pressure.

Discussion

To date, TLESRs could only be identified in signals recorded with a sleeve sensor or a sphinctometer. Comparison showed a good concordance between these techniques, but the sphinctometer seems to be inferior to the sleeve sensor when basal LES pressure is low.[30,31] The sleeve sensor with its 6-cm-long membrane overcomes displacement of the pressure sensor out of the esophagogastric junction during respiration and peristalsis and is considered the gold standard.[11] This study shows that an array of closely spaced point sensors at the esophagogastric junction is also a reliable tool to identify TLESRs. We found that the TLESR detection rate was not significantly different between high-resolution and sleeve sensor manometry. However, a proportion of the TLESRs that fulfilled the criteria when measured with the sleeve sensor did not fulfill the criteria when measured with high-resolution manometry and vice versa.

Although the criteria of TLESRs were developed on the basis of objective arguments, not all TLESRs are followed by gastroesophageal reflux. Because three independent methods for reflux detection were used (pressure, impedance, and pH monitoring), it is unlikely that many reflux episodes were missed in this study. Probably, a proportion of TLESRs are not accompanied by reflux because the gastroesophageal pressure gradient necessary to push gastric contents upward is insufficient even during episodes of complete relaxation of the LES. Both in pathophysiological studies and in the development of new drugs aiming at inhibiting the frequency of TLESRs, one would be more interested to detect those TLESRs that are actually accompanied by reflux.[28] The majority of TLESRs observed with both high-resolution and sleeve sensor manometry were accompanied with evidence of gastroesophageal reflux on manometry, impedance, or pH monitoring. However, the TLESRs that fulfilled the Holloway criteria exclusively on high-resolution manometry showed a significantly higher reflux rate than the TLESRs that fulfilled the criteria only on sleeve sensor manometry.[16] Nevertheless, it has to be mentioned that this concerned only a small proportion of the total number of TLESRs detected, and for the majority of the results, the two techniques were comparable.

In this study, most reflux episodes were detected by impedance monitoring followed by manometry, and least reflux was detected by monitoring of esophageal pH. A similar ratio between detection rates was found in a study by Shay and Richter.[25] Whereas manometry is not very specific for gastroesophageal reflux, pH monitoring is not able to detect reflux of non-acid gastric substances, has a low sensitivity and specificity for superimposed reflux, and misses virtually

all gas reflux episodes. Intraluminal impedance monitoring, however, is thought to detect at least 90 % of all reflux episodes.[27] Therefore, it is unlikely that with the combination of three reflux detection techniques, many episodes were missed. In the present study, approximately 70 % of the TLESRs were accompanied with evidence of reflux, leaving around 20 % that were not. This could in part be due to the fact that the patients were in an upright position during this study, because it is known that more reflux occurs in the right lateral recumbent position.[26,32] The relative position of the stomach with respect to the esophagus and the gastroesophageal pressure gradient are likely to play a role in this phenomenon.

Whereas we show that high-resolution manometry is an accurate device to detect TLESRs, several disadvantages of the technique should be taken into account. First, the equipment of high-resolution manometry is more sophisticated and therefore more expensive. Furthermore, more signals are gathered during high-resolution manometry, which makes interpretation elaborate and analysis of these measurements requires an experienced investigator. Whereas analysis and interpretation is thus more elaborate for high-resolution manometry, various studies describe its benefits. Previously, with the use of high-resolution manometry, topographic analysis of esophageal contraction was made possible, and it was shown that this provided additional information about esophageal function.[9,10] Recently, Fox et al. showed that high-resolution manometry detected clinically relevant esophageal dysfunctions not detected by conventional manometry.[12]

Although a paper by Castell et al. has suggested that a sleeve sensor underestimates the duration of LES relaxation, our data do not support this notion.[7] The observed difference between the durations of LES relaxation measured in our study with high-resolution or sleeve sensor manometry was small and not statistically significant. In the study by Castell et al., comparison was performed between LES relaxations measured with the sleeve sensor and a single sidehole.[7] It is well known now that manometry with a single sidehole is not an adequate technique for measurement of LES relaxation. Furthermore, these observations were made in swallow-induced LES relaxations, i.e., not in TLESRs.

It should be kept in mind, however, that the Holloway criteria were initially developed for detection of TLESRs with sleeve sensor manometry.[16] The criterion of relaxation duration of at least 10 s is necessary to separate TLESRs from swallow-induced LES relaxations. If measurement of relaxation with the sleeve sensor would underestimate duration of relaxation, this 10-s criterion would perhaps not be enough to separate swallow-induced relaxations from TLESRs

measured with sidehole manometry. Because TLESRs are much more often accompanied by reflux compared with swallow-induced relaxations of the LES, this would result in a lower reflux rate of the TLESRs measured only with high-resolution manometry. Our data show that this is not the case.

Results from this study imply that besides the currently used sleeve sensor and sphinctometer, high-resolution manometry can also be used to detect and study TLESRs. While the sleeve sensor records the highest external pressure exerted on the membrane, high-resolution manometry registers pressure on different sites in the esophagogastric junction. This study shows that high-resolution manometry is as least as reliable for the detection of TLESRs as the current gold standard sleeve sensor manometry.

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7

Intermittent spatial separation of diaphragm and lower esophageal sphincter favors acidic and weakly acidic reflux

A.J. Bredenoord
B.L.A.M. Weusten
R. Timmer
A.J.P.M. Smout

Dept. of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands
Gastrointestinal Research Unit, University Medical Center, Utrecht, The Netherlands

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Abstract

Background: In small hiatal hernias, the size of the hernia is variable. Intermittent complete reduction can be observed with high-resolution manometry as a transition from a double-peak (hernia) to a single-peak (reduced) high-pressure zone. The aim of this study was to investigate whether intermittent separation of the diaphragm and lower esophageal sphincter (LES) favors the occurrence of gastroesophageal reflux. Methods: In 16 patients with a small hiatal hernia (3 cm), prolonged high-resolution manometry was performed. Acid and weakly acidic reflux episodes were detected with pH-impedance monitoring. Results: The single pressure peak profile (reduced hernia) was present for 814 minutes (56.5 % of total time), and the double peak profile (unreduced hernia) was present for 626 minutes (43.5 % of total time). In all patients, both pressure profiles were observed. The transition rate between the 2 profiles was 7.5 ± 0.9 per hour. More reflux occurred when the LES and diaphragm were separated versus the reduced hernia state (23.1 ± 5.1 vs 12.2 ± 2.4 episodes per hour, respectively; $p<0.05$). The proportions of acidic reflux episodes during the single and double pressure peaks were similar (70 % and 67 %, respectively). In the two pressure-zone state, there was an increase in all reflux mechanisms except transient LES relaxation. Conclusions: In patients with a small hiatal hernia, intermittent reduction of the hernia occurs frequently. Spatial separation of the diaphragm and LES in the nonreduced state results in a 2-fold increase in acidic and weakly acidic reflux due to mechanisms other than transient LES relaxation.

Introduction

The antireflux barrier at the esophagogastric junction consists of the intrinsic sphincter or lower esophageal sphincter (LES) and the extrinsic sphincter, which is part of the crural diaphragm. When a hiatal hernia is present, a spatial dissociation of the LES and diaphragmatic sphincter exists. A hiatal hernia is observed more frequently in patients with esophagitis than in subjects without esophagitis, and several studies reported a correlation between the presence of hiatal hernia and the severity of esophagitis.[1-3] Furthermore, esophageal acid exposure is higher in patients with gastroesophageal reflux disease with hiatal hernia than in those without.[4,5] It has been suggested that patients with larger hiatal hernias are prone to a higher frequency of reflux episodes and higher esophageal acid exposure.[6,7] Patients with a hiatal hernia are particularly susceptible to reflux during normal swallow-associated LES relaxations and straining.[3,8-10] This can be explained by the fact that the LES and the diaphragm normally act in concert to maintain the gastroesophageal reflux barrier.[11,12] In all studies regarding the relationship between gastroesophageal reflux disease and hiatal hernia, patients were classified according to the presence or absence of a hiatal hernia. However, the esophagogastric junction is a dynamic region, and axial movements of the distal esophagus through the diaphragmatic hiatus occur. With high-resolution manometry, intraluminal pressures are recorded at small intervals along the longitudinal axis of the esophagus.[13] This technique makes it possible to obtain more detailed information on the gastroesophageal junction.[14-16] We have observed that spatial separation of the LES and diaphragm can be detected on high-resolution manometry as 2 separate high-pressure zones.[17] The aim of this study was to investigate whether the 2 high-pressure zones that can be identified on high-resolution manometry truly represent the 2 separate muscular components of the antireflux barrier and to investigate the effect of temporal spatial separation of the LES and diaphragm on the occurrence of gastroesophageal reflux.

Methods

Subjects

The studies described in this report are a main study in which the relationship between the occurrence of gastroesophageal reflux and the spatial separation of the extrinsic and intrinsic sphincter was assessed, as well as a validation study

assessing the reliability of high-resolution manometry as a tool for the identification of spatial separation of the extrinsic and intrinsic sphincter. Three patients with gastroesophageal reflux disease participated in the validation study (3 men; mean age, 46 years; range, 41–56 years). In the main study, 16 patients with gastroesophageal reflux disease (9 men and 7 women; mean age, 50 years; range, 18–81 years) were included. Patients in both groups had a hiatal hernia of approximately 3 cm as observed on upper endoscopy. All patients showed a pathologic esophageal acid exposure on previous 24-hour pH monitoring (time pH < 4, > 6.0 %). The median time with pH < 4 was 9.3 % (interquartile range, 7.2 %–12.3 %). Endoscopy revealed mild esophagitis (LA classification grade A) in 11 patients and moderate esophagitis (LA classification grade B) in 2 patients.
Written informed consent was obtained from all subjects, and the protocol was approved by the medical ethical committee of the University Medical Center Utrecht.

Protocol of the Validation Study
In 3 patients, a metal clip (Clip HX-600-090; Olympus, Tokyo, Japan) was placed endoscopically on the squamocolumnar junction. After placement of the clip, patients were allowed to recover for 2 hours. After recovery, a manometric catheter (see following text) was introduced transnasally and positioned such that at least the most distal side hole recorded gastric pressure. The patients were placed in a sitting position.
Recording of intraluminal pressures was started after a 10-minute adaptation period and a radiographic image was taken. After the image was taken, the patients consumed a standardized liquid meal of 300 mL (150 kCal/100 mL, Nutridrink; Nutricia, Zoetermeer, The Netherlands). Immediately after meal consumption, another radiographic image was made and recording was continued for 90 minutes with an image taken every 30 minutes, resulting in a total of 5 pictures. A marker was placed on the manometric tracings to be able to analyze the manometric tracings for the presence of 1 or 2 high-pressure zones at the moment the images were taken.

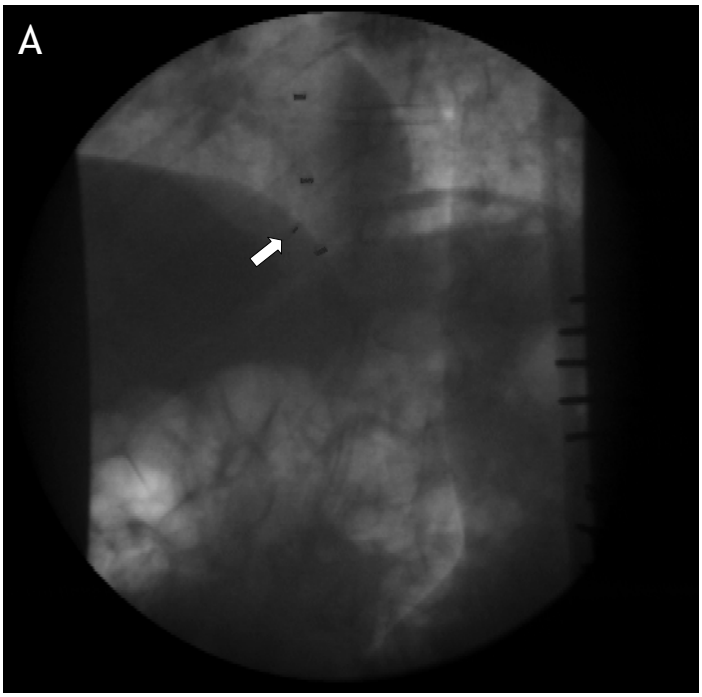
Protocol of the Main Study
The use of gastric acid–inhibitory drugs and drugs that influence gastrointestinal motility was discontinued 5 days before the study. After an overnight fast, the manometry catheter was introduced transnasally. The catheter was positioned such that at least the most distal side hole recorded gastric pressure and the high-resolution area of the catheter straddled the esophagogastric junction,

which was recognized as the high-pressure zone between the stomach and esophageal body. After positioning of the manometry catheter, the impedance and the pH catheter were introduced transnasally and positioned correctly (see following text). The subjects consumed a standardized reflux-eliciting meal consisting of a hamburger (McDonald's Quarter Pounder), 20 g of fresh onions, 44 g of potato chips, and 475 mL of orange juice (total of 967 kcal). The meal had to be finished in 30 minutes. After ingestion of the meal, recording was started and continued for 90 minutes. Subjects were seated during the course of the study and were requested to minimize head movements.

Manometric Technique

An 18-channel water-perfused silicone rubber catheter (outer diameter, 4.0 mm; length, 75 cm; channel diameter, 0.4 mm) was used for manometric recordings. The proximal part of the assembly incorporated 5 side holes at 1-cm intervals. Of these, the side hole most clearly showing swallow-associated pharyngeal contractions was selected for recording swallows. After selection of this side hole, perfusion of the other 4 pharyngeal side holes was discontinued because it has been suggested that pharyngeal stimulation with water may trigger transient lower esophageal sphincter relaxations (TLESRs).[18] There were 4 esophageal side holes at 5-cm intervals and 7 side holes at 1-cm intervals at the distal end of the catheter. The side holes in the manometry catheter were labeled according to their distance to the esophagogastric junction (side hole 0). The manometric catheter that was used for the validation experiment had 4 metal rings at -15, 18, 51, and 84 mm distance to side hole 0 to be recognized on radiography and to serve as a reference for actual size. All side holes were perfused at a rate of 0.08 mL/min using a pneumohydraulic perfusion system (Dentsleeve Pty Ltd, Wayville, South Australia).

Pressures were measured with external pressure transducers (Abbott, Sligo, Ireland). Pressure data were stored in digital format in two 12-channel data loggers (Medical Measurement Systems, Enschede, The Netherlands) using a sample frequency of 8 Hz. At the end of the study, all data were transferred to the hard disk of the computer. Intraluminal Impedance and pH Monitoring For intraluminal impedance monitoring, a 7-channel impedance catheter was used (Aachen University of Technology, FEMU, Aachen, Germany). This catheter (outer diameter, 2.3 mm) enabled recording from 7 segments. The 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 localized LES, with each recording segment 2 cm



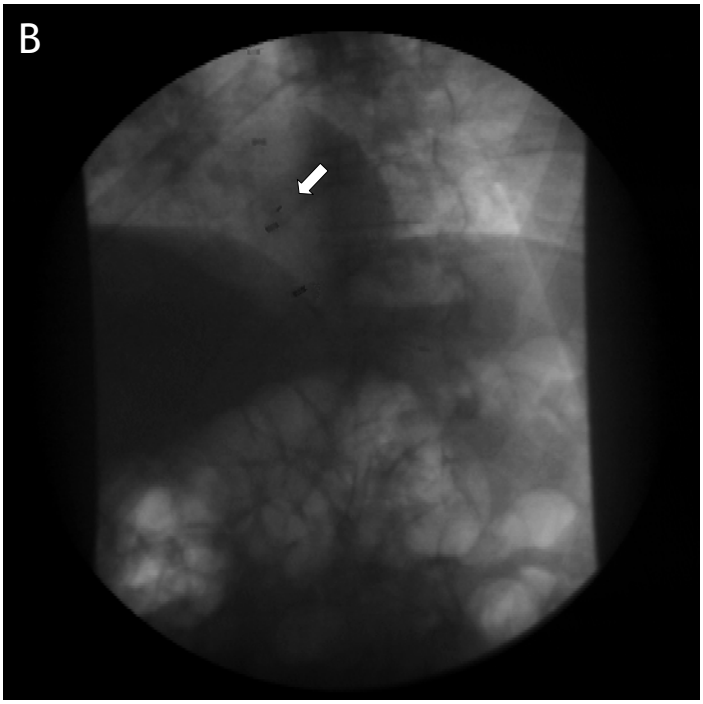


Figure 1. Radiographic images taken during the validation study. (Above) The metal clip at the squamocolumnar junction (arrow) is visible at the level of the diaphragm, located between the first and second ring on the catheter. steosynthesis aterial is present at the left humerus.
(Below) Radiographic image of the same subject 30 minutes after the previous image. The metal clip at the squamocolumnar junction is located proximal to the second ring on the catheter.

long. Impedance signals were stored in a digital system (Aachen University of Technology) using a sample frequency of 50 Hz.[19] Intraluminal pH monitoring was performed with a glass pH electrode (Ingold AG, Urdorf, Switzerland), and data were stored in a digital data logger (Orion, MMS, Enschede, The Netherlands) using a sampling frequency of 2 Hz. The pH glass catheter was positioned 5 cm above the upper border of the LES. Using a cable that connected the pH data logger with the impedance data logger, the pH signals were also stored on the impedance data logger so that synchronization was ensured.

Data Analysis

In the analysis, pressure readings were divided into 1-minute segments. For each of these segments, it was noted whether the patient's hernia was in the reduced (1 high-pressure zone) or in the unreduced (2 separate high-pressure zones) state. To qualify for the latter, the pressure in the trough had to be at least 0.5 kPa lower than the pressure in the high-pressure zones, measured in mid-inspiration. All pressures were calculated using the intragastric pressure as reference. In the impedance tracings, gas reflux was defined as a rapid (>3000 Ω/s) and pronounced retrograde moving increase in impedance in 2 consecutive impedance sites.[20] Liquid reflux was defined as a retrograde moving 40 % decrease in impedance in the 2 distal impedance sites. Mixed liquid-gas reflux was defined as gas reflux occurring during or immediately before liquid reflux. Reflux episodes identified with impedance were classified as acidic (nadir pH <4) or weakly acidic (nadir pH between 4 and 7). Analysis of the impedance and pH signals was performed while the investigator was blinded for the results of the manometric analysis.

For each reflux episode identified with combined pH-impedance monitoring, the underlying mechanism responsible for the episode was identified. Five different reflux mechanisms were classified into 5 categories: TLESR-associated, swallow-associated, strain-associated, low LES pressure associated, and other/unknown. For detection of TLESRs, we used the criteria developed by Holloway et al. modified for high-resolution manometry.[21,22] Reflux was considered to be swallow-associated if it occurred in the period between 2 seconds before and 4 seconds after a pharyngeal contraction. Straining was defined as a simultaneous increase in pressure in all channels, including the gastric channel. LES pressure was classified as low when basal end-expiratory LES pressure was < 0.5 kPa. End-expiratory pressures of the proximal and distal pressure peaks in the unreduced state and the single pressure peak in the reduced state were measured, and mean values for successive 30-minute periods after the meal were calculated.

Statistical Analysis and Presentation of Data

The Wilcoxon signed rank test was used to perform comparisons between the proximal extent of reflux episodes and the relative prevalence of reflux mechanisms, and paired *t* tests were used for all other comparisons between 2 groups. Repeated-measures analysis of variance was used to test whether changes occurred with time after the meal. Differences were considered statistically significant when $p<0.05$. Throughout the report, parametric data are presented as mean ± SEM and nonparametric data as median (interquartile range). Pressures are expressed in kPa (1 kPa=7.5 mm Hg).

Results

Validation Study

A total of 15 radiographs were taken. The diaphragm, the metal rings on the manometry catheter, and the clip at the esophagogastric junction were clearly visible on the radiographs (Figure 1). The maximal distance between the proximal margin of the diaphragm and the endoscopically placed clip was 28 mm on the radiographic images. Of the 15 images obtained, 7 were acquired during a moment that 2 high-pressure zones could be identified manometrically (Figure 2). When only 1 high-pressure zone was seen manometrically, the distance between the clip and the proximal margin of the diaphragm was always ≤ 14 mm. When 2 separate high-pressure zones could be identified, the distance between the proximal margin of the diaphragm and clip was always ≥ 12 mm. On 6 of the 7 images taken during the presence of 2 high-pressure zones, the proximal high-pressure zone was located at the side hole located immediately proximal or distal to the metal clip. The distal high-pressure zone was always located at one of the 2 side holes immediately distal to the proximal margin of the diaphragm as observed on radiography.

Main Study

The single pressure peak profile (reduced hernia) was present for 814 minutes (56.5 % of total time), and the double pressure peak profile (unreduced hernia) was present for 626 minutes (43.5 % of total time) (Figure 3). In all patients, both single and double pressure profiles were observed. The prevalence of the double-peak profile ranged in individual patients between 11.1 % and 91.1 % of the total time. The rate of transition between the 2 profiles was 7.5 ± 0.9 per hour. The

prevalence of the double-peak profile increased from 30.5 % in the first 30 minutes after the meal to 42.4 % in the second and 52.9 % in the third 30-minute period after the meal ($p<0.05$).

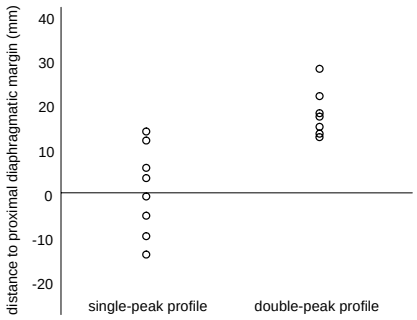


Figure 2. Distance between the endoscopically placed clip and the proximal margin of the diaphragm during the single and double pressure peak periods.

Table 1. Characteristics of all reflux episodes during reduced and unreduced hernia states

	Reduced	Unreduced
Proximal extent of liquid component	4 (3-4)	4 (3-4)
Volume clearance time (s)	17.1 ± 0.9	15.3 ± 0.8
Acid clearance time (s)	80.8 ± 8.8	70.9 ± 9.0
Magnitude of pH drop	1.9 ± 0.1	1.4 ± 0.1*
Nadir pH	3.4 ± 0.1	4.1 ± 0.1*
% acid (nadir pH < 4)	74.0	54.0*

* : $p<0.05$ compared with the reduced hernia state.

Table 2. Characteristics of TLESR-induced reflux episodes during reduced and unreduced state

	Reduced	Unreduced
Proximal extent of liquid component	4 (3-4)	4 (3-4)
Volume clearance time (s)	16.3 ± 1.0	14.7 ± 1.5
Acid clearance time (s)	58.2 ± 16.3	69.6 ± 19.1
Magnitude of pH drop	1.9 ± 0.3	1.4 ± 0.3
Nadir pH	4.1 ± 0.4	4.4 ± 0.4
% acid (nadir pH < 4)	65.0	49.0

NOTE. No statistically significant differences were found.

Table 3. Time-related changes in pH and pressure parameters

	0 - 30 min postprandial	30-60 min postprandial	60-90 min postprandial	p-value
pH drop during reflux episodes	1.7 ± 0.3	2.1 ± 0.3	2.0 ± 0.3	0.5
Nadir pH during reflux episodes	4.1 ± 0.3	3.7 ± 0.4	3.6 ± 0.3	0.09
Distal pressure zone (kPa) (unreduced state)	0.5 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.3
Proximal pressure zone (kPa) (unreduced state)	1.2 ± 0.1	1.4 ± 0.1	1.4 ± 0.1	0.1
Single pressure zone (kPa) (reduced state)	1.2 ± 0.1	1.5 ± 0.2	1.5 ± 0.2	0.02

The incidence of reflux episodes was significantly lower when the hernia was reduced (12.2 ± 2.4 episodes per hour) than when the LES was spatially separated from the diaphragm (23.1 ± 5.1 episodes per hour). This was also the case when acid (nadir pH < 4) and weakly acidic reflux (nadir pH 4–7) were analyzed separately (Figure 4).

The numbers of reflux episodes due to TLESRs were similar in the reduced and unreduced hernia state. TLESRs were responsible for 51.9 % of all reflux episodes during the reduced state, while TLESRs were only responsible for 30.3 % of the reflux episodes in the unreduced state; the difference was statistically significant.

The increase in reflux rate during spatial separation of the LES and diaphragm was due to reflux mechanisms other than TLESR, the most important being swallow-associated reflux (Figure 5).

Reflux episodes that occurred during the reduced state were accompanied by a larger decrease in pH and a lower nadir pH than those occurring during the unreduced state (Table 1). However, the characteristics of the TLESR-associated reflux episodes did not seem to be dependent on the hernia state (Table 2). The magnitude of the decrease in pH during reflux episodes was not significantly changed after the meal, while the nadir pH during reflux episodes tended to decrease with time after the meal (Table 3).

In the reduced hernia state, pressure in the single high-pressure zone increased with time after the meal (Table 3). There were no statistically significant postprandial changes with time in pressures in the proximal and distal pressure zone in the unreduced state (Table 3).

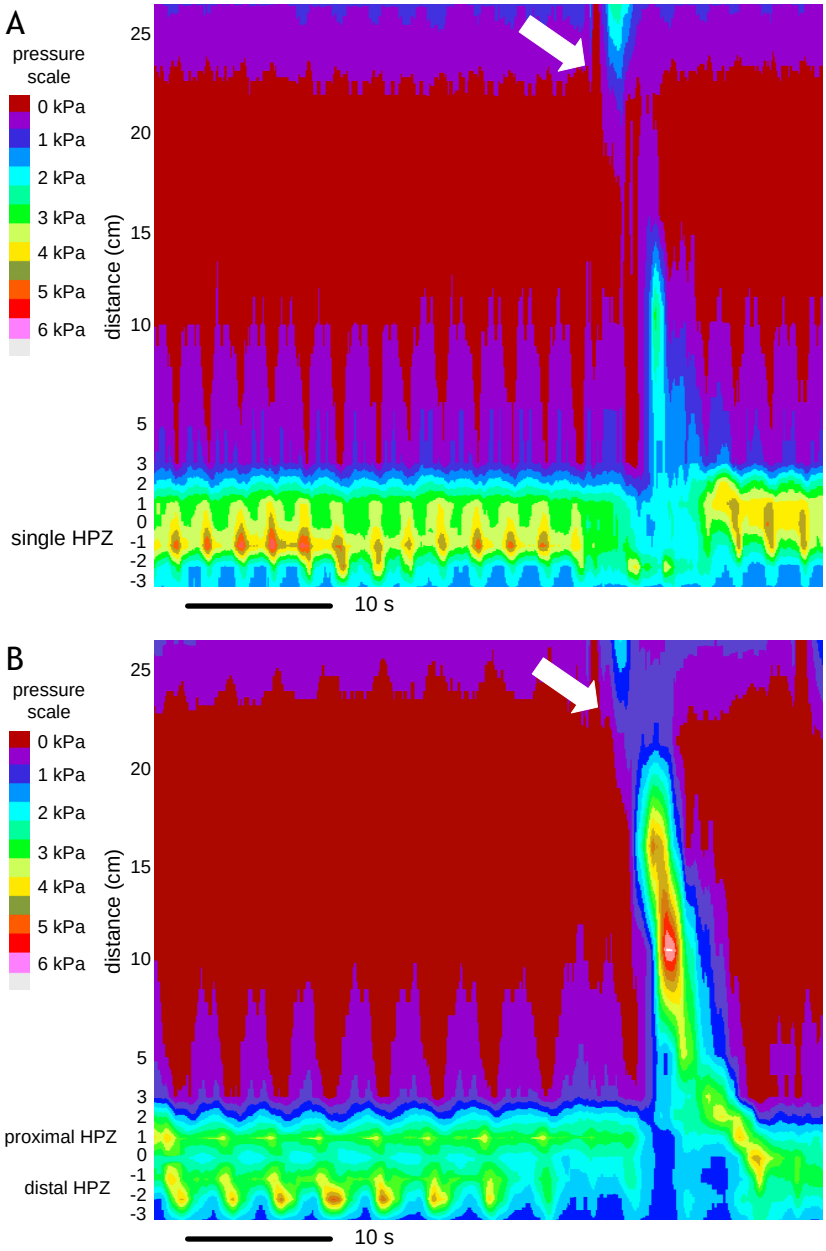


Figure 3. Contour plots of a single and double high-pressure zone configuration. In these plots, pressure amplitudes are presented in colors. A shows 1 high-pressure zone (HPZ). A dry swallow is marked with an arrow. B shows a tracing in the same patient when the proximal and distal HPZ are spatially separated. Relaxation of both components occurs during a dry swallow (arrow). The respiratory pressure variations are much larger in the distal HPZ (diaphragm).

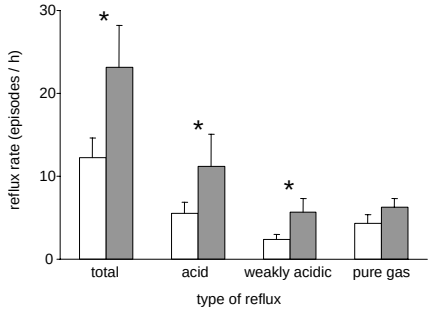


Figure 4. Reflux rate (episodes per hour) during the reduced (single pressure peak, open bars) and unreduced (double pressure peak, gray bars) hernia state. Significantly higher reflux rates were found during the unreduced state. *p<0.05

Discussion

So far, all studies investigating the effect of a hiatal hernia on gastroesophageal reflux have treated hiatal hernia as an "all or none" phenomenon. Patients were classified according to presence or absence of a hiatal hernia, based on investigations such as endoscopy, pull-through manometry, ultrasonography, and radiology.[23-27] With these investigations, a snapshot evaluation of the distance between diaphragm and LES can be obtained. However, there is increasing evidence that a hiatal or sliding hernia is a dynamic entity. The distance between the LES and diaphragm is variable, and intermittently the hernia is temporally reduced.With high-resolution manometry, often 2 high-pressure zones can be identified in patients with a hiatal hernia. The results obtained in our validation study confirm that the proximal high-pressure zone represents the LES and the distal high-pressure zone represents the diaphragm. Thus, high-resolution manometry allows us to study the distance between the LES and the diaphragm in patients with a hiatal hernia during a prolonged period. In all patients investigated in this study, transitions between the single and double pressure peak profiles were found, suggesting that intermittent reduction of a small hiatal hernia is the rule rather than the exception. We furthermore observed that the double peak pressure profile was least prevalent immediately after the meal.

This study has shown that in periods during which the LES and diaphragm were spatially separated (unreduced hernia profile), the reflux rate was almost doubled. While the number of reflux episodes during TLESRs remained unchanged, other mechanisms such as swallow-associated reflux and straining were responsible for this increase in reflux episodes. It has previously been shown that subjects with a hiatal hernia have more swallow-associated and strain-associated reflux episodes than subjects without a hiatal hernia.[3,9,10] A 24-

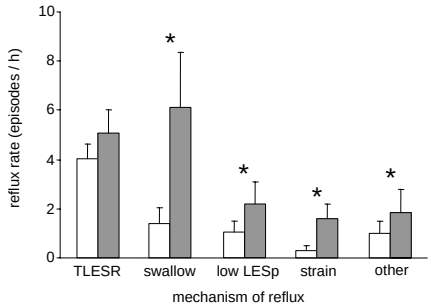


Figure 5. Mechanisms of reflux during the reduced (open bars) and unreduced (gray bars) hernia state. TLESRs were the most prevalent reflux mechanism during the reduced state. The increase in reflux rate in the unreduced state is due to other reflux mechanisms. *p<0.05

hour study by Van Herwaarden et al. showed that most reflux occurs during a TLESR in patients without a hiatal hernia, while other mechanisms become more important in patients with a hernia.[8] When, in our study, the 2 components of the antireflux barrier were spatially separated, most reflux occurred due to mechanisms other than TLESRs, and this thus determined the excessive amount of reflux. Because the amplitude of esophagogastric junction pressure in the double-peak configuration was not different from the pressure amplitude in the single-peak status, the observed differences are most likely not the result of a lower LES pressure. The configuration of the esophagogastric junction thus seems to be a more important factor in the occurrence of gastroesophageal reflux than the pressure in the junction. When all reflux episodes that occurred during a single pressure peak were compared with those occurring during a double pressure peak period, it was found that the former had a larger decrease in pH, reached a lower nadir pH, and were more often acidic (pH < 4). However, when the TLESR-related reflux episodes in the single and double pressure peak periods were compared, these differences were not found. The magnitude of the decrease in pH may also be dependent on factors besides gastric pH, such as volume of the refluxate and type of reflux mechanism. We did not perform comparisons of the characteristics of reflux episodes induced by mechanisms other than TLESRs during the double- and single-peak periods, because these were too rare in the periods with the single-peak profile to allow meaningful analysis. However, in our study, swallow-associated reflux was a prominent mechanism only in the unreduced hernia state, and it has been shown that only small amounts of acid, buffered by saliva in the hernia sac, are entering the esophagus during this mechanism.[10] It is thus likely that the observed differences in the magnitude of pH decrease and nadir pH reflect the differences in relative proportions of reflux mechanisms during the reduced and unreduced state.

Previously, we showed that in patients with a larger hiatal hernia (5 cm), the double-peak profile occurred more frequently than in patients with a small hiatal

hernia (3 cm) and the distance between the 2 pressure zones, when present, was larger.[17] It would be interesting to investigate whether the distance between the 2 pressure zones is also a determinant of the elicitation of gastroesophageal reflux, because we know patients with large hiatal hernias are more prone to have gastroesophageal reflux disease than patients with smaller hernias.[6,28]

In conclusion, we have shown that in patients with a small hiatal hernia, temporal reduction of the hernia occurs frequently. During spatial separation of the diaphragm and LES, both acid and weakly acidic reflux occur more often than during reduction of the hernia. This increase in reflux rate is due to reflux mechanisms other than TLESRs.

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8

Gastro-oesophageal reflux of liquids and gas during transient lower oesophageal sphincter relaxations

A.J. Bredenoord
B.L.A.M. Weusten
R. Timmer
A.J.P.M. Smout

Dept. of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands
Gastrointestinal Research Unit, University Medical Center, Utrecht, The Netherlands

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Abstract

Some transient lower oesophageal sphincter relaxations (TLOSRs) are accompanied by gastro-oesophageal reflux and others are not. We aimed to investigate what factors determine the occurrence and type of reflux during TLOSRs. In 12 healthy subjects prolonged high-resolution manometry was performed. Reflux was detected using pH-impedance monitoring. A total of 219 TLOSRs were detected; no differences were observed between the duration of TLOSRs with liquid-containing reflux (20.2 ± 1.0 s), gas reflux (17.0 ± 1.0 s) and no reflux (19.0 ± 1.0 s). Trans-sphincteric pressure gradient was similar in TLOSRs with liquid reflux (1.6 ± 0.1 kPa), gas reflux (1.5 ± 0.1 kPa) and no reflux (1.7 ± 0.3 kPa). Prevalence, duration and amplitude of oesophageal precontractions and sphincteric after-contractions were not different for TLOSRs with and without reflux. The total number of TLOSRs decreased significantly from 8.2 ± 0.8 in the first to 5.7 ± 0.5 in the second and 4.4 ± 0.6 in the third 70-min recording period. The number of TLOSRs accompanied by liquid-containing reflux decreased from 4.7 ± 0.9 to 3.0 ± 0.4 to 1.6 ± 0.4, while the numbers of TLOSRs with gas reflux remained unchanged (2.1 ± 0.6–2.1 ± 0.7–2.2 ± 0.6). Besides, time after the meal, no differences were observed in the characteristics of TLOSRs with and without gastro-oesophageal reflux. We concluded that factors, other than TLOSR characteristics, are important of whether or not a TLOSR is reflux-related.

Introduction

In 1980, Dent et al. showed that "inappropriate" lower oesophageal sphincter (LOS) relaxations were the most important mechanism through which acidic gastric contents enter the oesophagus in healthy subjects.[1] These LOS relaxations were called inappropriate because they were not induced by swallowing. Later, it was observed that these inappropriate LOS relaxations were also the most important reflux mechanism in patients with gastro-oesophageal reflux disease (GORD).[2] The terminology changed from inappropriate relaxation to transient lower oesophageal sphincter relaxation (TLOSR), as it became clear that these relaxations had an important physiological role which is venting of gastric air. Subsequent studies showed that TLOSRs are the result of a vagally mediated reflex, triggered by mechanoreceptors in the proximal stomach.[3,4] The reflex which results in a TLOSR can be influenced by various pharmacological agents acting on cholecystokinin A, cholinergic, opioid, nitric oxide, c-aminobutyric acid B and glutamate receptors.[5-11] It is thus most likely that this reflex will be the target of future pharmacotherapy for GORD.
Not all TLOSRs result in gastro-oesophageal reflux, but depending on posture, diet and reflux definition the proportion of TLOSRs, which is accompanied by acid reflux varies between 15 % and 100 % in controls and between 20 % and 98 % in patients with GORD.[8,12] Thusfar, it is unknown why some TLOSRs are accompanied by gastro-oesophageal reflux of gas and liquids and others are not. The aim of this study was, therefore, to investigate what factors determine the occurrence and type of gastro-oesophageal reflux during TLOSRs.

Methods

Subjects
Twelve healthy volunteers (five males; mean age 28 years, range 23–48 years) were studied. Subjects were free of any gastrointestinal symptoms and were not taking any medication. 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.

Protocol of the main study
After an overnight fast, the manometry catheter was introduced transnasally. The catheter was positioned such that at least the most distal sidehole recorded

gastric pressure and that the high-resolution area of the catheter straddled the LOS. After positioning of the manometry catheter, the impedance and the pH catheter were introduced transnasally and positioned correctly (see below). The subjects consumed a standardized reflux-eliciting meal consisting of a hamburger (McDonald's Quarter Pounder), 20 g of fresh onions, 44 g of potato chips and 475 ml of orange juice (in total 967 kCal). The meal had to be finished in 30 min. After ingestion of the meal, recording was started and continued for 3.5 h. The total recording period was divided into three recording periods of 70 min for further analysis. Subjects were seated during the course of the study and were requested to minimize head movements.

Manometric technique
An 18-channel water-perfused silicone rubber catheter (outer diameter 4.0 mm, length 75 cm, channel diameter 0.4 mm) was used for manometric recordings. Sideholes were located at 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 18, 22, 26, 30 and 37 cm proximal to the most distal sidehole (located at 0 cm). All sideholes were perfused at a rate of 0.08 ml/min using a pneumohydraulic perfusion system (Dentsleeve Pty Ltd, Wayville, SA, Australia). Pressures were measured with external pressure transducers (Abbott, Sligo, Ireland). Pressure data were stored in digital format in two 12-channel dataloggers (Medical Measurement Systems, Enschede, The Netherlands), using a sample frequency of 8 Hz. Intraluminal impedance and pH monitoring For intraluminal impedance monitoring a 10-channel impedance catheter was used (Aachen University of Technology, FEMU, Aachen, Germany). This catheter (outer diameter 2.3 mm) enabled recording from 10 segments. The recording segments were located at 0–2, 2–4, 4–6, 6–8, 8–10, 10–12, 12–14, 14–16, 16–18 and 19–21 cm above the upper border of the manometrically localized LOS, each recording segment being 2 cm long. Impedance signals were stored in a digital system (Medical Measurement Systems, Enschede, The Netherlands) using a sample frequency of 50 Hz.[13] Intraluminal pH monitoring was performed with a glass pH electrode (Ingold A.G., Urdorf, Switzerland) and data were stored in a digital datalogger (Orion, Medical Measurement Systems, Enschede, The Netherlands) using a sampling frequency of 2 Hz. The pH glass catheter was positioned 5 cm above the upper border of the LOS.

Data analysis
The analysis of the impedance-pH tracings was performed with the observer blinded for the manometric tracings and visa versa. In the impedance tracings,

gas reflux was defined as a rapid (>3000 Ω/s) and pronounced retrograde moving increase in impedance in two consecutive impedance sites.[14] Liquid reflux was defined as a retrograde moving 50 % fall in impedance in the two distal impedance sites. Mixed liquid–gas reflux was defined as gas reflux occurring during or immediately before liquid reflux. Reflux episodes identified with impedance were classified as acidic (nadir pH < 4) or weakly acidic (nadir pH between 4 and 7). TLOSRs were classified as gas reflux-associated, liquid-containing (pure liquid and mixed liquid/gas) reflux-associated and not reflux-associated.

Table 1. Characteristics of transient lower oesophageal sphincter relaxations (TLOSRs) with liquid-containing (pure liquid and mixed liquid/gas) reflux, pure gas reflux and no reflux

	Liquid-containing	Pure gas	No reflux
Duration (s)	20.2 ± 1.0	17.0 ± 1.0	19.0 ± 1.0
Trans-sphincteric pressure gradient (kPa)	1.6 ± 0.1	1.5 ± 0.1	1.7 ± 0.3
Prevalence of oesophageal pre-contraction (%)	46.7	32.6	26.3
Duration of oesophageal pre-contraction (s)	2.1 ± 0.4	2.9 ± 0.3	2.7 ± 0.2
Amplitude of oesophageal pre-contraction (kPa)	3.8 ± 0.8	4.0 ± 0.8	4.0 ± 1.5
Prevalence of sphincteric after-contraction (%)	87.0	80.8	57.4
Duration of sphincteric after-contraction (s)	16.5 ± 1.1	15.9 ± 0.6	18.6 ± 0.7
Amplitude of sphincteric after-contraction (kPa)	6.9 ± 0.7	7.0 ± 0.6	6.6 ± 0.7
Prevalence of diaphragmatic pre-contraction (%)	15.5	14.9	17.4
Amplitude of diaphragmatic pre-contraction (kPa)	8.5 ± 1.2	7.8 ± 1.5	9.2 ± 1.0

Note: No statistically significant differences were observed.

For detection of TLOSRs, we used the criteria developed by Holloway et al. modified for high-resolution manometry.[15-17] Isolated diaphragmatic contractions and oesophageal contractions before and sphincteric contractions after TLOSRs were identified.[18] Isolated diaphragmatic contractions were defined as a sphincteric pressure increase immediately before the onset of a TLOSR, with an amplitude of more than three times normal respiratory pressure variations, associated with a simultaneous decrease in intra-oesophageal pressure and an increase in intragastric pressure. Oesophageal pre-contractions were defined as a simultaneous pressure increase in two or more oesophageal channels with an amplitude of more than three times normal respiratory pressure variations occurring immediately before a TLOSR. Sphincteric after contractions were defined as a contraction following a TLOSR with a duration of at least three times the duration of regular swallow-associated contractions.

During TLOSRs, pressures at 1 cm above and below the LOS were measured at inspiration immediately before the onset of a reflux episode if present, or, if no reflux was present, at the first inspiration at maximal relaxation during the TLOSR. The trans-sphincteric pressure gradient during a TLOSR was calculated as the difference between these pressures.[19] All pressures were calculated using the intragastric pressure as reference.

Statistical analysis and presentation of data

Comparisons were performed using the Wilcoxon Rank Sum test. Differences were considered statistically significant when $p \leq 0.05$. In this study, data are presented as mean ± SEM.

Results

In total, 277 reflux episodes were detected, 70 of which were pure liquid, 86 were mixed gas-liquid and 121 were pure gas reflux episodes. Of the liquid and mixed gas-liquid reflux episodes 54 were acidic and 102 were weakly acidic. In total, 219 TLOSRs were observed. TLOSRs were the most important reflux mechanism, accounting for 84.9 ± 8.6 % of all liquid reflux episodes, 86.2 ± 5.1 % of all mixed reflux episodes and 77.6 ± 6.3 % of all gas reflux episodes. When reflux episodes were classified based on acidity, 90.1 ± 4.3 % of the acid reflux episodes and 82.6 ± 8.6 % of the weakly acidic reflux episodes were associated with TLOSRs.

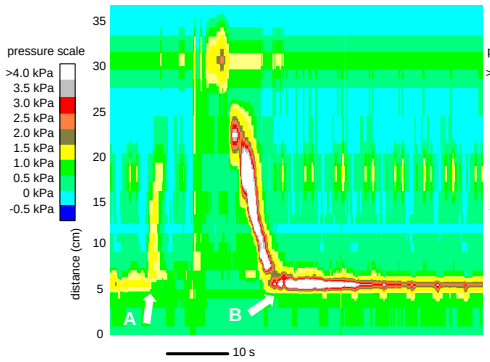

Figure 1. Transient lower oesophageal sphincter relaxation with oesophageal pre-contraction (A), swallow and sphincteric after-contraction (B).

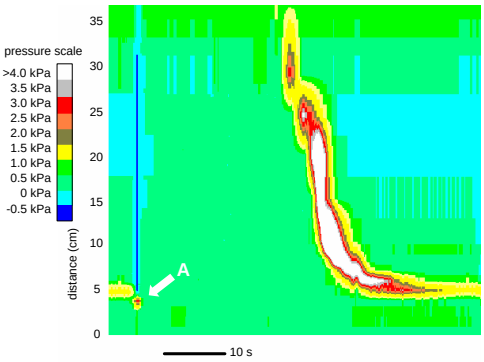

Figure 2. Transient lower oesophageal sphincter relaxation with diaphragmatic pre-contraction (A) and a simultaneous intra-oesophageal pressure decrease.

The proportion of TLOSRs that was accompanied by liquid (or mixed) reflux was 51.9 ± 7.0 %, and 34.1 ± 8.0 % of TLOSRs was accompanied by pure gas reflux. Thus, only 13.9 ± 4.0 % of the TLOSRs was not related to reflux.
The duration of TLOSRs with liquid (and mixed) reflux, gas reflux and no reflux were not significantly different (Table 1). A weak but statistically significant relationship was observed between the duration of TLOSRs and the proximal extent of liquid reflux ($r=0.3$, $P<0.001$). No differences were observed in trans-sphincteric pressure gradient between TLOSRs with liquid-containing reflux, TLOSRs with gas reflux and TLOSRs not accompanied by reflux (Table 1). No statistically significant relationship could be observed between the trans-sphincteric pressure gradient and the proximal extent of the liquid component of reflux episodes ($r=0.11$, $p=0.3$). Frequency, duration and amplitude of oesophageal pre-contractions and sphincteric after-contractions were all not significantly different for TLOSRs with and without reflux (Figure 1). There was no difference in the frequency of diaphragmatic precontractions before TLOSRs with liquid-containing reflux, gas reflux and no reflux (Table 1; Figure 2). In TLOSRs with a diaphragmatic pre-contraction, the mean duration between the end of the contraction and the onset of the reflux episode during the TLOSR, when present, was 10.1 ± 1.6 s.
The incidence of TLOSRs decreased significantly from the first post-prandial period to the third 70-min post-prandial recording period (Figure 3). The number of TLOSRs accompanied by liquid-containing reflux decreased, while the numbers of TLOSRs with gas reflux remained unchanged (Figure 3).

Discussion

After the first recognition of TLOSRs in 1980 evidence has accumulated showing that TLOSRs constitute the most important reflux mechanism in healthy subjects and in reflux disease patients. However, not all TLOSRs are accompanied by gastro-oesophageal reflux. Most studies using simultaneous pH monitoring and manometry showed that approximately 40 % of the TLOSRs in healthy subjects and 60 % of the TLOSRs in patients are accompanied by acid reflux. Using impedance monitoring Sifrim et al. found that >70 % of the TLOSRs in healthy subjects are accompanied by evidence of gas and/or liquid reflux. In a recent impedance study, in patients with reflux disease we found a similar proportion of reflux-associated TLOSRs.[16]

In the current study, we compared TLOSRs with liquid reflux, gas reflux and no reflux. The incidence and the type of reflux occurring during a TLOSR was not

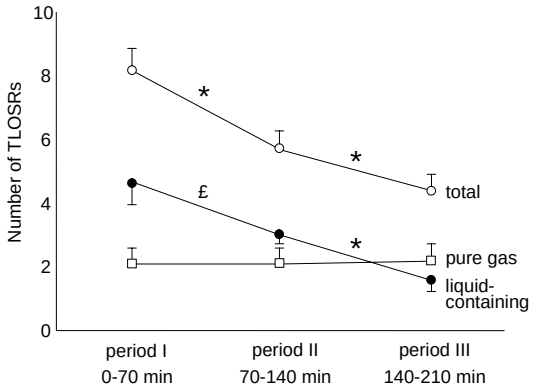

Figure 3. Total number of transient lower oesophageal sphincter relaxations (TLOSRs) (open circles) and number of TLOSRs with gas (squares) and liquid-containing (pure liquid and mixed) gastro-oesophageal reflux (black circles). * : $p<0.05$; £ : $p=0.08$.

dependent on the duration of the relaxation or the trans-sphincteric pressure gradient during the TLOSR; nor was the presence of oesophageal or diaphragmatic pre-contractions or sphincteric after-contractions. The only factor that seems to play a role in the prevalence and type of reflux during a TLOSR is time after the meal; a substantial reduction in liquid (and mixed) reflux occurred in the second and third period after the meal whilst the number of pure gas reflux-associated TLOSRs remained unchanged. This observation suggests that factors other than TLOSR characteristics determine whether or not reflux occurs and whether reflux is liquid, gaseous or mixed. Since there is a significant time effect after the meal, it is possible that the contents of the gastric cardia, immediately distal to the sphincteric complex, are of importance for the occurrence and type of gastro-oesophageal reflux during TLOSRs. Furthermore, the observation that the proportion of acid/non-acid reflux differs between the first and second post-prandial hour supports this notion.[20]

It has been shown that the proximal extent of a reflux episode is a determinant of whether or not a reflux episode is perceived.[21] It is not completely clear which factors lead to a more proximal extent of reflux episodes. It has been reported that reflux episodes in the early post-prandial period are more likely to reach the proximal oesophagus compared with reflux in the late post-prandial period.[22] We hypothesized that the trans-sphincteric pressure gradient is one of the determinants of the extent of reflux episodes. However, no relationship between the pressure gradient and the proximal extent of reflux episodes was found. In contrast, Scheffer and colleagues recently reported that the trans-sphincteric pressure gradient during TLOSRs is important for whether or not reflux occurs

during the TLOSR.[19] An explanation for the discrepant results could be that we used a meal constituting both solid and liquid components, while in the study of Scheffer et al. a pure liquid meal was used. Since it is unlikely mixing of solids and liquids results in a homogenous substance in the proximal stomach, the mechanisms of reflux after a solid meal might be more complex than after a liquid meal. Another difference is that in Scheffer's study reflux was defined as the presence of a common cavity or a pH drop below 4. In our study, reflux was quantified using impedance monitoring. In Scheffer's study, only 46 % of the TLOSRs was accompanied by evidence of reflux, compared with 86 % in our study. It has been shown that detection of reflux episodes on the basis of the common cavity phenomenon leads to an underestimation.[23]

Although a significant relationship was found between the duration of TLOSRs and the proximal extent of the refluxate, this relationship was weak and it can therefore only explain a very small part of the differences in proximal extent between reflux episodes. Future studies will determine whether other factors such as the viscosity of the refluxate and oesophageal compliance play a role in the proximal spreading of reflux episodes.[24]

Not infrequently, TLOSRs were preceded by oesophageal and diaphragmatic contractions. Furthermore, the majority of TLOSRs were followed by a prolonged sphincteric contraction. Our data indicate that these contractions play no functional role in venting of gas or liquids but rather are an epiphenomenon. Literature data suggests that these contractions are the result of vagal stimuli.[25] Animal studies showed that continuous vagal stimulation produced an oesophageal contraction at the onset of the stimulus and a contraction at the end of the stimulus.[26] Between the two contractions the sphincter was relaxed.[27]

In conclusion, no differences were observed in the characteristics of TLOSRs with and without evidence of gastro-oesophageal reflux of gas and liquids. However, with increasing time after a meal a significant change in incidence and type of reflux during TLOSRs occurred. This suggests that factors other than TLOSR characteristics are more important determinants of whether or not a TLOSR is reflux-related.

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Part III

Relationship between reflux symptoms and reflux episodes

9

Symptom association analysis in ambulatory gastro-oesophageal reflux monitoring

A.J. Bredenoord
B.L.A.M. Weusten
A.J.P.M. Smout

Dept. of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands
Gastrointestinal Research Unit, University Medical Center, Utrecht, The Netherlands

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Abstract

During the past three decades, prolonged monitoring of oesophageal pH has become increasingly popular among physicians. Most of the studies carried out with this technique focused on oesophageal acid exposure, defined as percentage of time with pH below 4. However, in most cases acid exposure variables are not very useful in the evaluation of patients with symptoms and signs of gastro-oesophageal reflux disease (GORD). An often neglected aspect of 24-hour pH recording is assessment of the temporal relation between reflux and symptoms. Various methods to quantify this relationship were developed. Here, we review these methods and the contribution of symptom association analysis to the evaluation of patients with symptoms suggestive of GORD.

Introduction

The use of prolonged monitoring of oesophageal pH as a measure of gastro-oesophageal reflux was first described in 1969.[1] More than a decade after its introduction as a hospital based technique for inpatients, oesophageal pH monitoring became rather popular when ambulatory data recorders became available.[2] Most of the studies carried out with the technique focused on measurement of oesophageal acid exposure, defined as percentage of time with pH below 4, in patients with various manifestations of GORD. Later, the notion emerged that 24-hour pH recording also makes it possible to investigate the temporal relation between reflux and symptoms. In this review, we focus on the contribution of symptom association analysis to the evaluation of patients with symptoms suggestive of GORD and we discuss the various methods for symptom analysis that are currently used.

Measurement of oesophageal acid exposure

Since the introduction of 24-hour oesophageal pH monitoring, numerous parameters have been proposed to provide a quantitative description of a patient's pH profile. Simple (for example, number of reflux episodes, percentage of time with pH below 4, number of reflux episodes lasting more than five minutes) as well as composite (for example, the DeMeester score) parameters are in use. Of these, the percentage of time with pH below 4 is generally accepted as the most useful.[3] Using this parameter, patients can be categorised as having either physiological or pathological (excessive) oesophageal acid exposure. However, several factors limit the usefulness of such a categorisation.

Firstly, significant day to day variation occurs. Wiener et al. found that the total per cent of time with pH below 4 varied between two consecutive 24-hour tests by up to a factor of 3.2-fold (218 % higher to 69 % lower).[4] Overall reproducibility for the diagnosis of GORD was 80 %, while reproducibility was much lower for patients with an acid exposure time that was borderline physiological or pathological. Data from other studies confirmed these results and although some would consider a reproducibility of 70–80 % to be reasonable, most would argue that it is not acceptable that 20–30 % of patients will receive a different diagnosis on repeated testing.[5-7]

Secondly, the published cut off values to distinguish pathological from physiological reflux differ considerably between various studies. For the parameter time with pH <4 in the upright position, values of 4.6–16.0 % were published, and for supine reflux, values of 1.2–11.2 %.[8-11] Furthermore, a

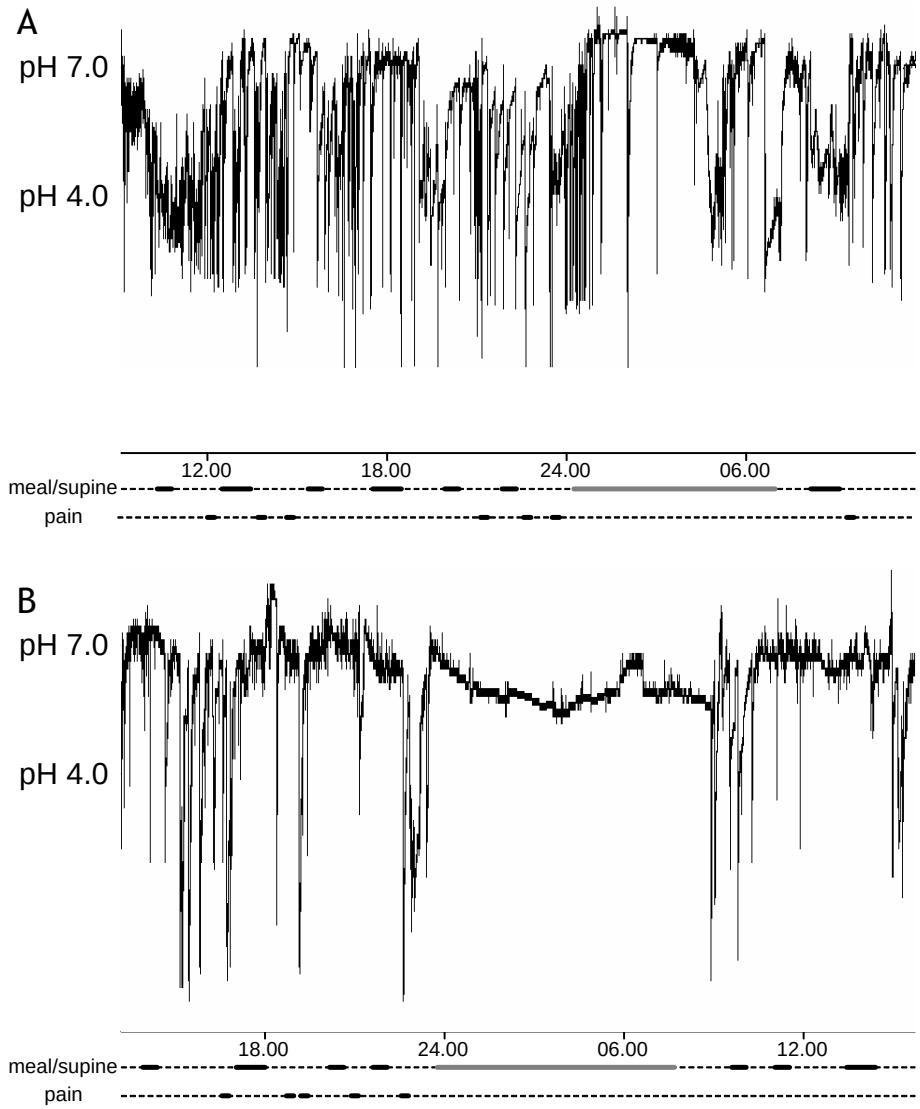

Figure 1. (A) Ambulatory 24-hour pH study in a patient with pathological acid exposure (time pH < 4 is 17.3 %). There were 165 acid reflux episodes. The patient had seven episodes of heartburn, five of which were related to acid reflux and two of which were not. This rendered a symptom index (SI) of 71.4 %. In this example, the symptom sensitivity index (SSI) was 3.0 % and the symptom association probability (SAP) was 96.5 % (these indices will be explained later in the text). (B) Ambulatory 24-hour pH study in a patient with symptoms of heartburn but a physiological acid exposure (time pH < 4 is 2.8 %). There were 24 reflux episodes. The patient experienced five episodes of heartburn, three of which were acid related which resulted in an SI of 60 %. In this example, SSI was 12.5 % and SAP was 99.7 %.

physiological increase in acid exposure time occurs with age.[12] These data indicate that distinguishing between pathological and physiological reflux is fraught with a large margin of error.

Once a "diagnosis" of pathological acid exposure has been made, how does this finding relate to reflux symptoms or endoscopic abnormalities? In case of heartburn and regurgitation, a pathological pH profile provides no evidence of whether the patient's complaints are indeed caused by acid reflux episodes.[13] Howard et al. found that patients with an abnormal oesophageal acid exposure often lack a positive correlation between symptom occurrence and reflux episodes.[14] Klauser et al. showed that of several symptoms only heartburn and regurgitation were slightly more frequent in patients with a pathological acid exposure time.[15] In addition, a subset of patients with reflux induced heartburn and regurgitation had a "normal" acid exposure time and can therefore not be identified solely on basis of their acid exposure time.[16-18] Pathological reflux also appears to be a poor predictor of supraoesophageal symptoms.

Many studies have shown that a high acid exposure time predisposes to erosive reflux disease, and in patients with high degree oesophagitis and Barrett's oesophagus, almost invariably a pathological pH profile is found.[13,19,20] These findings clearly help in our understanding of the pathophysiology of oesophagitis but do not implicate pH monitoring as a useful diagnostic tool. Obviously, ambulatory pH monitoring is not an alternative to endoscopy for assessment of oesophageal mucosal injury.

The importance of determining whether a patient's reflux is pathological or still within physiological limits has often been overstressed and the presence of pathological reflux does not provide evidence about the cause of the symptoms.[21]

Symptom-reflux association analysis

In addition to quantification of a patient's reflux profile, 24-hour oesophageal pH recording also provides the opportunity to assess the temporal relationship between the occurrence of reflux and the onset of symptoms. In the early days of oesophageal pH monitoring, the patient's symptoms were recorded by placing marks on the paper of the ink writer. Nowadays, portable digital dataloggers contain event marker buttons to be pressed by the patient when experiencing symptoms. Although the temporal relation between symptoms and reflux can be convincing during visual inspection of the pH tracings, a quantitative measure of such a relationship is desirable.[22] In the process of quantification of symptom-

reflux associations, several criteria should be accurately defined, such as the criteria for the definition of reflux episodes and the length of the time window after a reflux episode during which a symptom is defined as reflux related.

Reflux episodes
An essential step in the analysis of symptom-reflux association is to identify all reflux episodes that occurred during the measurement period. A reflux episode is usually defined as a drop in pH below 4 that lasts for more than 10 seconds. Reflux preceding the onset of symptoms does not necessarily have to reach values below 4. It has been shown that short pH falls of more than 1 unit but not below 4 do not contribute to time with pH <4, but are also capable of eliciting symptoms.[23,24] Thus incorporation of these pH drops in the symptom association analysis is likely to increase its yield.[25]

Time window
In the early days of analysis of symptom-reflux association, the choice of time window was arbitrary. The aim of a study by Lam et al. was to determine the characteristics of the optimal time window. Repetitive symptom association analysis was carried out using time windows of various onsets and durations.[26] One of the indices frequently used for symptom analysis, the symptom index (see below), showed a gradual increase for windows with increasingly early time onset, following a pattern that would be predicted on the basis of Poisson's theory. However, a relatively sharp cut off point was found at the time window starting at two minutes before pain onset and ending at pain onset. The authors concluded that two minute time windows beginning at two minutes before the onset of symptoms are recommended for symptom-reflux association analysis. It should be borne in mind that this study was performed in patients with noncardiac chest pain, most of whom had reflux as the cause of their symptoms. The two minute time window may not be optimal for the evaluation of other symptoms such as cough.

Methods for symptom analysis
The next question is how to express associations found between reflux and symptoms in a quantitative way. Ward et al. were the first to introduce an index to describe the relation between symptoms and reflux.[27] They proposed the symptom index (SI), which is defined as the percentage of symptom episodes that are related to reflux:

(Number of reflux related symptom episodes/Total number of symptom episodes) X 100 %

The distribution of SIs in a population of patients with heartburn appeared to be bimodal and the result of receiver operating characteristic analysis indicated that the optimal threshold for SI is 50 %, but thresholds of 25 % and 75 % have also been suggested.[28,29] The SI and oesophageal acid exposure do not necessarily correlate. It has been shown that a substantial proportion of patients with a positive SI have physiological acid exposure.[14] Figure 1 shows examples of 24-hour pH recordings with a positive SI in patients with pathological and physiological reflux, respectively.

The major shortcoming of the SI is that this index does not take the total number of reflux episodes into account. The higher the frequency of gastro-oesophageal reflux, the higher the likelihood that a symptom is found to be associated with reflux by chance. Therefore, in patients with frequent gastro-oesophageal reflux who report only one symptom episode during 24-hour pH monitoring, an SI of 100% might well occur by chance.

For this reason the symptom sensitivity index (SSI) was proposed as an additional parameter.[30] SSI is defined as:

(Number of symptom associated reflux episodes/Total number of reflux episodes) X 100 %

SSI values of 10 % or higher are considered to be positive. Calculation of both SI and SSI for one and the same pH monitoring test may yield discordant results. However, conclusions can be drawn from discordant test results. For example, the combination of a high SSI and a low SI indicates that the patient's oesophagus is sensitive to reflux but causes other than acid reflux are likely to contribute to the symptoms.

Both the SI and SSI suffer from the disadvantage that they do not integrate all factors determining the relationship between symptoms and reflux. As a consequence, the probability that SI becomes positive increases with an increasingly high number of reflux episodes and SSI is more likely to be positive when the number of symptom episodes is high.

The Leuven group introduced the binomial symptom index (BSI), a complex formula that calculates the probability that symptoms are related to reflux episodes by summating a number of partial probabilities.[31] Apart from its complexity, BSI suffers from the disadvantage that it only takes into account episodes with a pH drop below 4, whereas it has been shown that drops of more than one pH unit that do not reach a pH of 4 constitute up to one third of the reflux related symptom episodes.[24,32]

Weusten et al. subsequently developed the symptom association probability (SAP), a parameter that expresses the likelihood that the patient's symptoms are related to reflux.[33] It is calculated by dividing 24-hour pH data into consecutive two minute segments. For each of these two minute segments, it is determined whether reflux occurred, providing the total number of two minutes 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 (Figure 2). Subtraction of S+R+ from total R+ results in S-R+ and subtraction of S+R- from total R- results in S-R-. A 2X2 contingency table is then constructed in which the number of two minute 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. SAP is calculated as (1-p) X 100 %. By statistical convention, SAP > 95 % is positive (Figure 3). Manual calculation of SAP is cumbersome and time consuming but automatic calculation of this parameter is easy and fast. It should be borne in mind that SAP is a statistical parameter that quantifies the probability that the observed distribution is not brought about by chance. As with all other statistical tests for association, a statistically significant relationship between two parameters does not necessarily imply causality.

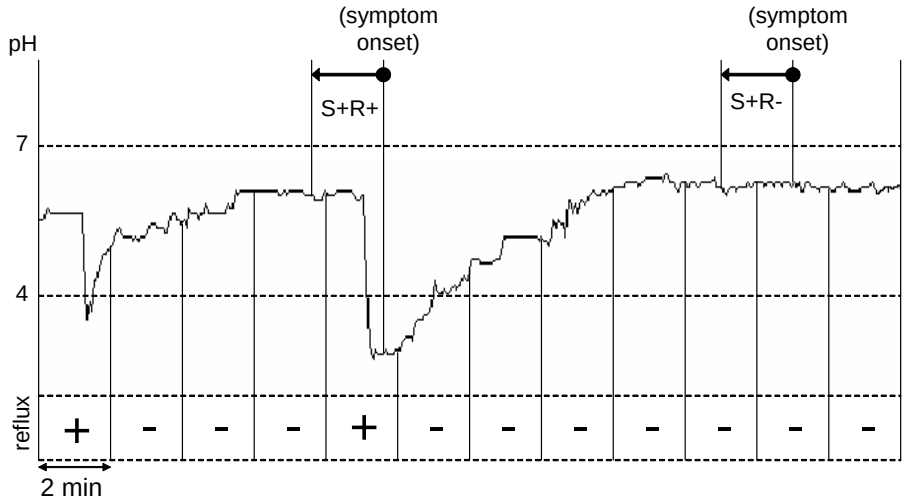

Figure 2. Schematic presentation of the calculation of the symptom association probability (SAP). The recording is divided into two minute segments. In this example, two of these contain a reflux episode. The arrows above the pH signal indicate when the patient pressed the event marker bottom. The first symptom (S) is preceded by acid reflux (R) (that is, S+R+), the second symptom is not (S+R-).

2 X 2 table

	S+	S-
R+	1	1
R-	1	9

Fisher-exact: p=0.318

SAP=100%*(1-p)=68.2%

Figure 3. Two by two table of the calculation of the symptom association probability (SAP). S, symptom; R, reflux.

Armstrong et al. described a method of symptom association analysis that used the Komolgorov-Smirnov test to compare the frequency distribution of the pH values recorded during symptom episodes with the frequency distribution of the pH values during the rest of the measurement.[34] If the two distributions of pH are significantly different, it can be concluded that the patient's pain is dependent on oesophageal pH. It should be noted however that with this technique the relation between oesophageal pH and symptoms is tested, not the relation between reflux episodes and symptoms. As short pH drops can elicit symptoms but will not have a great effect on pH frequency distributions, the technique is likely to underestimate the impact of short lived reflux episodes. Furthermore, the statistical test involved is not adequately powered if only a few symptoms occur.

Symptom association analysis can also be carried out with the use of receiver operating characteristics.[35] Essential to this type of analysis are plots in which on the X axis the number of symptom associated reflux episodes divided by the total number of symptoms (SI) is shown and on the Y axis the number of reflux episodes without heartburn divided by the total number of reflux episodes is displayed. The area under the curve is thus a measure of symptom association. As this method makes use of the SI, it suffers from the disadvantages inherent with this parameter.

Practical issues of symptom analysis

Computerised symptom association analysis is incorporated in most commercial ambulatory pH monitoring software. As manual inspection of the tracings can sometimes reveal artefacts that are not identified by the computer, it is strongly recommended that such a visual check is carried out. Furthermore, editing of symptom events by the investigator is useful as patients can indicate on their symptom diary whether they pressed the event marker accidentally or whether

the event marker was pressed for symptoms considered irrelevant in the context of 24-hour oesophageal pH testing.
Thorough instruction of the patient is one of the most important prerequisites of a successful 24-hour pH test. It has to be stressed that the patient has to press the event marker button each time a symptom is perceived. A diary on which the patient can fill in the nature of every symptom makes it possible to perform symptom analysis for different symptoms. As a result, a patient can have a positive SI, SSI, and SAP for heartburn, but not for cough, and vice versa. Furthermore, the patient has to be instructed not to reduce his normal daily activity and to consume his usual meals in order to elicit symptoms. Obviously, a 24-hour pH study during which no symptoms occur does not contribute to the evaluation of these symptoms.

Contribution to the diagnostic workup

Before the advent of 24-hour pH monitoring, the relation between symptoms and acid could only be investigated using provocation tests such as the acid perfusion test according to Bernstein and Baker.[36] In this test, hydrochloric acid and saline solutions are instilled into the oesophagus of the patient who is blinded for the sequence of instillation. The test is considered to be positive when acid infusion reproduces the patient's symptoms and saline does not. Several comparative studies showed that oesophageal pH monitoring is superior to provocation testing in identifying the cause of patients' symptoms.[37-40] Discordance between the acid perfusion test and pH monitoring implied that other factors of gastro-oesophageal reflux besides the acidity of the refluxate were responsible for symptom generation. Comparison of the two tests also led to the conclusion that symptomatic gastro-oesophageal reflux, abnormal oesophageal acid exposure, and mucosal acid sensitivity are three separate although related aspects of GORD.[14] As illustrated in figures 1 and 4, there is a subset of patients with a normal oesophageal acid exposure time who exhibit a positive temporal association between symptoms and oesophageal acid exposure.[22,28,41-43] Whereas in the Rome II classification this frequently encountered condition is classified as functional heartburn, the Rome III consensus will incorporate it into GORD.[44]
Watson et al. have shown that in a group of patients with heartburn and regurgitation and physiological oesophageal acid exposure, those with a positive SI showed a considerably better symptomatic response to omeprazole than those with a negative SI, suggesting that SI is a good predictor of response to proton

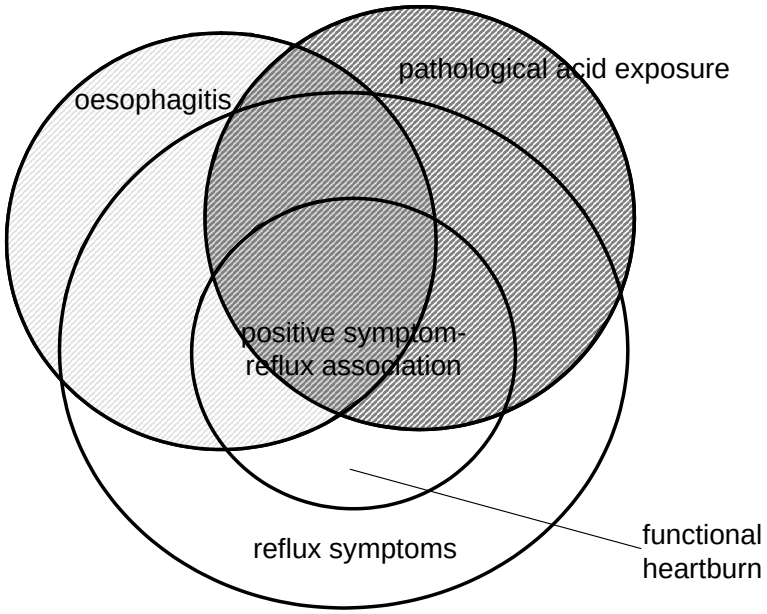

Figure 4. Diagram of the various elements of gastro-oesophageal reflux disease (GORD). When GORD is defined as either mucosal damage and/or symptoms induced by gastro-oesophageal reflux, all GORD patients fall in the circles ''oesophagitis'' and/or ''positive symptom-reflux association''. Patients with symptoms of heartburn and/or regurgitation but no oesophagitis and no relation between symptoms and reflux on pH-metry do not fall under the definition of GORD. Patients who have neither pathological acid exposure nor oesophagitis but do have a positive symptom association are classified by the Rome II criteria as functional heartburn.

pump inhibitor (PPI) therapy.[45] A recent study by Taghavi et al. compared the predictive value of symptom association analysis for outcome after a short term treatment with a high dose of omeprazole (PPI test).[46] Whereas the positive predictive values of SI, SSI and SAP were high, the negative predictive values were relatively low. This implies that patients may react satisfactorily to treatment with PPIs while there is no demonstrable relation between the onset of their symptoms and reflux. Whereas the authors of this study interpret this finding as imperfection of the association indices, it seems more likely that false positive responses to PPIs played a role. Diaz et al. also showed that SAP is a good and independent predictor of the success of antireflux surgery; failure to reach a positive SAP value for the principal symptom reduced the likelihood of responding favourably to antireflux surgery.[47] It has also been suggested that patients with physiological acid exposure and a positive SI benefit as much from antireflux surgery as patients with pathological acid exposure.[48]

Oesophageal pH monitoring is not only used for evaluation of typical oesophageal reflux symptoms such as heartburn and regurgitation, but also for evaluation of atypical reflux symptoms. Whereas the acute onset of heartburn and regurgitation makes it possible to investigate the temporal correlation with reflux events, this is not possible with symptoms lacking a crisp onset, such as globus sensation and hoarseness. In the case of unexplained chronic cough however, symptom association analysis showed a temporal relation between acid reflux and cough in one third of patients.[49] Combined oesophageal pH and pressure monitoring makes it possible to distinguish between reflux-cough and cough-reflux sequences, as coughs spells can be recognised manometrically. Making this distinction is important because reflux induced coughing should be treated differently from cough induced reflux.
Studies using symptom association analysis of combined 24-hour pH and pressure signals in patients with non-cardiac chest pain have shown that an oesophageal origin of the pain can be identified in a small subset of patients only.[32,50,51] In these patients reflux is the likely cause of the symptoms far more often than oesophageal dysmotility. Despite the relatively low yield of 24-hour pH and pressure monitoring, this investigation is still considered useful as a positive diagnosis contributes significantly to the patient's well being.[52]

Future prospects

Although acid gastro-oesophageal reflux is responsible for symptoms of heartburn and regurgitation in a large proportion of patients, these symptoms sometimes occur without any evidence of acid reflux. Several studies have shown that besides acid, heartburn can also be elicited by hyperosmolar solutions, certain foods, bile acids, oesophageal contractions, and oesophageal distension.[53-59]
Studies using the Bilitec 2000, a fibreoptic spectrophotometric probe that makes use of the absorbance spectrum of bilirubin for the detection of duodenogastro-oesophageal reflux, showed that reflux of bile can only be held responsible for a minor proportion of symptoms.[60,61] Another study calculated that only 7 % of patients with GORD had a positive SAP for bile reflux, as detected by the bilirubin absorbance technique, which is 2 % above the percentage that is expected to be found by pure chance.[62] However, reflux detection using the bilirubin absorbance technique has several limitations. The most important of these is that clearance of material trapped in the probe gap takes much longer than oesophageal clearance of bile. As a consequence, individual reflux episodes

cannot be detected with sufficient accuracy. Furthermore, the signal-response relationship of this device is distorted in an acid environment, a situation that often occurs in the oesophagus of patients with GORD.[63]

Intraluminal impedance monitoring appears to hold much more promise for symptom association analysis. With this technique, movements of liquid and air within the oesophageal lumen, either in an antegrade or retrograde direction, can be monitored. Using impedance monitoring, reflux can be detected independently of the acidity of the refluxate.[64] The temporal resolution of reflux detection by intraluminal impedance monitoring is high, which makes it suitable for symptom association studies (Figure 5). Using this technique, Vela et al. showed that heartburn and regurgitation in patients off acid secretion inhibiting medication were caused by both acid and non-acid reflux, while during acid suppression non-acid reflux was responsible for symptom generation.[65] In patients using acid suppression, addition of impedance monitoring to pH monitoring leads to a higher SI, SSI, and SAP.[66,67] Preliminary data also suggest that a positive SI for non-acid reflux predicts a good symptomatic response to fundoplication.[68]

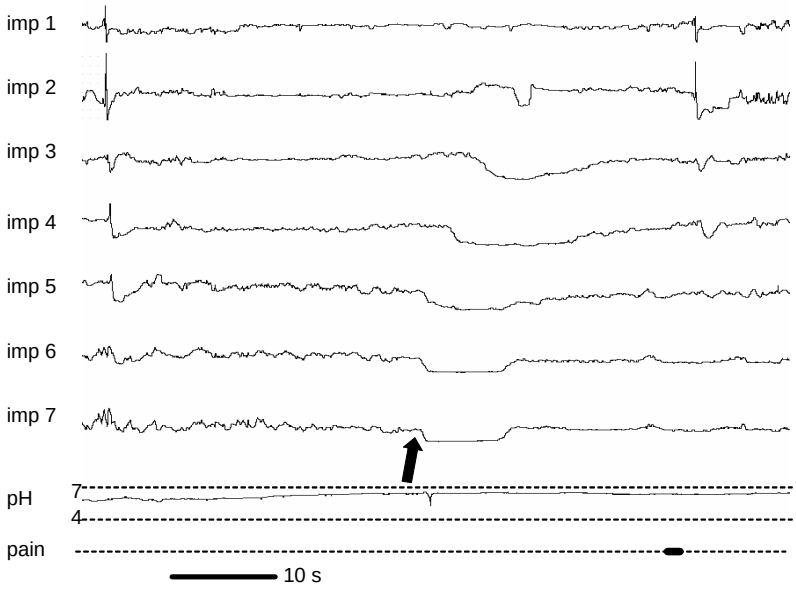

Figure 5. Combined oesophageal pH-impedance measurement. There is a decrease in impedance starting in the most distal impedance segment (arrow) and moving in a proximal direction, indicating liquid reflux. No drop in pH below 4 is measured and thus this episode would not have been identified on pH-metry alone. The symptom event marker (''pain'') is pressed by the patient less than two minutes after the onset of this reflux episode, classifying this symptom as non-acid reflux associated.

As already mentioned, acid reflux can be the cause of chronic cough. A recent study showed that combined pH impedance monitoring can identify reflux as a causative agent for cough in more patients compared with pH monitoring alone.[69] One of the restrictions of 24-hour reflux monitoring is that the frequency of symptoms varies from day to day, which implies that a single 24-hour period may not be representative. Recently, a wireless system for ambulatory pH monitoring has become available. A capsule containing a pH electrode and a radiotransmitter placed in the distal oesophagus transmits data to an external datalogger.[70] It appears that pH monitoring carried out with this technique is tolerated better by patients than conventional catheter based pH-metry, and measurement time can therefore be increased. It was shown that 48 hour ambulatory pH monitoring doubles the SI and SAP in patients with atypical reflux symptoms in comparison with 24-hour monitoring.[71]

Conclusions

Reflux of gastric content may lead to symptoms and mucosal inflammation. While the latter can be detected endoscopically, symptom-reflux association analysis is the only method that can adequately identify reflux as the cause of short lived symptoms with sudden onset, such as heartburn, regurgitation, chest pain, and cough. Such analysis should therefore be included in every 24-hour pH study evaluating these complaints. Indices that express the strength of the symptom-reflux association numerically, such as the SI and SAP, constitute the most important information that can be obtained from a 24-hour pH study.

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Addition of esophageal impedance monitoring to pH monitoring increases the yield of symptom association analysis in patients off PPI therapy

A.J. Bredenoord
B.L.A.M. Weusten
R. Timmer
J.M. Conchillo
A.J.P.M. Smout

Dept. of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands
Gastrointestinal Research Unit, University Medical Center, Utrecht, The Netherlands

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Abstract

Background: The additional yield of esophageal impedance monitoring in identification of reflux as the cause of reflux symptoms is unknown. Objectives: To compare the yield of symptom–reflux association analysis of combined esophageal pH-impedance data with the yield of analysis of pH data alone. Methods: In 60 patients with symptoms of heartburn and regurgitation combined, 24-hour pH-impedance monitoring was performed. Acid-suppressive medication was stopped 1 wk in advance. Patients (48) with at least one symptom during the measurement period were selected for further analysis. Patients were instructed to note the time and nature of their symptoms. Eleven types of reflux episodes were defined, based on combinations of magnitude of the pH drop, nadir pH, and nature of the refluxate (gas and liquid) on impedance tracings. Symptom association analysis—symptom index, the symptom sensitivity index, and the symptom association probability (SAP)—was performed for each definition of reflux. Results: The proportion of patients with a positive SAP (≥95.0 %) varied between 62.5 % and 77.1 %, depending on the definition of reflux episodes. When both pH and impedance parameters were used to identify reflux, a higher proportion of patients had a positive SAP than with pH alone (77.1 % vs 66.7 %, $p<0.05$). Symptom association analysis for acidic and weakly acidic reflux separately did not result in a higher yield than analysis with all reflux episodes pooled, regardless of pH. Conclusion: In patients off proton pump inhibitor, the addition of impedance monitoring to esophageal pH monitoring leads to an increase in the proportion of patients in whom an association between reflux episodes and symptoms can be identified.

Introduction

The gold standard for assessment of the relationship between symptoms of gastroesophageal reflux such as heartburn and regurgitation and reflux episodes is 24-hour pH-metry with symptom association analysis.[1-3] In a subset of patients no clear relationship is found between the onset of symptoms and the occurrence of gastroesophageal reflux, defined as pH drops below 4. It has been suggested that in some of these patients symptoms are induced by reflux episodes associated with only small changes in pH and a nadir pH above 4.[4] However, until recently, this hypothesis could not be tested since these reflux episodes could not be detected by means of pH-metry.

Some years ago, multiple intraluminal impedance monitoring was introduced as a new and reproducible technique to detect gastroesophageal reflux.[5,6] Detection of gastroesophageal reflux with this technique is irrespective of its acidity, which makes that also reflux with a nadir pH above 4 can be detected.[7] Studies using intraluminal impedance monitoring have shown that approximately one third of all reflux episodes are weakly acidic in patients off therapy.[8] In a 2-hour study of five patients with gastroesophageal reflux disease (GERD), Vela et al. showed that weakly acidic reflux episodes could also induce symptoms of heartburn and regurgitation.[9] However, in patients who do not use acid secretion inhibitors, only a minority of symptoms seems to be induced by weakly acidic reflux.[10] It is thus uncertain whether detection of these episodes with impedance monitoring will increase the yield of symptom association analysis. Therefore, the aim of this study was to investigate the yield of addition of impedance monitoring to pH monitoring in patients with symptoms suspected for GERD.

Methods

Subjects

In 60 patients with typical reflux symptoms (32 males; aged 28–73 yr, median 49 yr) ambulatory combined impedance and pH monitoring was performed. Those with at least one symptom of heartburn, regurgitation, or chest pain during the measurement period were selected for further analysis. Written informed consent was obtained from all subjects and the protocol was approved by the medical ethical committee of the University Medical Center Utrecht.

Study Protocol

The use of gastric acid-inhibitory drugs and drugs that might influence gastrointestinal motility was discontinued 5 days before the study. Esophageal manometry was performed to determine the distance from nostrils to lower esophageal sphincter (LES). After this, the impedance and the pH catheter were introduced transnasally and positioned based on the manometric findings (see below).

The patients were instructed to press the event marker button on the pH datalogger whenever they experienced a symptom. The nature and time of onset of their symptoms had to be written down in a specially designed diary. Furthermore, they were instructed to consume three meals and two beverages with snack at fixed times during the 24-hour measurement period. The period spent in supine position was also noted in the diary.

Esophageal Impedance and pH Monitoring

For intraluminal impedance monitoring a 7-channel impedance catheter (Aachen University of Technology, FEMU, Aachen, Germany) was used. This catheter (outer diameter 2.3 mm) enabled recording from seven segments, each recording segment being 2 cm long. The 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 localized LES. Impedance signals were stored in a digital system (Aachen University of Technology) using a sample frequency of 50 Hz.[11] Intraluminal pH monitoring was performed with a glass pH electrode (Ingold A.G., Urdorf, Switzerland) and pH data were stored in a digital datalogger (Orion, MMS, Enschede, The Netherlands) using a sampling frequency of 2 Hz. The pH glass catheter was positioned 5 cm above the upper border of the LES. Using a cable that connected the pH datalogger with the impedance datalogger the pHsignalswere also stored on the impedance datalogger ensuring synchronization.

Data Analysis

Analysis of the tracings was performed independently by two experienced investigators. The analysis was performed manually. Thereafter, the two investigators conjointly analyzed the reflux episodes that were not recognized by both of them. A consensus decision was made on each of these episodes. Signals recorded during consumption of meals and beverages were not taken into account during analysis of the data.

In the impedance tracings, gas reflux was defined as a rapid (>3000 Ω/s) retrograde moving increase in impedance in at least two consecutive impedance

sites.[12] Liquid reflux was defined as a retrograde moving 40 % fall in impedance in the two distal impedance sites.[8] The pH tracings were analyzed for pH drops below 4. Furthermore, all pH drops ≥1 unit and drops ≥0.5 unit occurring within 5 s were identified. Drops <0.5 unit were judged to be not distinguishable from baseline noise, and were therefore not analyzed.

Using the combination of pH and impedance findings, 11 different definitions of reflux episodes were used, based on combinations of criteria such as the nature of the refluxate detected with impedance monitoring [liquid-containing (pure or mixed liquid) or gas], the magnitude of the pH drop (none, ≥0.5 unit, or ≥1.0 unit), and the nadir pH reached (acidic: pH <4; weakly acidic: pH 4–7) (Table 1). The reflux definitions listed in Table 1 fall into three broad categories: reflux episodes detected with pH-metry without use of impedance, liquid-containing reflux episodes (mixed liquid–gas and pure liquid) detected with impedance, and all reflux episodes detected with impedance (liquid-containing and pure gas).

Symptom–reflux association analysis was performed for each of the 11 definitions of reflux episodes listed in Table 1. A separate analysis was performed for weakly acidic reflux episodes, defined as liquid-containing reflux episodes with a nadir pH between 4 and 7, and the yields of symptom association analysis for acidic (pH < 4), for weakly acidic reflux (pH 4–7) and for all reflux episodes pooled (independent of pH) were compared.

Table 1. The 11 definitions of reflux episodes distinguished in this study

Reflux episodes identified by pH signal analysis
pH drop < 4.0
pH drop < 4.0 and/or pH fall ≥ 1.0 unit
pH drop < 4.0 and/or pH fall ≥ 0.5 unit
Reflux episodes identified by impedance signal analysis
Liquid-containing reflux episodes (liquid and mixed gas/liquid)
With nadir pH < 4.0
With nadir pH < 4.0 and/or pH fall ≥ 1.0 unit
With nadir pH < 4.0 and/or pH fall ≥ 0.5 unit
All (irrespective of pH)
Liquid-containing and pure gas reflux episodes
With nadir pH < 4.0
With nadir pH < 4.0 and/or pH fall ≥ 1.0 unit
With nadir pH < 4.0 and/or pH fall ≥ 0.5 unit
All (irrespective of pH)

The first step in the symptom–reflux association analysis was the determination, for each reflux episode, whether it was symptomatic or not. Reflux episodes were labeled as symptomatic if a symptom occurred within the 2-min time window starting at the onset of the reflux episode.[13] Only symptoms of heartburn and regurgitation were evaluated. Thereafter, the symptom index (SI), the symptom sensitivity index (SSI), and the symptom association probability (SAP) were calculated.

The SI was calculated according to Wiener et al. as the percentage of symptoms that was reflux related, i.e., the percentage of symptom episodes that was preceded, within 2 min, by a reflux episode.[14] The SSI was defined according to Breumelhof and Smout as the percentage of reflux episodes that was symptomatic, i.e., the percentage of reflux episodes that was followed by a symptom within 2 min.[15] The SAP was defined according to Weusten et al. as the statistical relation between symptoms and reflux episodes.[16] The SAP is calculated by dividing the 24-hour 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 to calculate the probability (p) that the observed distribution was brought about by chance and that the symptom and reflux episodes were unrelated. The SAP is calculated as (1−p)×100 %. The cut-off values used in this study that quantify for a positive test were SI ≥ 50 %, SSI ≥ 10 %, and SAP ≥ 95 %.

Statistical analysis and presentation of data

Comparison of proportions of positive and negative SI, SSI, and SAP tests were performed using McNemar exact testing. Comparison of the proportion of patients with a positive SAP test for weakly acidic and acidic reflux calculated separately and calculated by pooling all reflux episodes was performed in a separate analysis. Differences were considered statistically significant when $p \leq 0.05$. Throughout the manuscript data are presented as mean ± SEM.

Results

Of the 60 patients studied, 48 had at least one episode of heartburn or regurgitation during the 24-hour study and the tracings of these patients were selected for further analysis. The mean number of reflux episodes that occurred during the 24-hour study ranged from 42.5 ± 3.8 to 96.4 ± 6.4, depending on the definition of reflux (Table 2). As anticipated, more reflux episodes were identified with the impedance-based criteria than with the classical pH-based criterion (pH drop below 4). However, the classical pH drop definition not only led to false-negative but also to false-positive reflux detection (Figure 1).

Table 2. Number of reflux episodes (mean ± SEM) and subjects (%) with a positive symptom association (SI, SSI, and SAP)

	Reflux episodes	SI ≥ 50.0 %	SSI ≥ 10.0 %	SAP ≥ 95.0 %
pH drop < 4.0	48.6 ± 4.0	23 (47.9 %)	20 (41.7 %)	32 (66.7 %)
pH drop < 4.0 and/or fall ≥ 1.0 unit	67.6 ± 4.9	29 (60.4 %)	16 (33.3 %)	32 (66.7 %)
pH drop < 4.0 and/or fall ≥ 0.5 unit	96.4 ± 6.4	30 (62.5 %)	12 (25.0 %)	32 (66.7 %)
Liquid-containing reflux with a nadir pH < 4.0	42.5 ± 3.8	22 (45.8 %)	22 (45.8 %)	31 (64.6 %)
Liquid-containing reflux with a nadir pH < 4.0 and/or fall ≥ 1.0 unit	50.4 ± 4.1	28 (58.3 %)	21 (43.8 %)	34 (70.8 %)
Liquid-containing reflux with a nadir pH < 4.0 and/or fall ≥ 0.5 unit	55.3 ± 4.3	28 (58.3 %)	22 (45.8 %)	36 (75.0 %)
All liquid-containing reflux episodes (independent of pH)	64.4 ± 4.4	28 (58.3 %)	19 (39.6 %)	35 (72.9 %)
Liquid, mixed and gas reflux with a nadir pH < 4.0	47.5 ± 4.0	23 (47.9 %)	20 (41.7 %)	30 (62.5 %)
Liquid, mixed and gas reflux with a nadir pH < 4.0 and/or fall ≥ 1.0 unit	55.2 ± 4.2	29 (60.4 %)	19 (39.6 %)	33 (68.8 %)
Liquid, mixed and gas reflux with a nadir pH < 4.0 and/or fall ≥ 0.5 unit	62.1 ± 4.3	30 (62.5 %)	19 (39.6 %)	37 (77.1 %)*
All liquid, mixed and gas reflux episodes detected with impedance (independent of pH)	84.6 ± 5.1	30 (62.5 %)	15 (31.3 %)	36 (75.0 %)

*: $p<0.05$ vs the highest SAP obtained without impedance monitoring.

Table 3. Number of subjects (%) with a positive SAP for acid and weakly acidic reflux separately, a positive SAP for at least one of these two reflux types and a positive SAP as calculated from all reflux episodes independent of pH

	Acid (nadir pH < 4)	Weakly acidic (nadir pH 4-7)	Acid and/or weakly acidic reflux	All reflux episodes (independent of pH)
Liquid-containing reflux episodes	31 (64.6 %)	10 (20.8 %)	34 (70.8 %)	35 (72.9 %)
Liquid-containing and pure gas reflux episodes	30 (62.5 %)	8 (16.7 %)	35 (72.9 %)	36 (75.0 %)

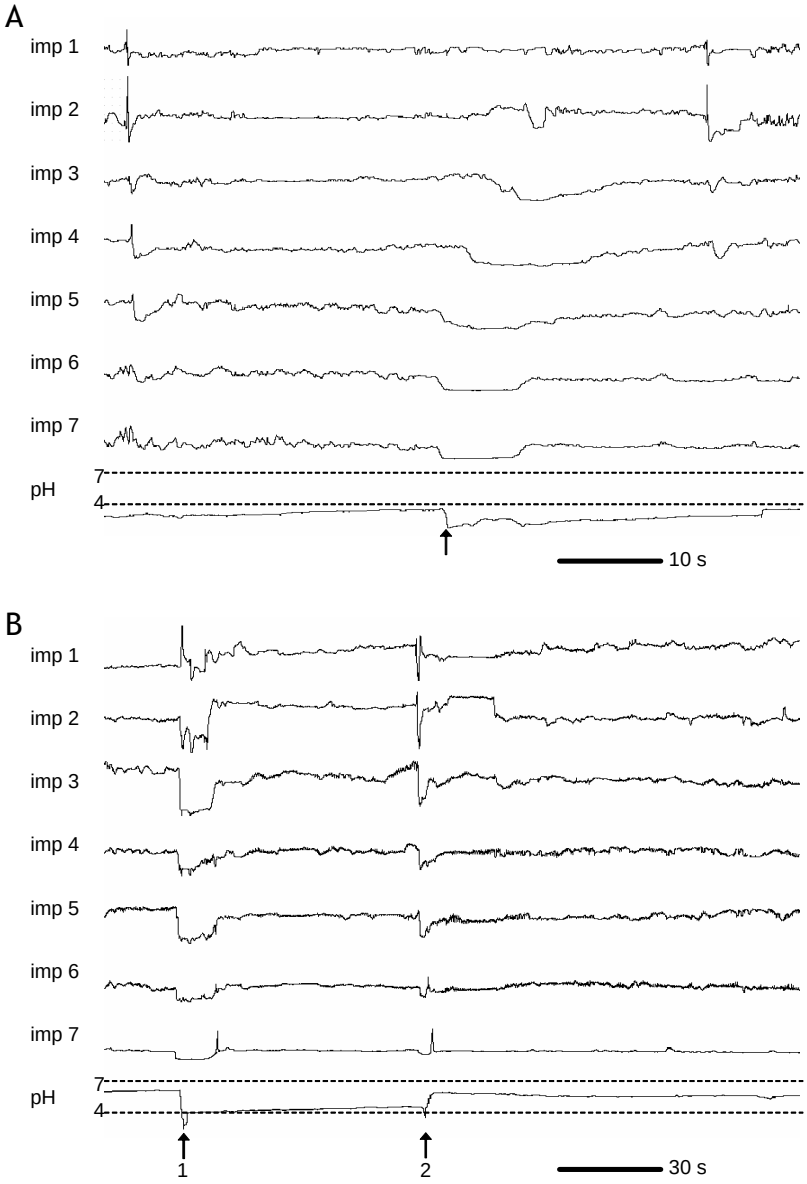

Figure 1. Examples of false-negative and false-positive detection of reflux episodes that may occur when the classical criterion of a pH drop below 4 is used, and that are unmasked by concomitant impedance monitoring. (A) In this example of false-negative detection, the "superimposed" reflux episode indicated by the arrow is not detected as such by classical pH criteria since the pH is still below 4 as the consequence of a preceding reflux event (not shown). (B) In this example of false-positive detection, the second drop in pH passing the pH 4 threshold (2) is not caused by reflux but by a swallow (antegradely propagated impedance drop).

The proportion of patients with a positive SI varied between 45.8 % and 62.5 % and the proportion of patients with a positive SSI varied between 25.0 % and 45.8 %, depending on the definition of reflux episodes (Table 2). A positive SAP was found in 62.5–77.1 % of the patients (Table 2). For liquid-containing reflux episodes, the highest proportion of patients with a positive SAP was reached with those episodes that were associated with a nadir pH <4 and/or a pH fall ≥0.5 unit (75.0%). For reflux episodes that showed evidence on impedance of liquid and/or gas reflux the highest number of cases with a positive SAP was found with episodes that had a nadir pH <4.0 and/or a pH fall ≥ 0.5 unit (77.1 %). The difference between the highest proportion of positive SAP values obtained with impedance (77.1 %) and without impedance monitoring (66.7 %) was statistically significant (p=0.03).
Only a minority of patients had a positive SAP for weakly acidic reflux (Table 3). Table 3 also shows the proportion of patients having a positive SAP for acidic, weakly acidic reflux, or a positive SAP for both (70.8 % for liquid-containing reflux episodes and 72.9 % for liquid-containing and gaseous reflux episodes). These proportions were not different from those found when the SAP was calculated independently of the pH of the reflux, i.e., when all (acidic and weakly acidic) reflux episodeswere pooled before calculation of the SAP.

Discussion

Recent studies have suggested that impedance monitoring is helpful in the clinical evaluation of patients with proton pump inhibitor (PPI)-resistant symptoms, unexplained cough, excessive belching, and rumination.[9,17-20] It has been shown that symptoms of heartburn and regurgitation can be induced by weakly acidic reflux but it remained unknown whether the use of impedance monitoring results in identification of a larger proportion of patients whose symptoms are induced by gastroesophageal reflux. In this study, we have used three different methods for reflux–symptom association analysis, i.e., the SI, SSI, and SAP. The SI and SSI are relatively simple indices, representing the percentage of symptom episodes that is preceded by reflux (SI) and the percentage of reflux episodes that is followed by a symptom (SSI). The major shortcoming of the SI is that it does not take the total number of reflux episodes into account. The higher the number of reflux episodes, the higher the chance that a symptom occurs within 2 min after a reflux episode by coincidence. Likewise, the SSI fails to take the number of symptom episodes into account, and a high number of

symptom episodes is likely to result in a high index. The advantage of the SAP is that it takes all relevant factors into account, but its disadvantage is that this parameter is difficult to calculate manually.

Theoretically, incorporation of weakly acidic reflux episodes into reflux–symptom association analysis will have different effects on the three indices (SI, SSI, and SAP). Since the SI is defined as the percentage of reflux-induced symptoms with the total number of symptoms as the denominator, this index will most likely increase by incorporation of weakly acidic reflux episodes. In contrast, the SSI is likely to decrease with the incorporation of more reflux episodes as this index is defined as the percentage of reflux-related symptoms, with the total number of reflux episodes as the denominator. Because of the complexity of the calculations involved, the effect of incorporation of a higher number of reflux episodes on the value of the SAP cannot be predicted easily.

A recent study of Taghavi et al. compared the predictive value for GERD of the different symptom indices with as a gold standard for GERD the response to a short-term treatment with omeprazole, the PPI test.[21] While these authors found relatively high positive predictive values for the SI, SSI, and SAP, the negative predictive values of the indices were relatively low. However, the PPI test is far from ideal as a gold standard, as other conditions such as functional dyspepsia and peptic ulcer disease may also respond favorably to treatment with omeprazole.[22] It is therefore not surprising that the negative predictive values of the symptom association parameters were found to be relatively low.

This study has shown that reflux episodes defined on the basis of impedance parameters provide a consistently higher SI and SAP than reflux episodes defined on the basis of pH changes only. This results in identification of a larger proportion of patients in whom reflux is the likely cause of their symptoms. In particular, small increases in the SAP, induced by incorporation of impedance monitoring, from, for example, 87 % to 97 % will change the patient's diagnosis (threshold 95 %) and might have therapeutic implications.

It has been shown that a positive SAP for acid reflux, detected with pH-metry, predicts the outcome of medical and surgical therapy for GERD.[21,23] However, this has not yet been investigated for a positive SAP for reflux detected with impedance, which includes acidic and weakly acidic reflux. It is thus uncertain whether investigation of patients using combined impedance-pH monitoring leads to a better selection for treatment. Furthermore, it is uncertain whether symptoms due to weakly acidic reflux episodes will respond to acid-suppressive therapy.

In some studies, separate symptom association analysis was performed for acid and weakly acidic reflux. In our study, we show such a procedure does not result in the identification of a higher proportion of patients with reflux-related symptoms than a symptom analysis in which all reflux episodes are pooled before the relation between reflux episodes and symptoms is tested. A theoretical rationale for dividing reflux episodes into acid and weakly acidic reflux episodes could be that some patients have predominantly acid reflux while others have predominantly weakly acidic reflux, but this does not seem to be the case. Another rationale would prevail if the treatment would be different for these two types of reflux, but currently both are treated with anti-secretory therapy since drugs that reduce the incidence of reflux episodes, such as GABA-B receptor agonists, are still under development.[24] Furthermore, no strict distinction can be made by the symptoms associated with acid and weakly acidic reflux, as heartburn and regurgitation can be produced by reflux episodes with various pH values.[10] Future research will determine whether classification of reflux episodes into acidic and weakly acidic remains useful or that it is only a historical remnant of the era in which esophageal pH monitoring was the only available technique for quantification of gastroesophageal reflux. Most symptomatic weakly acidic reflux episodes are associated with a small but noticeable drop in pH. This suggests that hypersensitivity to acid plays an important role in the generation of symptoms by weakly acidic reflux episodes, but other factors, such as the presence of pepsin in the refluxate and esophageal distention by the refluxate, are also likely to play a role.[10,25]

The number of symptoms experienced by patients with GERD is dependent on both the sensitivity to acid of the patient's esophagus and the total number of reflux episodes. Patients with a pronounced esophageal hypersensitivity but a normal esophageal acid exposure may experience heartburn after reflux episodes that induce only small changes in pH.[26] When reflux definitions with stringent criteria for reflux episodes are used, patients are likely to have a number of symptoms not related to reflux (defined by these criteria) and thus have a low SAP score. For example, when the definition for reflux episodes used is "liquid-containing reflux episodes with a nadir pH < 4", all symptoms that follow a weakly acidic reflux episode (pH 4–7) are classified as not reflux-related and these will lower the SAP score. Incorporating more criteria into the definition of reflux (e.g., inclusion of pH falls of more than 0.5 unit) will result in identification of more patients with a hypersensitivity to acid. In our study, widening the criteria for reflux from liquid reflux episodes with a nadir pH < 4 (acid reflux) to all liquid reflux episodes (acid and weakly acidic) changed the

SAP from a negative to a positive score in 4 of the 48 patients (Table 2). Of these four patients, three had a physiological acid exposure and the mean acid exposure time of the four patients was 3.1 %. Identification of these patients is important since it is likely that they will respond favorably to high-dose proton pump inhibiting therapy. It has been shown that in a group of patients with symptoms of heartburn and regurgitation and a physiological esophageal acid exposure, those with a positive SI have a better response to omeprazole.[27]

The proportion of patients with a positive SAP score for the various reflux definitions varied between 62.5 % and 77.1 %. This implies that the majority of these patients have a positive association between reflux and symptoms. The fact that the patients in this study were selected by experienced gastroenterologists and that our tertiary care clinic is specialized in motility disorders might account for the high yield of symptom association analysis in this study. Furthermore, the instruction of the patients before the 24-hour measurement was performed meticulously.

In this study, we found that approximately one third of the reflux episodes defined as pH drop to below 4 and/or pH drop ≥0.5 unit (96.4 ± 6.4) is not accompanied by evidence of reflux on impedance (62.1 ± 4.3). An example of this phenomenon is displayed in figure 1. In previous studies, reflux detected with pH-metry only was rare.[28,29] However, in those studies, reflux was defined as a pH drop <4.0. Preliminary data from Hila et al. suggested that small pH drops are not accurate for reflux detection, as they were often not associated with evidence of reflux on impedance but occurred during swallowing.[30] It is uncertain whether these pH drops are indeed not good indicators of reflux or that these pH drops indicate reflux episodes that are missed by impedance because they occur during swallows. It is well known that during swallow-induced LES relaxation reflux often occurs.[31]

In conclusion, although reflux–symptom association analysis based on pH-metric data can identify reflux as the source of heartburn and regurgitation in the majority of patients, addition of impedance monitoring leads to identification of a significantly higher proportion of patients who suffer from reflux-induced symptoms. Thus, impedance monitoring has an additional value for the evaluation of heartburn and regurgitation in patients off PPI therapy. Performing separate symptom association analysis for acidic and weakly acidic reflux episodes does not result in a higher yield than performing symptom association analysis for all reflux episodes pooled.

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Symptomatic gastro-oesophageal reflux in a patient with achlorhydria

A.J. Bredenoord
A. Baron
A.J.P.M. Smout

Dept. of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands
Gastrointestinal Research Unit, University Medical Center, Utrecht, The Netherlands

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Abstract

With traditional pH monitoring only reflux with a pH drop below 4 can be detected. Intraluminal oesophageal impedance monitoring detects reflux independently of its acidity. In combination with pH monitoring, this makes it possible to study acid, weakly acidic and weakly alkaline reflux. All of these types of reflux can trigger symptoms. The temporal relation between symptoms and reflux episodes can be investigated using symptom association analysis. We performed 24-hour pH monitoring in a 72-year-old female with daily heartburn. Not a single acid reflux episode was detected and achlorhydria was suspected. Upper endoscopy revealed an atrophic gastritis and antibodies against parietal cells and intrinsic factor were found. The diagnosis of autoimmune atrophic gastritis was made and 24-hour impedance pH monitoring was performed. Again no acid reflux was observed, but 22 weakly acidic and 5 weakly alkaline reflux episodes were observed. A positive relationship between weakly acidic reflux episodes and heartburn episodes was found, demonstrating that the heartburn of this achlorhydric patient resulted from gastro-oesophageal reflux of weakly acidic material. We conclude that impedance monitoring provides important information as to whether or not symptoms are related to reflux episodes, even in patients with achlorhydria.

Intraluminal impedance monitoring makes it possible to detect gastro-oesophageal reflux, independent of its pH.[1] This is useful because other factors apart from acidity are important in symptom generation.[2] Here, we describe a patient with achlorhydria in which impedance monitoring was used to identify gastro-oesophageal reflux as the cause of her symptoms.

A 72-year old female presented at our department. She complained of a retrosternal burning sensation which occurred at least five times a day. Eighteen months previously, her general practitioner prescribed monthly vitamin B12 injections after a routine blood test had revealed a megaloblastic macrocytic anaemia. She had underwent laparoscopic cholecystectomy for symptomatic gall stones four years previously.

Oesophageal manometry and 24-hour pH monitoring were performed. Results of oesophageal manometry were unremarkable. Ambulatory 24-hour pH monitoring showed an oesophageal acid exposure time of 0 %; the lowest pH value that was reached was 5.5 (Figure 1). Nine episodes of heartburn were reported by the patient but none was acid reflux related, resulting in a negative symptom index (SI) and symptom association probability (SAP) (both 0 %).

After the results of pH monitoring had shown total absence of acid reflux, achlorhydria was suspected and further investigations were felt to be warranted. A blood test revealed normal values for blood cell counts and volumes and a slightly elevated serum vitamin B12 level (1080 pmol/l; normal 148–625). Serum gastrin was slightly high (135 ng/l; normal <75 for females). Tests for antibodies against parietal cells and intrinsic factor were positive. Upper endoscopy revealed an atrophic reddish mucosa of the gastric corpus and fundus. No oesophageal abnormalities were observed. Rapid urease tests were negative, indicating the absence of Helicobacter pylori. Microscopy revealed inflammation and intestinal metaplasia but no H pylori. A diagnosis of autoimmune atrophic gastritis was thus made. However, it was still unclear whether the patient's symptoms were the result of reflux of gastric contents.

Therefore, we decided to perform a 24-hour combined pH-impedance measurement. Again, pH data showed an acid exposure time of 0 %, and no acid reflux episodes were measured. Analysis of the impedance signals showed 22 weakly acidic and five weakly alkaline reflux episodes. The patient experienced 11 episodes of heartburn, eight of which were preceded by a weakly acidic reflux episode, resulting in a positive SI and SAP for weakly acidic reflux (72.7 % and 100.0 %, respectively). The options of endoscopic or surgical antireflux treatments were considered but the patient responded well to intermittent sucralfate.

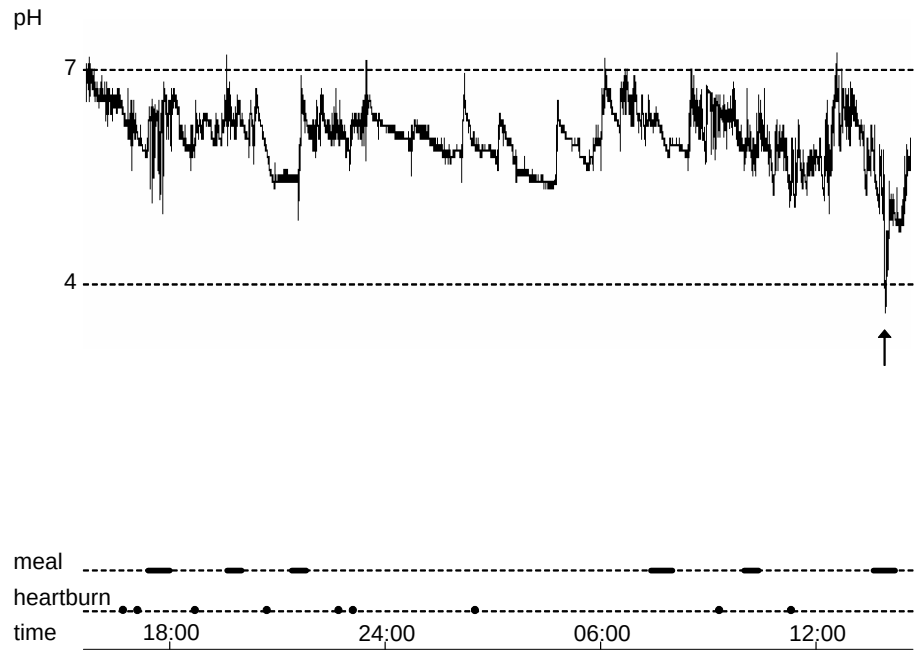

Figure 1. Tracing of 24-hour pH monitoring. No acid reflux episodes occurred. The drop in pH indicated by the arrow was caused by ingestion of (acidic) food.

There is little information in the literature on reflux symptoms in patients with achlorhydria. Palmer described 22 cases of oesophagitis in patients with achlorhydria, also suggesting that non-acid reflux can induce oesophageal inflammation.[3] However, in Palmer's report, no mention was made of the symptoms experienced by his patients. Orlando and Bozymski described heartburn in a patient with pernicious anaemia which they felt was most likely induced by bile reflux.[4] Their patient's heartburn resolved on treatment with cholestyramine, a resin that binds bile salts. Our patient underwent a cholecystectomy a few years previously, a condition which may facilitate entry of bile into the stomach.[5] Bile may have been responsible for symptom generation in our patient. Although the study of Orlando and Bozymski suggests a relationship between reflux and symptoms, it does not prove such a relationship as confidently as can be done using symptom association analysis.

In conclusion, combined impedance-pH monitoring can be used to evaluate symptoms in patients with achlorhydria. The relationship between symptoms and weakly acidic and weakly alkaline reflux episodes can be investigated with this technique, which may have consequences for patient management.

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Determinants of perception of heartburn and regurgitation

A.J. Bredenoord
B.L.A.M. Weusten
W.L. Curvers
J.M.M. Roelofs
A.J.P.M. Smout

Dept. of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands
Gastrointestinal Research Unit, University Medical Center, Utrecht, The Netherlands

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Abstract

Background and aim: It is not known why some reflux episodes evoke symptoms and others do not. We investigated the determinants of perception of gastro-oesophageal reflux. Methods: In 32 patients with symptoms suggestive of gastro-oesophageal reflux, 24-hour ambulatory pH and impedance monitoring was performed after cessation of acid suppressive therapy. In the 20 patients who had at least one symptomatic reflux episode, characteristics of symptomatic and asymptomatic reflux episodes were compared. Results: A total of 1807 reflux episodes were detected, 203 of which were symptomatic. Compared with asymptomatic episodes, symptomatic episodes were associated with a larger pH drop ($p<0.001$), lower nadir pH ($p<0.05$), and higher proximal extent ($p<0.005$). Symptomatic reflux episodes had a longer volume and acid clearance time ($p<0.05$ and $p<0.002$). Symptomatic episodes were preceded by a higher oesophageal cumulative acid exposure time ($p<0.05$). The proximal extent of episodes preceding regurgitation was larger than those preceding heartburn; 14.8 % of the symptomatic reflux episodes were weakly acidic. In total, 426 pure gas reflux episodes occurred, of which 12 were symptomatic. Symptomatic pure gas reflux was more frequently accompanied by a pH drop than asymptomatic gas reflux ($p<0.05$). Conclusions: Heartburn and regurgitation are more likely to be evoked when the pH drop is large, proximal extent of the refluxate is high, and volume and acid clearance is delayed. Sensitisation of the oesophagus occurs by preceding acid exposure. Weakly acidic reflux is responsible for only a minority of symptoms in patients off therapy. Pure gas reflux associated with a pH drop ("acid vapour") can be perceived as heartburn and regurgitation.

Introduction

Symptoms suggestive of gastro-oesophageal reflux disease (GORD) are a common reason for consultation. In the past decades the relationships between oesophageal acid exposure and reflux symptoms have been explored extensively, in particular with 24-hour oesophageal pH monitoring. However, several questions concerning the generation of reflux symptoms have remained unanswered. For instance, it is not clear why some patients suffer from symptoms such as heartburn and regurgitation whereas others, with an apparently similar reflux profile, do not.[1] Likewise, why do some reflux episodes evoke symptoms while other reflux episodes in the same patient do not? Studies using multiple pH sensors at different positions in the oesophagus have shown that symptomatic reflux episodes have a more proximal extent, a longer duration, and a lower pH compared with reflux episodes that remain asymptomatic.[2-4] Furthermore, studies on the effect of acid secretion inhibiting therapy on oesophageal sensitivity to acid instillation suggested that exposure of the oesophagus to acid leads to hypersensitivity for subsequent reflux episodes.[5,6] While these studies have increased our understanding of perception of acid gastro-oesophageal reflux (that is, of episodes associated with a fall in pH below 4), the techniques used in these studies did not allow assessment of symptoms induced by non-acid refluxate.[7]

Recently, multiple intraluminal impedance was introduced as a new and reproducible technique to monitor gastro-oesophageal reflux.[8,9] With this technique detection of gastro-oesophageal reflux is irrespective of acidity, so that reflux with a nadir pH between 4 and 7 (weakly acidic reflux) and with a nadir pH above 7 (alkaline reflux) can also be detected.[10] Studies using impedance monitoring have shown that, in patients who are not on acid suppressant therapy, approximately one third of all reflux episodes are weakly acidic.[11] It is not clear to what extent reflux of material with a pH > 4 leads to symptoms. The aim of this study was therefore to identify factors, acidic, weakly acidic, and weakly alkaline, that are important in the elicitation of reflux symptoms.

Methods

Subjects

In 32 patients with typical reflux symptoms (17 males, 15 females; age 27–65 years (median 53)), ambulatory 24-hour combined impedance and pH monitoring

was performed. The 20 studies in which at least one reflux related symptom episode occurred were selected for further analysis. Written informed consent was obtained from all subjects and the protocol was approved by the medical ethics committee of the University Medical Centre Utrecht.

Study protocol

The use of gastric acid inhibitory drugs and drugs that might influence gastrointestinal motility was discontinued five days before the study. Stationary oesophageal manometry was performed to determine the distance from the nostrils to the lower oesophageal sphincter (LOS). After this, impedance and the pH catheter were introduced transnasally and positioned based on the manometric findings (see below).

Patients were instructed to press the event marker button on the pH datalogger whenever they experienced a symptom suggestive of reflux. The nature and time of onset of their symptoms was written down on a specially designed diary. Patients were instructed to distinguish between regurgitation and heartburn. Regurgitation was defined as the sensation of effortless return of gastric or oesophageal fluid into the mouth or throat, and heartburn was defined as a burning retrosternal sensation. Furthermore, patients were instructed to consume three meals and two beverages with snacks at fixed times during the 24-hour measurement period. The period spend in the supine position was also noted in the diary.

Oesophageal impedance and pH monitoring

For intraluminal impedance monitoring a seven channel impedance catheter was used (Aachen University of Technology, FEMU, Aachen, Germany). This catheter (outer diameter 2.3 mm) enabled recording from seven segments, each recording segment being 2 cm long. The 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 localised LOS. Impedance signals were stored in a portable digital system (Aachen University of Technology, FEMU, Aachen, Germany) using a sample frequency of 200 Hz.[12] Intraluminal pH monitoring was performed with a glass pH electrode (Ingold AG, Urdorf, Switzerland) and data were stored in a separate digital datalogger (Orion, MMS, Enschede, the Netherlands) using a sampling frequency of 2 Hz. The pH glass catheter was positioned 5 cm above the upper border of the LOS. Using a cable that connected the pH datalogger with the impedance datalogger the pH signals were also stored on the impedance datalogger enabling synchronisation.

Data analysis

Analysis of the tracings was performed independently by two experienced investigators. Thereafter, the two investigators conjointly analysed the reflux episodes that were not recognised by both of them. A consensus decision was made on each of these episodes. Signals recorded during consumption of meals and beverages were not taken into account during analysis of the data.

In the analysis of the impedance tracings, gas reflux was defined as a rapid (>3000 Ω/s) and pronounced retrograde moving increase in impedance in at least two consecutive impedance sites.[13] Liquid reflux was defined as a fall in impedance of >40 % of baseline impedance that moved in a retrograde direction in the two distal impedance sites.[11] Mixed liquid-gas reflux was defined as gas reflux occurring during or immediately before liquid reflux. In the subsequent analysis, mixed reflux was considered as liquid reflux with a gas reflux component, and mixed reflux episodes were combined with pure liquid reflux episodes. Gas reflux episodes were analysed separately. For all reflux episodes, the proximal extent of both the gas and liquid component was noted as well as the time needed to reach this proximal sensor, and the ascending velocity of the components of the refluxate was calculated. Clearance time of the volume of the refluxate was defined as the time in seconds from the 40 % drop in impedance until impedance recovered to above this point again, as measured in the impedance segment at the level of the tip of the pH probe.[14]

For each liquid, gas or mixed reflux episode, as observed in the impedance tracings, the change in pH and the nadir pH during the reflux episode was noted. Reflux episodes that caused a change in pH of less than 0.5 units were not unambiguously distinguishable from baseline noise, and these were scored as a pH drop of 0. Reflux episodes were classified as acid when the pH dropped below 4; reflux episodes were classified as weakly acidic when nadir pH was between 7 and 4.[10] Reflux was classified as weakly alkaline reflux when the nadir pH was above 7. For reflux episodes with a nadir pH of less than 4, the acid clearance time was measured, defined as the time during which pH was below 4.[15]

In order to assess the potential sensitising effect of preceding oesophageal acid exposure on symptom perception, the total time with pH below 4 was measured in the 15, 30, 45, 60, 75, and 90 minute time segment preceding the onset of each reflux episode.[16]

Reflux episodes were considered symptomatic if a symptom occurred within the two minute time window starting at the onset of the reflux episode.[17] The time between the onset of the reflux episode and the occurrence of the symptom was measured. Only the symptoms heartburn and regurgitation were evaluated and

other symptoms such as chest pain, belching, coughing, and hoarseness were not taken into account.

Statistical analysis and presentation of data
Analysis was performed on a per subject basis. Comparison of symptomatic and asymptomatic reflux episodes within subjects was performed using the Wilcoxon signed rank test. Comparison of the properties of reflux episodes preceding heartburn and regurgitation was performed using the Wilcoxon rank sum test. Comparisons of proportions were calculated using the Chi^2 test. Relationships between parameters were expressed using the Spearman correlation coefficient. Differences were considered statistically significant when $p \leq 0.05$. Throughout the manuscript data are presented as median (interquartile range).

Results

In the 20 24-hour impedance recordings, median percentage of time with pH <4 was 7.9 (5.3–11.0) %; three patients had physiological acid exposure (time pH <4 less than 6.0 %). A total of 1807 reflux episodes were detected, 728 of which were classified as pure liquid reflux, 426 as pure gas, and 653 as mixed gas-liquid. The majority of reflux episodes occurred while patients were in the upright position (1628 upright v 179 supine). Acid clearance time of the acid reflux events was significantly longer than the volume clearance time of these reflux events (50.0 (24.8–62.8) v 12.3 (10.1–15.3) seconds; $p<0.001$). A total of 301 symptoms were reported. Of these, 203 episodes were associated with a reflux episode (67.4 %), ranging from 3 to 26 in individual patients. There was no relationship between the number of symptoms reported by individual patients and their acid exposure time ($r=0.136$, $p=0.5$).

Upright liquid reflux
In patients in the upright position, 1231 reflux episodes with a liquid component (pure liquid and mixed gas-liquid) occurred. Of these, 189 reflux episodes were associated with a symptom and 1042 were not. Median time interval between the onset of a reflux episode and the onset of the associated symptom was 14.0 (9–30.5) seconds.
Symptomatic liquid reflux episodes were significantly more often acidic (nadir pH<4) than asymptomatic reflux episodes and were more often accompanied by a pH fall of more than 0.5 units or 1.0 unit (Table 1). A gaseous component in the

liquid refluxate (mixed gas-liquid reflux) was present as frequently in asymptomatic as in symptomatic reflux episodes.
As shown in figure 1, median nadir pH was significantly lower and the median pH drop was significantly larger with symptomatic than with asymptomatic reflux episodes, and symptomatic reflux episodes had a significantly higher proximal extent. The ascending velocity of the liquid reflux component was not different between symptomatic and asymptomatic reflux episodes. Median acid clearance time (recovery of pH to 4) as well as volume clearance time (impedance recovery) were significantly longer with symptomatic than with asymptomatic reflux episodes (Figure 2).
Symptomatic reflux episodes were preceded by a significantly higher oesophageal cumulative acid exposure time compared with asymptomatic reflux episodes (Figure 3). The difference in preceding oesophageal acid exposure was apparent for time windows with a length of up to 75 minutes.
Statistically significant but weak relationships were found between the extent of the liquid component of the refluxate and the drop in pH ($r=-0.330$, $p<0.0001$), nadir pH ($r=0.333$, $p<0.0001$), and acid clearance time ($r=-0.108$, $p<0.002$). Acid clearance time did not correlate with pH drop ($r=0.04$, NS) but correlated weakly with nadir pH ($r=-0.215$, $p<0.0001$) and volume clearance ($r=0.127$, $p<0.0001$).

Table 1. Characteristics of liquid reflux episodes

	asymptomatic	symptomatic	p-value
acid (nadir pH < 4)	69 (50-75) %	94 (67-100) %	0.001
fall > 0.5 unit	83 (64-92) %	100 (100-100) %	0.001
fall > 1.0 unit	76 (56-85) %	100 (80-100) %	0.002
gas component	55 (33-67) %	52 (38-75) %	0.6

Values are median (interquartile range)

Table 2. Characteristics of pure gas reflux episodes

	asymptomatic	symptomatic	p-value
pH drop	0.0 (0.0-0.5)	1.3 (0.5-2.8)	0.03
nadir pH	6.2 (5.3-6.4)	4.7 (2.6-6.9)	0.04
proximal extent (cm)	18 (18-18)	18 (15-18)	0.7
ascending velocity (cm/s)	57 (25-90)	37 (17-170)	0.6
acid clearance (s)	10.5 (6.5-21.0)	9.5 (2.2-19.0)	0.6

Values are median (interquartile range)

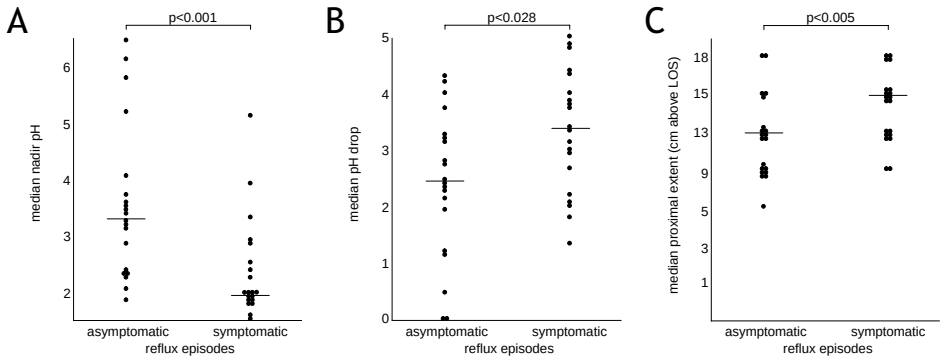

Figure 1. Characteristics of asymptomatic and symptomatic liquid reflux episodes in the upright position in 20 patients with gastro-oesophageal reflux disease. (A) Median nadir pH. (B) Median pH drop. (C) Median extent of the reflux episodes. Horizontal lines indicate group medians. Comparisons were performed using the Wilcoxon signed rank test. LOS, lower oesophageal sphincter.

Upright gas reflux

A total of 397 episodes of pure gas reflux (belches) were identified, 12 of which were symptomatic. These 12 symptomatic gas reflux episodes without a liquid component were found in seven different subjects. Comparison of asymptomatic and symptomatic gas reflux episodes in these seven subjects showed that symptomatic gas reflux episodes were more frequently accompanied by a detectable pH drop (≥0.5 unit) than asymptomatic reflux episodes (100 (67–100) v 63 (21–63) %; p=0.028). A fall in pH of more than 1.0 unit was also more frequently encountered in symptomatic pure gas reflux episodes than in asymptomatic gas reflux episodes (100 (33–100) v 33 (15–47) %; p=0.028). The proportion of reflux episodes that were accompanied by a drop in pH below 4 was not higher in symptomatic than in asymptomatic reflux episodes (33 (0–100) % v 13 (0–41) %; p=0.22). The majority of gas reflux episodes (87.6 %) reached the most proximal impedance segment. Symptomatic gas reflux episodes were associated with a larger drop in pH and a lower nadir pH than asymptomatic gas reflux episodes (Table 2). No differences in ascending velocity of the gaseous refluxate or acid clearance were observed between asymptomatic and symptomatic reflux episodes (Table 2).

Supine reflux

Of the 1381 reflux episodes with a liquid component, only 150 occurred while patients were in the supine position. Both volume and acid clearance of the supine reflux episodes were significantly longer than those of the upright episodes (18 v 14 seconds ($p<0.004$) and 77 v 48 seconds ($p<0.015$)). Only two of the 150 liquid reflux episodes in the supine position were followed by a symptom in the two minute time window after the onset of the reflux episode. Both of these symptomatic reflux episodes were acidic (nadir pH < 4) whereas 91 (60.7 %) of the 148 asymptomatic liquid reflux episodes were acidic. In the supine position, only 29 pure gas reflux episodes occurred, versus 397 in the upright position.

Heartburn versus regurgitation

The 203 symptomatic reflux episodes consisted of 166 episodes of heartburn and 37 episodes of regurgitation. Thirteen patients suffered from both symptoms, one patient suffered from regurgitation only, and six suffered from heartburn only during the measurement period. Table 3 shows the results of comparison of the characteristics of the reflux associated with these two types of symptoms. Reflux episodes inducing regurgitation had a significantly higher proximal extent of the liquid component than episodes inducing heartburn (Table 3). Also, a gaseous component was more often present in reflux episodes preceding regurgitation than in those preceding heartburn (68 v 40 %; $p=0.003$). Other characteristics such as ascending velocity, size of the pH drop, nadir pH, and acid and volume clearance times were not significantly different between these two symptoms.

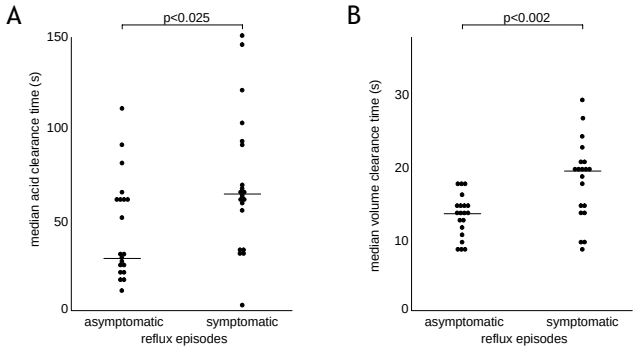

Figure 2. Acid (Left) and volume (Right) clearance times (medians per patient) of asymptomatic and symptomatic liquid reflux episodes

Discussion

The relation between gastro-oesophageal reflux episodes and the conscious perception thereof is complex and despite many studies the mechanisms responsible for the development of reflux symptoms are incompletely understood. This is the first study in which impedance technology was used to investigate the determinants of symptomatic and asymptomatic reflux. Application of this technique made it possible to investigate the role of weakly acidic reflux and gas reflux in symptom generation.

Ambulatory pH studies have shown that the perception of acid reflux episodes (nadir pH < 4) is dependent on the proximal extent of the refluxate, nadir pH reached, and the magnitude of the pH drop.[2-4] Using impedance monitoring, we were able to show that the same factors are important for symptom generation by both acid and weakly acidic reflux and even by gas reflux. The weak correlations between the above mentioned factors indicate that they are largely independent. Determinants of reflux symptoms identified in this study constitute therapeutic targets, and reduction of acidity of the refluxate with a proton pump inhibitor or reduction of the proximal extent of the refluxate with endoscopic therapy can significantly reduce symptoms.[18] Impedance monitoring also made it possible to show that not only acid clearance times but also volume clearance times are significantly longer in symptomatic reflux episodes. Previously, the importance of the volume of the refluxate in symptom generation had been inferred from indirect measures such as proximal extent and acid clearance times but it had never been shown before that symptomatic reflux episodes actually have longer volume clearance times.[19] It has to be pointed out however that volume clearance times also depend on the effectiveness of oesophageal peristalsis. The fact that most symptoms occurred relatively shortly after a reflux episode (median 14 seconds) also suggests that the time that acid is present in the oesophagus is less important for the generation of symptoms than the volume and protonic content of the refluxed material.

Acid clearance time was significantly longer than volume clearance time. This confirms the concept that clearance in the oesophagus starts with peristalsis removing most of the refluxed volume and is followed by acid neutralisation by swallowed saliva.[15]

In a previous study using multiple pH sensors we found that the ascending velocity of the refluxate was higher in healthy volunteers than in GORD patients, suggesting a role for this parameter in the disease, but in this study the

ascending velocity of the refluxate was found not to be a determinant of reflux perception.[20]

The characteristics of reflux episodes not only appear to determine whether or not a reflux episode is perceived but also the nature of the sensation. In particular, the proximal extent of reflux episodes preceding regurgitation was higher than the proximal extent of reflux episodes preceding heartburn. Other parameters such as nadir pH and pH drop were not significantly different between heartburn and regurgitation.

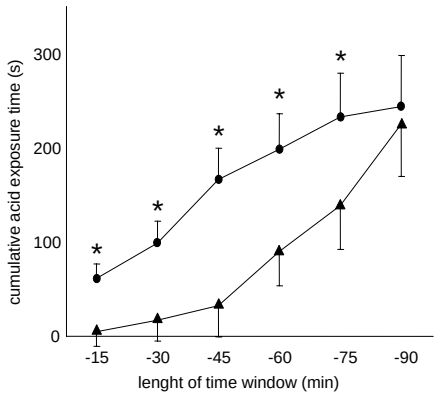

Figure 3. Cumulative acid exposure in the time windows 15–90 minutes duration preceding asymptomatic and symptomatic reflux episodes in the upright position. *p<0.05 (Wilcoxon signed rank test).

Table 3. Characteristics of heartburn and regurgitation

	heartburn	regurgitation	p-value
pH drop	3.5 (1.9-4.4)	2.6 (1.8-4.5)	0.7
nadir pH	2.2 (1.8-3.3)	2.3 (1.9-3.2)	0.7
proximal extent (cm)	11 (9-15)	15 (11-18)	0.002
ascending velocity (cm/s)	5.0 (3.3-9.2)	6.0 (3.2-8.8)	0.9
volume clearance (s)	13 (8-21)	11 (8-18)	0.4
acid clearance (s)	57 (30-120)	60 (30-100)	0.9

Values are median (interquartile range)

The vast majority (85.2 %) of the liquid reflux related symptoms occurred after an acid reflux episode (pH<4) and only 14.8 % were associated with weakly acidic reflux (pH between 4 and 7). This finding and the observation that the magnitude of the pH drop and nadir pH are important for symptom generation indicate that

weakly acidic reflux is not a very important cause of typical reflux symptoms in patients who do not take acid suppressive drugs. Performing symptom association analysis with and without inclusion of weakly acidic reflux episodes in a larger group of patients can determine whether or not a subgroup of patients exists in whom weakly acidic reflux causes typical reflux symptoms. A larger contribution of weakly acidic reflux and weakly alkaline reflux is more likely to occur in patients with reflux symptoms after gastrectomy. For evaluation of symptoms of chronic cough and acid suppression resistant symptoms, it has already been shown that the combination of impedance and pH monitoring is more useful than pH monitoring alone.[7,21] Impedance measurements also provide information about the proximal extent of reflux episodes, an important factor in symptom generation which is not provided by routine pH-metry.

The results of several studies suggest that the sensitivity of the oesophagus for acid is dependent on the preceding acid exposure. Various studies showed that oesophageal sensitivity, defined as the inverse of time to onset of pain after acid infusion, decreases after acid suppression with cimetidine or famotidine.[5,22,23] Furthermore, after a 30 day course of omeprazole 60 mg there was a 35 % reduction in intensity scores during an acid perfusion test.[6] Conversely, a study in healthy volunteers showed an increase in oesophageal perception of acid after preceding perfusion of the oesophagus with acid.[24] These observations prompted the hypothesis that oesophageal acid exposure leads to sensitisation for subsequent reflux episodes. In other words, the chance that a reflux episode is perceived would be dependent on acid exposure during the preceding period.[16] Some evidence for this phenomenon was provided by a study by Beedassy et al. in which time periods preceding symptomatic and asymptomatic reflux episodes were compared.[25] However, in Beedassy's study, reflux episodes recorded from different subjects were pooled, which can yield misleading results, as patients with higher oesophageal acid exposure times are more likely to have more symptomatic reflux episodes. Comparison of symptomatic and asymptomatic reflux episodes in a per subject analysis is therefore more appropriate than pooled data analysis. The results of our analysis indicate that acid exposure in the 75 minute period preceding a reflux episode is a determinant of whether or not a subsequent reflux episode will be perceived as a symptom.

Surprisingly, some reflux symptom episodes (heartburn, regurgitation) were induced by pure gas reflux. This is the first study to report that symptoms, other than belching, can be elicited by gastro-oesophageal reflux without a liquid component. Oesophageal distension by the refluxed gas might play a role. It has been reported that balloon distension of the oesophagus may induce symptoms of

heartburn and chest pain.[26,27] Another possibility is that very small droplets of acid (''acid vapour'') accompany the refluxing gas. Many of the pure gas reflux episodes were accompanied by a drop in pH. This phenomenon was previously observed in studies using impedance measurements and high frequency intraluminal ultrasound of the oesophagus.[13,28,29] Our finding that symptomatic gas reflux episodes are accompanied by a significantly larger pH drop compared with asymptomatic gas reflux episodes supports the concept that minute amounts of acid can induce a sensation of heartburn.[30] Theoretically, a third explanation could be that the fluid component of the refluxate is not detected by the impedance technique because the liquid volume is too small. However, validation studies have shown that the impedance technique is very sensitive for the detection of even small volumes of liquid materials and therefore this explanation does not seem very likely.[8,31]

Reflux episodes in the supine position occurred much less frequently but lasted significantly longer than upright reflux episodes (both acid and volume clearance time were longer). Reduced saliva production during sleep and the absence of primary peristalsis are likely to be the cause.[32] Notwithstanding the prolonged duration of reflux episodes during the night, nocturnal heartburn was very rare in our study, with only two symptoms observed. Arousal seems to be a more frequent complaint caused by nocturnal reflux.[32] It is important to realise that although differences between symptomatic and asymptomatic reflux episodes were found in this study, considerable overlap in the properties of symptomatic and asymptomatic reflux episodes is present. Hence, in individual patients, even proximally extending reflux episodes with a longlasting large pH drop may go unnoticed. It is therefore not possible to establish thresholds for the duration, pH drop, or proximal extent above which reflux episodes would consistently provoke symptoms. As noted previously, while we showed that, on average, weakly acidic reflux does not play a major role in symptom elicitation, it can be important in a subgroup of patients.

In conclusion, this study used impedance technology to show that whether or not a reflux episode is perceived as a symptom is determined by the proximal extent of the refluxate, nadir pH, magnitude of the drop in pH, as well as by volume and acid clearance time. Reflux episodes inducing regurgitation have a more proximal extent than episodes inducing heartburn. Furthermore, this study has provided further evidence of sensitisation of the oesophagus by preceding acid exposure. Weakly acidic reflux (pH between 4 and 7) is responsible for a minority of symptoms only. Acidic gas reflux without a liquid component or ''acid vapour'' can be perceived as heartburn and regurgitation.

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Characteristics of gastroesophageal reflux in patients with and without excessive gastroesophageal acid exposure

A.J. Bredenoord
B.L.A.M. Weusten
R. Timmer
A.J.P.M. Smout

Dept. of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands
Gastrointestinal Research Unit, University Medical Center, Utrecht, The Netherlands

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Abstract

In some patients with a physiological esophageal acid exposure an association between reflux episodes and symptoms can be demonstrated. Besides acidity other factors such as proximal extent may determine whether a reflux episode is perceived or not. We aimed to investigate the reflux profile of GERD patients with physiological acid exposure. Methods: 24-h impedance-pH monitoring was performed in 14 GERD patients with excessive acid exposure (pH+), 14 GERD patients with physiological acid exposure (pH-) and 14 controls. All patients had a positive symptom-reflux association during 24-hour monitoring (SAP+). Results: The incidence of acid reflux episodes in pH- SAP+ patients (25.5 ± 4.9) and controls (20.2 ± 3.9) was comparable but lower than in pH+ SAP+ patients (69.8 ± 7.3). However, no differences in number of weakly acidic reflux episodes were observed between pH- SAP+ patients, pH+ SAP+ patients and controls (27.2 ± 3.8 vs 26.8 ± 4.6 and 21.0 ± 3.7, respectively). The proportion of reflux episodes that reached the proximal esophagus was significantly higher in the pH+ SAP+ (33.5 %) and pH- SAP+ (36.0 %) patients than in the controls (19.5 %). Volume clearance time was longer in pH+ SAP+ (12.5 (12.5-17.0) s) compared to pH- SAP+ patients (12.0 (11.0-16.5) s) and controls (9.5 (10.0-12.5) s)($p<0.05$). Acid clearance time was also longer in pH+ SAP+ patients (55.0 (32.0-64.0) s) compared to the pH- SAP+ (16.5 (11.4-40.0) s) and controls (14 (12.0-19.1) s)($p<0.01$). Conclusions: In pH- SAP+ patients a higher proportion of reflux episodes reach the proximal esophagus than in controls. This can in part explain their symptoms.

Introduction

Ambulatory 24-hour esophageal pH monitoring is a technique that is widely used for the investigation and diagnosis of patients with suspected gastroesophageal reflux disease (GERD). The technique provides quantitative information on esophageal acid exposure. In addition, 24-hour pH monitoring makes it possible to assess the temporal relationship between symptoms and reflux episodes. Various indices have been developed to express this relationship numerically, the most robust of these being the symptom association probability (SAP).[1] A positive diagnose of GERD can be confidently made in patients who have both an excessive esophageal acid exposure and a positive SAP, but not all patients exhibit both abnormalities. In a subgroup of patients with reflux symptoms a normal, physiological, esophageal acid exposure is found in combination with a positive SAP. Using the Rome II criteria this condition should be labeled as functional heartburn.[2,3] Since these patients have similar symptoms and a similar response to anti-secretory therapy as other reflux disease patients they will be classified under GERD by the soon to be published Rome III criteria.[4]

It has been shown that these patients with a positive relationship between symptoms and reflux episodes but physiological esophageal acid exposure have a lower sensory threshold to esophageal acid perfusion and balloon distention suggesting that their symptoms result from a heightened perception of physiological reflux events.[5-7] The condition can therefore be referred to as hypersensitive esophagus.

On the other hand, besides hypersensitivity other pathophysiological factors might play a role in this group. In patients with GERD a higher proportion of reflux episodes reaches the proximal esophagus compared to controls.[8,9] It has been shown that the proximal extent of the refluxate is an important determinant of whether or not a reflux episode is symptomatic.[10,11] The proximal extent of reflux episodes has never been studied in patients with a physiological distal esophageal acid exposure (pH-) and a positive SAP. Furthermore, weakly acidic reflux episodes (nadir pH above 4) do not contribute to esophageal acid exposure time but can trigger symptoms.[12] With multi-channel esophageal impedance monitoring both acidic and weakly acidic reflux episodes can be detected and the proximal extent of these episodes can be measured.[13] This technique detects at least 95% of all reflux episodes and was found to be well reproducible.[14,15]

The aim of this study was therefore to investigate the spatiotemporal characteristics of weakly acidic and acidic reflux episodes in pH- SAP+ patients

and compare these to GERD patients with an excessive acid exposure and a positive SAP+ (pH+ SAP+) and healthy controls.

Methods

Subjects

We analyzed pH-impedance tracings obtained from 14 healthy volunteers (5 men: mean age 37 years, range 23-52 years), 14 pH+ GERD patients (8 men: mean age 46 years, range 26-64 years) and 14 pH- GERD patients (6 men: mean age 42 years, range 27-59 years). All patients suffered from typical reflux symptoms (heartburn, regurgitation and chest pain). The two subgroups of GERD patients were consecutive patients referred to our departments for 24-hour esophageal pH-impedance monitoring who fulfilled the criterion that their symptoms were associated with acid reflux episodes as demonstrated by a positive SAP (≥ 95.0 %).[1] Excessive esophageal acid exposure was defined as time with pH<4 ≥ 6.0 %, based on normal values that were obtained in the motility lab of our department.[16] Thus, one group of patients had an esophageal acid exposure of ≥ 6.0 % and a positive SAP (pH+ SAP+) and the other group of patients had an esophageal acid exposure < 6.0 % and a positive SAP (pH- SAP+). Written informed consent was obtained from all subjects and the protocol was approved by the medical ethical committees of the University Medical Center Utrecht and the St Antonius Hospital Nieuwegein, the Netherlands.

Study protocol

The use of gastric acid-inhibitory drugs and drugs that might influence gastrointestinal motility was discontinued 5 days before the study. Stationary esophageal manometry was performed to determine the distance from the nostrils to lower esophageal sphincter (LES). Thereafter, the impedance and the pH catheter were introduced transnasally and positioned based on the manometric findings (see below).

During the 24-hour study the patients were instructed to press the event marker button on the pH datalogger whenever they experienced a symptom suggestive of reflux. The nature and time of onset of these symptoms had to be written down in a specially designed diary. Furthermore, patients were instructed to consume 3 meals and 2 beverages at fixed times during the 24-hour measurement period. The period spent in supine position was also noted in the diary.

Intraluminal impedance and pH monitoring

For intraluminal impedance monitoring a 7-channel impedance catheter was used (Aachen University of Technology, FEMU, Aachen, Germany). This catheter (outer diameter 2.3 mm) enabled recording from 7 segments, each recording segment being 2 cm long. The 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 localized LES. Impedance signals were stored in a digital system (Aachen University of Technology, FEMU, Aachen, Germany) using a sample frequency of 50 Hz.[17] Intraluminal pH monitoring was performed with a glass pH electrode (Ingold A.G., Urdorf, Switzerland) and data were stored in a digital datalogger (Orion, MMS, Enschede, the Netherlands) using a sampling frequency of 2 Hz. The pH glass catheter was positioned 5 cm above the upper border of the LES. Using a cable that connected the pH datalogger with the impedance datalogger the pH signals were stored on both dataloggers to enable synchronization.

Data analysis

In the analysis of the impedance tracings, gas reflux was defined as a rapid (>3000 Ω/s) and pronounced retrograde moving increase in impedance in at least two consecutive impedance sites.[18] Liquid reflux was defined as a fall in impedance of ≥ 40% of baseline impedance that moved in retrograde direction in the two distal impedance sites.[19] Mixed liquid-gas reflux was defined as gas reflux occurring during or immediately before liquid reflux. Liquid and mixed reflux episodes were classified as acidic when the pH dropped below 4; reflux episodes were classified as weakly acidic when nadir pH was between 7 and 4.[20] Weakly alkaline reflux was defined as liquid or mixed reflux with a nadir pH above 7. In the analysis, the periods of meal consumption were disregarded.

Reflux episodes were considered to have reached the proximal esophagus when they had a proximal extent of more than 15 cm above the LES. Reflux episodes were considered distal reflux episodes when the proximal spread was not higher than 5 cm above the LES. Reflux profile in subjects was classified as abnormally proximal spreading when more than 39 percent of the reflux episodes reached the proximal esophagus.[21]

Statistical analysis and presentation of data

Comparisons of parametric data were performed using one-way ANOVA followed by post-hoc analysis using the Student-Newman-Keuls test. Comparisons of nonparametric data were performed using the Wilcoxon Rank sum test. Differences were considered statistically significant when $p \leq 0.05$. Throughout the

manuscript parametric data are presented as mean ± SEM and nonparametric data as median (interquartile range).
Sample size was set to 14 in order to adequately power this study to detect a two-sided 50 % difference in number of proximal reflux episodes between pH-SAP+ patients and controls. Alpha was set to 5 % and beta to 80 %.

Results

As expected, esophageal acid exposure was significantly higher in the pH+ SAP+ patients (9.8 %) than in the pH- SAP+ patients (3.5 %) and in the controls (2.9 %). pH+ SAP+ patients also had significantly higher numbers of liquid and mixed (liquid-gas) reflux episodes compared to the pH- and control group (Figure 1). No differences were found in the incidence of pure gas reflux (Figure 1). The pH+ SAP+ patients had a statistically significant higher total number of reflux episodes (97.6 ± 8.4) than the pH- patients (53.7 ± 5.1) and the controls (42.2 ± 4.5), mainly because the incidence of acid reflux episodes was higher in the pH+ patients (Figure 2). No statistically significant differences were observed in the number of weakly acidic and weakly alkaline reflux episodes (Figure 2). The proportion of liquid and mixed reflux episodes that was acidic was significantly higher in pH+ patients (71.2 %) compared to controls (47.5 %) and pH- patients (45.6 %).
Both in the pH+ SAP+ and in the pH- SAP+ patients a higher number of reflux episodes reached the proximal esophagus (32.7 ± 6.2 and 19.3 ± 2.8 respectively) compared to the controls (8.2 ± 1.5, $p<0.05$), although there was a considerable overlap between all groups. Likewise, the proportion of reflux episodes that reached the proximal esophagus was higher in the pH+ SAP+ (33.5 %) and pH-SAP+ (36.0 %) patients compared to the controls (19.5 %, $p<0.05$) (Figure 3). The number of reflux episodes reaching the mid-esophagus was larger in the pH+ SAP+ patients (55.8 ± 8.1) than in the pH- SAP+ patients (27.0 ± 4.1) and the controls (25.6 ± 2.9). The number of distal reflux episodes was similar in the pH+ (9.1 ± 2.8) and pH- patients (7.4 ± 1.9) and the controls (8.4 ± 1.3). The proportion of distal reflux episodes was significantly higher in the controls compared to the pH+ SAP+ and pH- SAP+ patients (19.9 % vs 13.8 % and 9.3 %, respectively, $p<0.05$). Of the 158 symptomatic reflux episodes in the pH+ patients 58 (36.7 %) were due to reflux episodes that reached the proximal esophagus, 86 (54.4 %) were due to reflux episodes that reached the mid-esophagus and 14 (8.8 %) were due to reflux episodes that reached the distal

esophagus. Of the 55 symptomatic reflux episodes in the pH- SAP+ patients, 27 (49.1 %) were due to reflux episodes that reached the proximal esophagus, 23 (41.8 %) were due to reflux episodes that reached the mid-esophagus and 5 (9.1 %) were due to reflux episodes that reached the distal esophagus. Thus, in the pH+ SAP+ patients, 14.5 % of the proximal reflux episodes, 11.0 % of the mid-esophageal reflux episodes and 10.6 % of the distal reflux episodes are symptomatic, the differences being not statistically significant. In the pH- SAP+ patients a statistically significantly higher proportion of proximal reflux episodes was symptomatic compared to the proportions of mid-esophageal and distal reflux episodes that were symptomatic (15.1 % vs 6.1 % and 4.9 %, $p<0.05$). Compared to normal values obtained in a large cohort of healthy subjects, 7 pH+ SAP+ and 7 pH- SAP+ patients had a higher than normal total number of proximal reflux episodes.

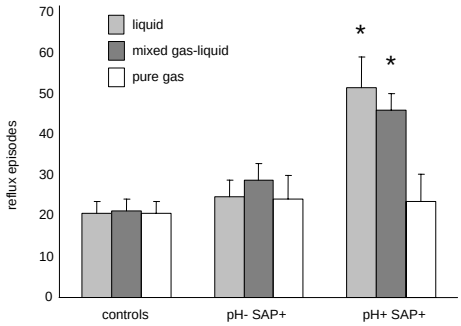

Figure 1. Number of liquid, mixed gas-liquid and pure gas reflux episodes during 24-hour study in controls, GERD patients with physiological esophageal acid exposure (pH- SAP+) and GERD patients with excessive esophageal acid exposure (pH+ SAP+). * : $p<0.05$ vs other groups

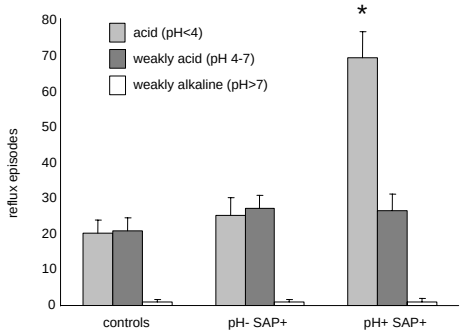

Figure 2. Number of acid and weakly acidic reflux episodes (in 24-hour study) in controls, GERD patients with physiological esophageal acid exposure (pH- SAP+) and GERD patients with excessive acid exposure (pH+ SAP+). * : $p<0.05$ vs other groups

The mean magnitude of the drop in pH was higher in the pH+ SAP+ patients (2.8 (2.4-3.8)) compared to the controls (2.1 (1.0-2.9)) and the pH- SAP+ patients (2.2 (1.0-3.5))($p<0.05$). Likewise, the nadir pH during reflux episodes was lower in pH+ SAP+ patients (2.9 (2.2-3.2)) compared to the controls (4.1 (3.6-5.2)) and the pH- SAP+ patients (3.9 (2.9-4.9))($p<0.05$). The pH+ SAP+ also had a significantly longer volume clearance time (12.5 (12.5-17.0) s) compared to the

pH- SAP+ patients (12.0 (11.0-16.5) s) and controls (9.5 (10.0-12.5) s)($p<0.05$). The acid clearance time was also significantly longer in pH+ SAP+ patients (55.0 (32.0-64.0) s) compared to the pH- SAP+ patients (16.5 (11.4-40.0) s) and controls (14 (12.0-19.1) s)($p<0.01$).
Symptomatic reflux episodes had a significantly longer acid clearance time in both pH+ SAP+ patients (56 (25-110) s) and pH- SAP+ patients (50 (18-82) s) compared to asymptomatic reflux episodes in pH+ SAP+ (40 (11-90) s) and pH- SAP+ patients (15 (7-60) s)($p<0.05$). Likewise, symptomatic reflux episodes had a longer volume clearance time in both pH+ SAP+ (15 (10-23) s) and pH- SAP+ patients (14 (10-20) s) compared to asymptomatic reflux episodes in pH+ SAP+ (13 (9-20) s) and pH- SAP+ patients (12 (9-15) s)($p<0.05$).

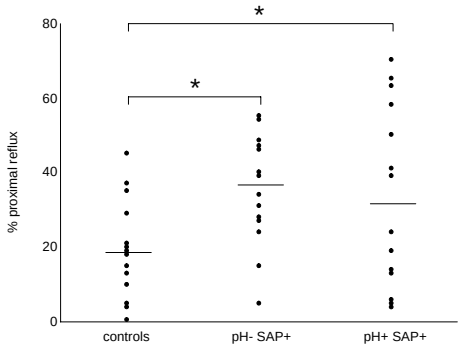

Figure 3. Proportion of reflux episodes reaching the most proximal impedance segment in controls, GERD patients with physiological esophageal acid exposure (pH-SAP+) and GERD patients with excessive esophageal acid exposure (pH+ SAP+).
* : $p<0.05$ vs controls

Discussion

It has previously been shown that patients with a physiological esophageal acid exposure and a positive relationship between symptoms and reflux episodes (pH-SAP+) are more sensitive to esophageal acid perfusion and balloon distention.[6,7] It thus seems that in these patients the symptoms result from esophageal hypersensitivity to physiological events. Characteristics of reflux episodes such as proximal extent and volume of the refluxate have never been investigated in pH-SAP+ patients. These and other factors determine whether a reflux episode becomes symptomatic or not.[11] The most important finding of our study is that pH- SAP+ patients have a proportionally higher number of proximal reflux episodes compared to controls. We found that the percentage of proximal reflux episodes of pH- SAP+ patients (36.0 %) is similar to that of pH+ SAP+ patients (33.5 %) and much higher than that of healthy subjects (19.5 %). Furthermore,

compared to normal values obtained in a large cohort of healthy subjects, in our study half of the pH+ SAP+ and pH- SAP+ patients had an abnormally high number of proximal spreading reflux episodes, compared to only 1 of the 14 healthy controls.[21]

Gastroesophageal reflux episodes in GERD patients with physiological distal esophageal acid exposure are thus not entirely "physiological" and exhibit similarities with reflux episodes in other GERD patients. Until today patients with reflux symptoms and a physiological acid exposure are classified as functional heartburn.[3] In the Rome III consensus report that is currently in preparation patients with reflux symptoms and a physiological distal esophageal acid exposure will be categorized on the basis of the result of symptom association analysis.[4] Those with a positive association will be classified as GERD, and patients in whom the relation between symptoms and reflux episodes can not be established remain to be classified as functional heartburn. Recently, by using double-probe pH monitoring Cicala et al. have shown that both patients with erosive and non-erosive reflux disease had a higher incidence of proximal reflux episodes compared to controls. However, in their study patients were not stratified based on symptom association analysis.[22] The results of our study support the classification of patients with a positive SAP under GERD, irrespective of distal esophageal acid exposure, as features of their reflux profile resemble that of other patients with GERD. An important additional argument is that patients with physiological acid exposure but a positive relationship between symptoms and reflux events show a better response to acid suppressive therapy than those with no relationship between symptoms and reflux events.[23] The SAP seems to be a reliable predictor of the success of both medical and surgical therapy for GERD.[24,25] Furthermore, patients with physiological acid exposure and a negative symptom-reflux association have been shown to score higher on anxiety and hysteria questionnaires than those with a positive symptom-reflux association.[26] Thus, in patients with a positive reflux-symptom association the symptoms appear to originate from the combination of esophageal hypersensitivity and proximally spreading reflux episodes while in patients with a negative symptom-reflux association the origin of their symptoms is less clear. These observations lend support to the decision to classify only the first group as GERD in the new Rome classification.

Proximal extent of reflux episodes is influenced by various factors such as esophageal tone, viscosity of the refluxate, gastroesophageal pressure gradient and compliance of the gastroesophageal junction.[27-29] Furthermore, differences in proximal extent were observed between ambulatory and stationary

conditions.[30] Several of these factors have been shown to play a role in the pathophysiology of GERD. It is not clear which of these mechanisms cause the abnormal number of proximal reflux episodes in patients with a hypersensitive esophagus.

Various reports thus suggest that the proximal extent of reflux episodes is an important determinant of whether a reflux episode is perceived or not.[10,11,22] In this study we observed that pH- SAP+ patients have more proximal reflux episodes compared to controls and we suggest that these are in part responsible for the symptoms of these patients. Previously, it has been observed that treatment with the Gatekeeper, an endoscopic antireflux procedure, decreases both proximal extent of reflux episodes and reduces symptoms.[31] It is interesting to speculate whether the relationship between symptom reduction and reduction of proximal extent was a causal one. Future studies will determine whether agents that increase the viscosity of gastric contents are also able to decrease proximal extent of reflux episodes and to reduce symptoms.

It is not surprising that pH+ SAP+ patients have more acid reflux episodes compared to the controls and pH- SAP+ patients, as the patients were classified based on their esophageal acid exposure in this study. However, the number of weakly acidic reflux episodes was similar in all groups and the excess of reflux episodes found in the patients with GERD was thus mainly because of the large number of acid reflux episodes, which confirms the findings made in a recent study using 24-hour pH-impedance.[19] The authors of that study concluded that the observed differences between patients and controls might be explained by differences in gastric acid distribution.

In conclusion, we have shown that in patients with a physiological esophageal acid exposure and a positive relationship between symptoms and reflux events (pH- SAP+) a higher proportion of the reflux episodes reached the proximal esophagus. We hypothesize that the symptoms in these patients result from a combination of hypersensitivity and an increased proximal spread of reflux episodes.

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Part IV

Belching and gas reflux

14

Aerophagia, gastric, and supragastric belching: a study using intraluminal electrical impedance monitoring

A.J. Bredenoord
B.L.A.M. Weusten
D. Sifrim
R. Timmer
A.J.P.M. Smout

Dept. of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands
Center for Gastroenterology Research, Catholic University of Leuven, Leuven, Belgium
Gastrointestinal Research Unit, University Medical Center, Utrecht, The Netherlands

Gut 2004;53:1561–5.

Abstract

Background: Patients with aerophagia are believed to have excessive belches due to air swallowing. Intraluminal impedance monitoring has made it possible to investigate the validity of this concept. Methods: The authors measured oesophageal pH and electrical impedance before and after a meal in 14 patients with excessive belching and 14 healthy controls and identified patterns of air transport through the oesophagus. The size of the gastric air bubble was measured radiographically. In four patients prolonged oesophageal manometry was performed simultaneously. Results: In all subjects, impedance tracings showed that a significant amount of air is propulsed in front of about a third of the swallow induced peristaltic waves. Two types of retrograde gas flow through the oesophagus (belch) were observed. In the first type air flowed from the stomach through the oesophagus in oral direction ("gastric belch"). In the second type air entered the oesophagus rapidly from proximal and was expulsed almost immediately in oral direction ("supragastric belch"). The incidence of air-containing swallows and gastric belches was similar in patients and controls but supragastric belches occurred exclusively in patients. There was no evidence of lower oesophageal sphincter relaxation during supragastric belches. Gastric air bubble size was not different between the two groups. Conclusions: In patients with excessive belching the incidence of gaseous reflux from stomach to oesophagus is similar to that in healthy subjects. Their excess belching activity follows a distinct pattern, characterised by rapid antegrade and retrograde flow of air in the oesophagus that does not reach the stomach.

Introduction

Air swallowing during eating and drinking is a normal physiological event: in a study in healthy subjects, swallowing a 10 ml liquid bolus was found to be accompanied by ingestion of 8–32 ml of air.[1] In the upright position ingested air will accumulate in the proximal stomach. It has been shown that distention of the proximal stomach elicits transient relaxations of the lower oesophageal sphincter (LOS) allowing the ingested air to be vented.[2-6] Ingestion of drinks containing carbon dioxide provokes belching through the same mechanism.[7,8] Once the air has passed the LOS and entered the oesophageal body, oesophageal distention leads to upper oesophageal sphincter relaxation, enabling gas to escape to the pharynx.[9,10]

Postprandial belching is normal, with three to four belches per hour occurring with a normal diet. Belching is a common symptom in patients with gastro-oesophageal reflux disease and functional dyspepsia but can also occur as an isolated symptom.[11] In many patients with troublesome repetitive belching the eructation appears to be the result of a behavioural disorder in which excessive air swallowing is the primary event. This poorly defined disease entity is referred to as aerophagia. Until recently, technical limitations stood in the way of an adequate analysis of the events associated with belching and aerophagia. With the advent of the intraluminal impedance recording technique, it has become possible to monitor the passage of air through the oesophagus, either in aboral or oral direction.[12,13]

The aim of this study was to investigate whether patients with frequent belching indeed swallow excessive amounts of air which leads to gastric distention and gaseous gastro-oesophago-pharyngeal reflux.

Methods

Subjects

We studied 14 healthy volunteers (eight males; mean age 32.8 years, range 23–46 years) and 14 patients (eight males; mean age 57.7 years, range 28–75 years) with complaints of excessive belching. Extensive diagnostic testing in the patients revealed no organic abnormalities. Written informed consent was obtained from all subjects and the protocol was approved by the medical ethics committees of the University Medical Center Utrecht and the Catholic University of Leuven.

Study protocol

After an overnight fast, radiographs of the upper abdomen were made in anteroposterior and lateral orientation while subjects were standing. Thereafter a routine oesophageal manometry was performed to determine the distance from nostrils to the LOS. After the manometry, the impedance catheter and the pH catheter were introduced transnasally and positioned based on the manometric findings (see below). In four of the 14 patients with excessive belching we also introduced a manometric catheter and this catheter recorded pressures for the duration of the study. Subjects were in an upright position and after an adaptation period of at least 10 minutes, recording was started and subjects were asked to minimise head movements and to breathe normally. Patients were asked to press the event marker button on the datalogger every time they had an audible belch. After 45 minutes of continuous recording a standardised meal was consumed consisting of a hamburger (McDonald's Quarter Pounder), 20 grams of fresh onions, 44 grams of chips, and 475 ml of orange juice (in total 967 kCal). The meal had to be finished in 30 minutes. Postprandially, radiographic images were taken in anteroposterior and lateral direction with the subject in upright position. A postprandial recording period of 90 minutes completed the protocol.

Impedance and pH monitoring

For impedance monitoring a seven channel impedance catheter was used (Aachen University of Technology, FEMU, Aachen, Germany). This catheter (outer diameter 2.3 mm) enabled recording from seven segments, each recording segment being 2 cm long. The 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 LOS (Figure 1). Impedance signals were stored in a digital system (Aachen University of Technology, FEMU, Aachen, Germany) with a sampling frequency of 1000 Hz. Intraluminal pH monitoring was performed with a catheter with a glass pH electrode (Ingold AG, Urdorf, Switzerland) and data were stored in a digital datalogger (Orion, MMS, Enschede, the Netherlands) using a sampling frequency of 1 Hz. The pH glass catheter was positioned 5 cm above the manometrical upper border of the LOS.

Manometry

An 18 channel water perfused silicone rubber catheter (outer diameter 4.0 mm, length 75 cm, channel diameter 0.4 mm) was used for manometry. Pressures were recorded from four pharyngeal sideholes, four oesophageal sideholes, a sleeve sensor, and a gastric sidehole. This manometric assembly was positioned

in such a way that the sleeve sensor membrane straddled the entire LOS (Figure 1). All channels were perfused with degassed water at a rate of 0.08 ml/min using a pneumohydraulic perfusion system (Dentsleeve Pty Ltd, Wayville, South Australia).
Pressures were recorded with external pressure transducers (Abbott, Sligo, Ireland) and were stored 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.

Data analysis
The size of the gastric air bubble was measured from the anteroposterior and lateral radiographs using transparent millimeter blocked paper. The projection of the impedance catheter was used as a reference for actual size. In the impedance signals reflux episodes were identified and classified as liquid, gas, or mixed liquid-gas reflux based on previously described criteria.[12] Furthermore, using the pH tracings, liquid reflux, and mixed liquid-gas reflux were classified as acidic or non-acidic, using a threshold of pH=4. Percentage of time with pH<4 was calculated using commercially available software (MMS, Enschede, the Netherlands). The period of meal consumption was not taken into account for analysis.

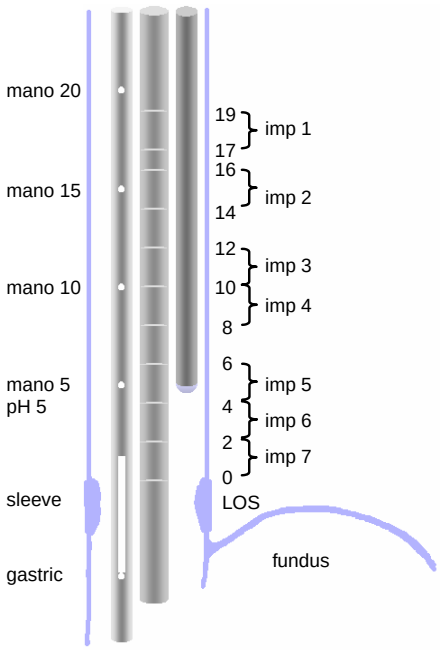

Figure 1. Schematic representation of pH, manometric, and impedancometric assemblies used in this study. From left to right: manometric, impedance, and pH catheter.

Statistical analysis and presentation of data

Pearson's test was used to calculate the degree of correlation between gastric air bubble size in anterior and lateral projection. Differences between healthy volunteers and patients were compared using the t test and the Mann-Whitney test for parametric and non-parametric data respectively. The Wilcoxon test was used for comparisons between number of belches before and after the meal. Differences were considered statistically significant when $p \leq 0.05$) Throughout the manuscript data are presented as mean ± SEM.

Results

Gastric air bubble surface areas measured radiographically in anteroposterior and in lateral projection correlated extremely well ($p<0.001$, $r=0.978$). There were no differences between gastric air bubble size in healthy volunteers and patients with excessive belching (Table 1). Furthermore, there were no differences in the number of liquid and mixed reflux events between healthy controls and patients (Table 1). Results of pH metric studies were also comparable between the two groups (Table 1).

Table 1. Radiographic, impedancometric, and pH metric data in controls and patients

	Controls	Patients
Air bubble size AP fasting (cm^2)	11.5 ± 1.3	14.0 ± 5.4
Air bubble size L fasting (cm^2)	9.9 ± 3.5	18.3 ± 9.1
Air bubble size AP postprandial (cm^2)	11.9 ± 1.7	10.5 ± 2.9
Air bubble size L postprandial (cm^2)	11.0 ± 1.3	12.5 ± 3.4
Number of swallows fasting / h	79.5 ± 8.5	70.0 ± 14.5
Number of air swallows fasting / h	21.5 ± 3.4	30.4 ± 9.4
Number of liquid reflux fasting / h	0.6 ± 0.4	0.9 ± 0.4
Number of gas reflux fasting / h	4.7 ± 1.0	4.4 ± 0.8
Number of mixed reflux fasting / h	0.8 ± 0.3	3.4 ± 2.8
Number of swallows postprandial / h	64.2 ± 6.1	49.5 ± 5.9
Number of air swallows postprandial / h	24.4 ± 2.8	21.8 ± 5.8
Number of liquid reflux postprandial / h	1.8 ± 0.4	1.8 ± 0.4
Number of gas reflux postprandial / h	3.0 ± 0.6	3.7 ± 0.8
Number of mixed reflux postprandial / h	4.2 ± 0.7	6.2 ± 3.1
Number of episodes with pH < 4	5.6 ± 1.2	3.0 ± 1.4
% of time with pH < 4	6.0 ± 2.3	4.3 ± 2.0

Radiographs were taken in anteroposterior (AP) and lateral (L) direction. Differences between controls and patients are not statistically significant.

The rates of swallowing were similar in patients and controls, both before and after the meal (Table 1). In approximately one third of the total number of swallows, a significant amount of air (impedance increase of >1000 Ω) preceded

the liquid bolus and moved from proximal to distal in the oesophagus (Figure 2). The incidence of air swallowing was similar in healthy controls and in patients. Two types of retrograde air/gas flow were observed. The first type was characterised by a rapid increase in impedance that moved from distal to proximal (Figure 3A), representing gas reflux from the stomach. The frequency of this pattern was similar between patients and controls. The second type was characterised by a very rapid increase in impedance that moved from proximal to distal, followed by a retrograde decrease in impedance to baseline (Figure 3B). This pattern was only observed in patients and not in controls and corresponded in time with the belches as indicated by the patients with the event marker. None of these belches was accompanied by impedancometric evidence of gastro-oesophageal reflux or venting of air from the stomach.

The second belch pattern differed from the pattern of air swallowing in that the increase in impedance was not moving at the velocity of a peristaltic wave but much faster (1.37 ± 0.19 m/s) and in that the sudden increase of impedance moving in antegrade direction was followed by a decrease moving in retrograde direction. In 13.5 % of cases the initial increase of impedance was followed by a peristaltic wave, obscuring the retrograde decrease. In 83.9 ± 2.3 % of the supragastric belches the air reached the most distal impedance sensor. The average rate of belching was 40.9 ± 15.2 per hour before the meal and 67.7 ± 23.8 per hour after the meal, the difference not being statistically significant.

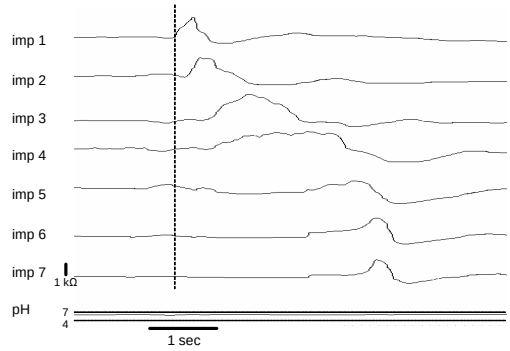

Figure 2. Air swallowing. Air (high impedance) is propulsed in front of a bolus (low impedance) and moves aborally.

Manometry was performed concomitantly in four aerophagia patients. None of the supragastric belches was accompanied by a common cavity phenomenon or LOS relaxation. Instead, manometry revealed two distinct patterns. In 43.8 % of the supragastric belches an initial decrease in oesophageal pressure preceded the increase in impedance. Invariably, this was followed by a pressure rise in all channels, including the intragastric channel (Figure 4). In 42.0 % of the

supragastric belches a pharyngeal contraction could be recognised that preceded the increase in impedance and the simultaneous pressure increase in all channels (Figure 5). After the pressure increase, when pressure reached baseline pressure, the rapid retrograde decrease in impedance occurred. In 10.9 % of the supragastric belches both a pharyngeal contraction and a decrease in oesophageal pressure were observed. In the remaining few supragastric belches manometric tracings were not interpretable.

Discussion

Excessive belching is often thought to result from aerophagia: swallowing of air too frequently or in too large quantities. In the Rome II consensus aerophagia is described as a repetitive pattern of swallowing or ingesting air and belching, usually an unconscious act unrelated to meals, and presumably a learned habit.[14] Despite the fact that almost every gastroenterologist has seen patients with this disorder, surprisingly little research in this field has been performed and not much is known about the mechanisms involved. Generally, it is thought that excessive belching in these patients is the result of venting air from the stomach after a period of excessive air swallowing.

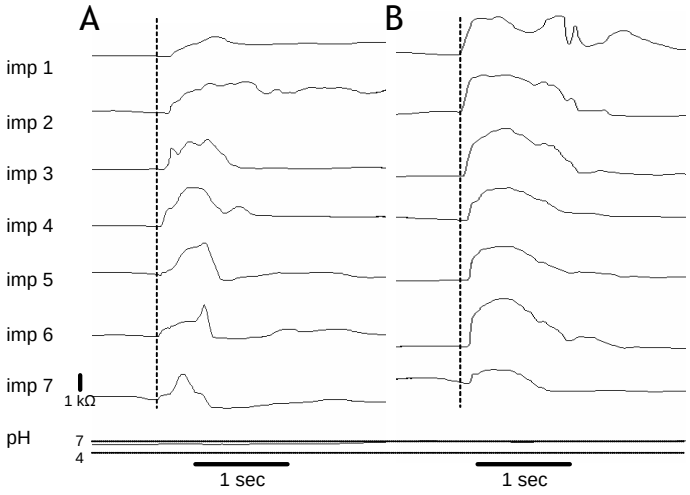

Figure 3. Two different types of belches. (A) The gastric belch is characterised by an increase in impedance that moves in oral direction. (B) A supragastric belch is characterised by an episode with high impedance, the onset of which starts in the proximal channels and moves distally; the end of which is cleared in the opposite direction.

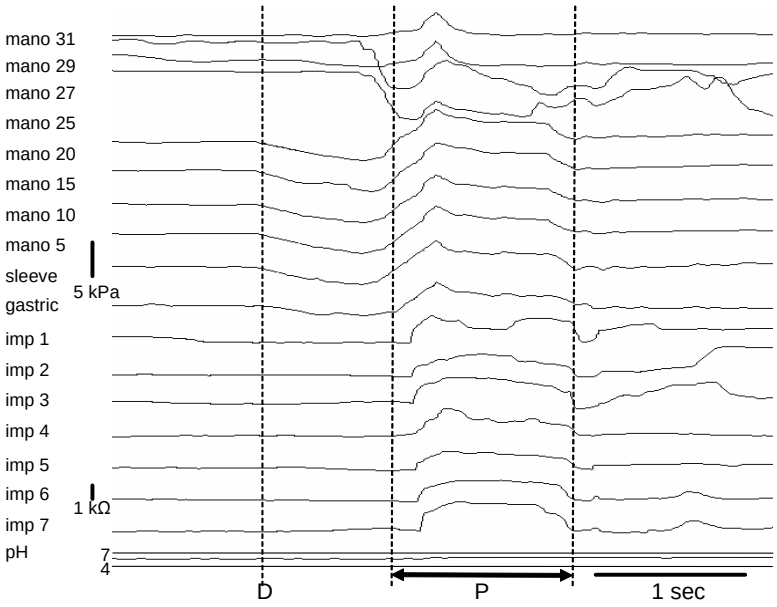

Figure 4. pH, manometric, and impedancometric recordings of a supragastric belch. A decrease in oesophageal pressure (D) precedes the influx of air is followed by a simultaneous increase in pressure (P) in all channels. This increase in pressure is much larger than as seen with a common cavity phenomenon.

With multiple intraluminal impedance recordings we were able to demonstrate two different types of belching. The first type, characterised by an increment of intraluminal impedance moving in oral direction, represents venting of gas from the stomach and can be referred to as gastric belching. The second type, characterised by a rapid antegrade impedance rise followed by a rapid retrograde return to baseline, represents oesophageal air ingestion followed by immediate expulsion. As the ingested air does not reach the stomach in this type of belching, it can be referred to as supragastric belching. Whereas gastric belches were found both in patients and healthy volunteers, supragastric belches were only seen in patients with excessive belching (aerophagia). The observation that patients with excessive belching did not differ from healthy controls with respect to the swallowing of air and the size of the gastric air bubble on radiographic images supports the concept that the mechanism of belching in these patients does not involve the stomach. Likewise liquid and mixed reflux episodes were not more frequent in the patients with repetitive belching.

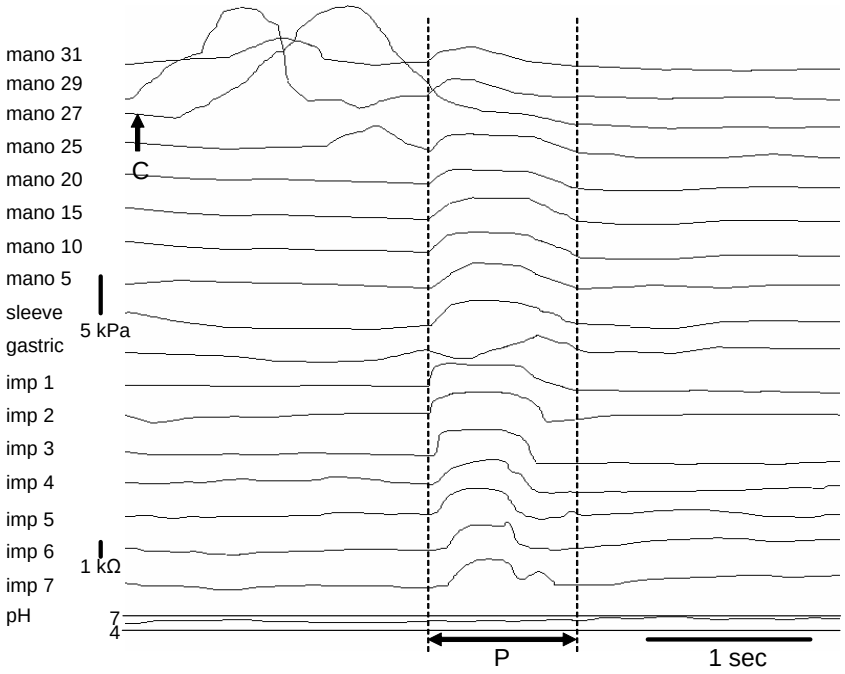

Figure 5. pH, manometric, and impedancometric recordings of supragastric belch. Air influx is preceded by a pharyngeal contraction (marked with C) and followed by an simultaneous increase in pressure (P) in all channels.

Manometry did not show lower oesophageal sphincter relaxations or common cavity phenomenon at moments that patients pushed the event marker to indicate they had a belch.

The question remains what mechanism results in this air flow? This air could enter the oesophagus because of either a backward pushing force induced by a pharyngeal contraction or by a forward sucking force generated by a negative pressure gradient in the oesophagus.[15] Our manometric findings indicate that both mechanisms may play a role: immediately before the increase in electrical impedance both pharyngeal contractions (42.0 %) and decreases in oesophageal body pressure (43.8 %), and combinations of the two mechanisms (10.9 %) were observed. In both mechanisms a sudden increase in abdominal and oesophageal pressure was observed that ended with the decrease in impedance. This pressure increase was simultaneously in the gastric and oesophageal channels and is presumably caused by an abdominal strain, necessary to evacuate the oesophageal air.

Most patients with excessive belching believe that their belching results from some kind of organic disorder. Often, patients are convinced that they have an unusually high production of gas in the stomach or intestine. Multiple intraluminal impedance monitoring makes it possible to obtain more insight in the mechanism of excessive belching in these patients. The incidence of supragastric belches did not increase significantly after the meal, in contrast to other functional disorders like functional dyspepsia or the rumination syndrome, where eating a meal triggers symptoms.

Complaints of excessive belching in patients with aerophagia and supragastric belching are probably not relieved by transient LOS relaxation inhibitors like baclofen, as these belches do not originate from the stomach. Instead, more is to be expected from treatment modalities such as behavioural therapy.[16] Perhaps the incidence of supragastric belching can be reduced by making patients aware that these belches are self-induced. There might be a role for impedance monitoring in the development of a biofeedback treatment programme, because impedance monitoring makes it possible to differentiate between gastric and supragastric belches. Indeed, most patients are convinced their symptoms are caused by expulsion of gastric gas. Some physicians try to convince their patients of the fact that these belches are self-induced by showing them that they themselves can also belch. Anecdotally, it was reported that excessive belching was reduced with hypnosis as well.[17] Some aerophagia patients report that, initially, belching relieved some kind of unpleasant sensation in the upper abdomen, but after a while the belching became bothersome itself. We suspect that excessive belching is some kind of learned behaviour and is initially induced consciously. After a while, however, this control is lost.

We can conclude that patients with excessive belching do not have more frequent gaseous reflux from stomach to oesophagus and pharynx than healthy subjects. Their repetitive and bothersome belches originate from a distinct belch pattern, characterised by air that does not reach the stomach.

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Psychological factors affect the frequency of belching in patients with aerophagia

A.J. Bredenoord
B.L.A.M. Weusten
R. Timmer
A.J.P.M. Smout

Dept. of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands
Gastrointestinal Research Unit, University Medical Center, Utrecht, The Netherlands

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Abstract

In patients with excessive belching (aerophagia) an organic cause is seldom found and a psychogenic cause often suspected. Aim: To investigate the effects of attention and distraction on the frequency of belching in patients with aerophagia. Methods: In 10 patients with aerophagia combined esophageal manometry and impedance monitoring was performed for 2 hours, consisting of 4 30-min recording periods. Period I: patient unaware that recording had commenced. Period II: patient informed of recording in progress. Period III: distraction by filling in questionnaires. Period IV: no distraction. Results: A total of 1258 belches was measured, 51 of which were the result of air that escaped from the stomach (gastric belches). 1207 belches (96 %) were events during which air was expelled in oral direction almost immediately after entering the esophagus from proximally (supragastric belches). Gastric belches were distributed equally over the first (1.5 (0.5-2.0)), second (1.5 (0.5-2.0)), third (1.0 (0-2.0)) and fourth (1.0 (0-2.0)) recording period. In contrast, the incidence of supragastric belches increased significantly from 0 (0-32) in period I to 30 (18-60) in period II, after patients were told that recording was started. During period III (questionnaires) the incidence of supragastric belches decreased to 14 (4-30). In period IV the incidence of supragastric belches increased to 21 (10-49). Conclusions: When patients with excessive belching are unaware that they are being studied or when they are distracted the incidence of belching is significantly reduced. These findings underline the importance of psychological factors and provide rationale for behavioural therapy.

Introduction

Belching is a physiological phenomenon that leads to venting of gastric air. It is commonly reported as a symptom by patients with functional dyspepsia and patients with gastroesophageal reflux disease, but in these patients other symptoms are predominant.[1,2] However, every gastroenterologist occasionally encounters patients who consult primarily because of excessive belching. These patients present with frequent audible belches, occurring unrelated to meals. Recently, we have shown that the vast majority of the belches in these patients do not originate from the stomach, but result from air that is injected or sucked into the esophagus from proximal direction and is expelled almost immediately in oral direction, before reaching the stomach.[3] We designated these belches "supragastric" belches, in contrast to regular gastric belches that result from venting of previously ingested air from the stomach.
In patients with excessive belching (aerophagia) an organic cause is seldom found and a psychogenic cause is often suspected. In a large retrospective analysis of these patients a high prevalence of anxiety and depression has been found.[4] Furthermore, repetitive belching also seems to occur as the initial representation of some neuro-psychiatric disorders.[5-7] These findings strongly suggest that aerophagia is a behavioural disorder, in which patients somehow have lost conscious control over previously learned abnormal behaviour. We hypothesized that if the frequency of belching can be influenced by attention and distraction, this would strongly suggest that psychological factors are important in this disorder.
Aim of this study was therefore to investigate the effects of attention and distraction on the frequency of belching in patients with aerophagia.

Methods

Subjects
We studied 10 patients with excessive belching (6 males: mean age 51 years, range 26-79 years). All patients exhibited frequent audible belching during consultation. Upper endoscopy, an abdominal radiograph and 24-hour pH monitoring were unremarkable in these patients. Written informed consent was obtained from all subjects and the protocol was approved by the medical ethical committee of the University Medical Center Utrecht.

Study protocol

The use of inhibitors of gastric acid secretion and drugs that influence gastrointestinal motility was discontinued 5 days before the study. After an overnight fast the manometry catheter was introduced transnasally. After positioning of the manometry catheter, the impedance catheter was introduced transnasally and positioned based on the manometric findings (see below). Subjects were in an upright position and were asked to minimize head movements in order to avoid axial displacement of the catheters. After an adaptation period of at least 10 min recording of esophageal impedance and pressures was performed for 2 hours. These 2 hours consisted of 4 30-min recording periods. During period I patients were under the impression that recording had not yet commenced. Period II started with informing the patients that recording was now in progress. During period III patients were being distracted by having them filling in questionnaires (SF36, QOLRAD, GORD-HRQL and other non-validated symptom questionnaires), administrated in such a way that it took them exactly 30 min to complete. During period IV the patients were not distracted. After the completion of the study a debriefing followed and the real intentions of the study were made clear to the patients.

Manometric technique

A water-perfused silicone rubber catheter (outer diameter 4.0 mm, length 75 cm, channel diameter 0.4 mm) was used for manometric recording. The proximal part of the assembly incorporated five sideholes at 1-cm intervals. Of these, the sidehole most clearly showing pharyngeal contractions was selected for recording swallows. After selection of this sidehole, perfusion of the other four pharyngeal sideholes was discontinued since it has been suggested that pharyngeal stimulation with water may trigger transient lower esophageal sphincter relaxations. There were four esophageal sideholes at 5-cm intervals. The distal end of the catheter incorporated a 6-cm long reverse perfused sleeve sensor and a gastric sidehole. All sideholes were perfused at a rate of 0.08 ml/min using a pneumohydraulic perfusion system (Dentsleeve Pty Ltd, Wayville, South Australia). The sleeve sensor was perfused at a rate of 0.30 ml/min.

Pressures were measured with external pressure transducers (Abbott, Sligo, Ireland). Pressure data were stored in digital format in two 12-channel dataloggers (Medical Measurement Systems, 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 a computer.

Intraluminal impedance monitoring

For intraluminal impedance monitoring a 10-channel impedance catheter was used (Aachen University of Technology, FEMU, Aachen, Germany). This catheter (outer diameter 2.3 mm) enabled recording from 10 segments, each recording segment being 2 cm long. The recording segments were located at 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-14, 14-16, 16-18 and 19-21 cm above the upper border of the manometrically localized lower esophageal sphincter (LES). Impedance signals were stored in a digital system (Solar, Medical Measurement Systems, Enschede, The Netherlands) using a sample frequency of 50 Hz.[8]

Data analysis

In the analysis of the impedance tracings, gastric belches were defined as a rapid (>3000 Ω/s) and pronounced rise in impedance that moved in retrograde direction over at least two consecutive impedance sites.[9] Supragastric belches were defined as a rapid and pronounced rise in impedance that initially moved in distal direction, followed immediately by expulsion in retrograde direction.[3]
End-expiratory LES pressure, recorded with the sleeve sensor, was calculated using the intragastric pressure as reference.

Statistical analysis and presentation of data

Sample size of this study was selected in order to detect a 50 % increase in belching frequency after patients were informed that recoding has been commenced. Analysis was performed using the Wilcoxon Signed Rank test. Differences were considered statistically significant when $p \leq 0.05$. Throughout the manuscript data are presented as mean ± SD or median (interquartile range). Pressures are expressed in kPa (1 kPa=7.5 mmHg).

Results

Frequency of belching

One patient stopped belching immediately after introduction of the catheters and was excluded from further analysis. In the remaining 9 patients, a total of 1258 belches was measured, 51 of which were the result of air that escaped from the stomach (gastric belches) (Figure 1). The remaining 1207 belches (96 %) were events during which air was expelled in oral direction almost immediately after entering the esophagus from proximally. During these belches air did not reach the stomach and these will be referred to as supragastric belches (Figure 1). The

number of supragastric belches in the two-hour recording period varied between patients from 21 to 395 (Figure 2). Gastric belches were distributed equally over the four recording periods (Figure 3). In contrast, the incidence of supragastric belches increased significantly ($p<0.05$) after the first period when patients were told that recording was started (Figure 4). During filling in of the questionnaires in the third period the incidence of supragastric belches decreased again ($p<0.05$) (Figure 4), while the incidence of supragastric belches tended to increase again in the fourth period during which there was no distraction ($p=0.086$). The total number of supragastric belches were equally divided over the first and second half of each 30-min recording period (period I: 80 vs 94 belches, period II: 294 vs 213 belches, period III: 67 vs 78 belches, period IV: 201 vs 180 belches).

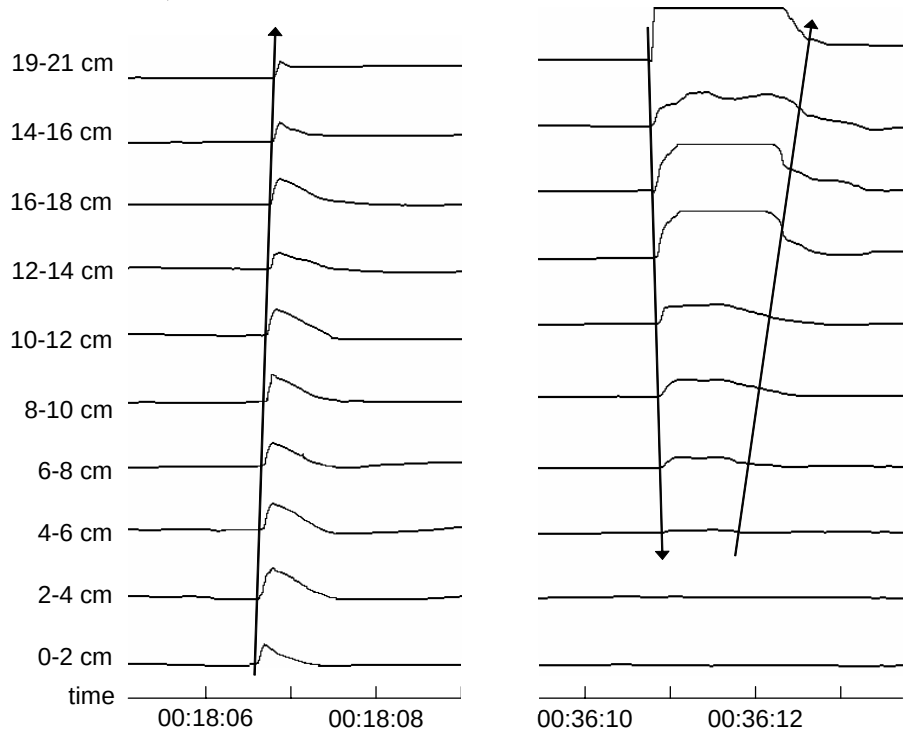

Figure 1. Impedance tracings of a gastric (left) and a supragastric belch (right).

Mechanisms of supragastric belching

Two distinct mechanisms of supragastric belches could be distinguished. Seven patients created a negative intrathoracic pressure (1.25 ± 0.29 kPa below baseline esophageal pressure) after which air moved into the esophagus (air suction). In one patient a pharyngeal contraction was observed during which the

air moved into the esophagus (pharyngeal injection). One patient used both mechanisms (suction and injection). After the air arrived in the esophagus, it was almost immediately expulsed in oral direction during a simultaneous pressure increase (strain) in all esophageal and gastric channels with a mean increase in pressure of 3.70 ± 2.49 kPa. Air expulsion occurred in all patients by means of straining.

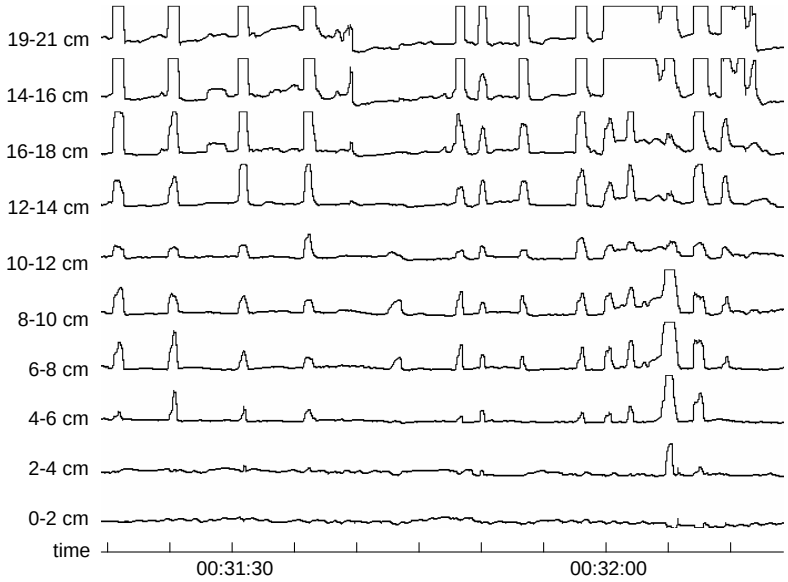

Figure 2. Impedance tracing. Each peak represents a supragastric belch. This patient shows belched more than 15 times per minute.

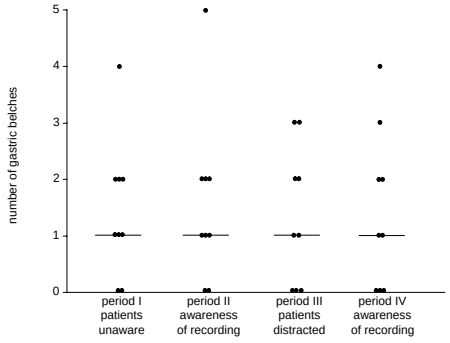

Figure 3. Number of gastric belches in each recording period. Horizontal bars represent medians.

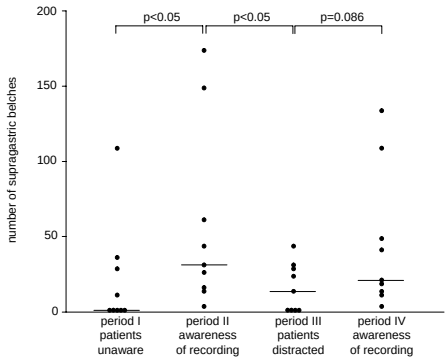

Figure 4. Number of supragastric belches in each recording period. Horizontal bars represent medians.

Discussion

Patients with aerophagia are often convinced that their excessive belching results from either excessive swallowing of air or that they suffer from intragastric fermentation or other gas-producing process. Almost without exception extensive diagnostic evaluation of patients with these disturbing complaints reveals no organic abnormalities and it is often suspected that the symptoms of these patients have a psychological origin. In our study we tested whether we could influence the frequency of belching by modulating the patient's awareness of being studied and by distraction.

The effect of the attention modulating procedures was remarkable. After informing the patients that the measurement had commenced, the frequency of belching was more than doubled. During the subsequent distraction period implemented by letting the patients fill in questionnaires the belching rate decreased substantially. After patients were no longer distracted the belching rate doubled again. These results suggest that psychological factors are important in aerophagia, indicate that aerophagia most likely is a behavioural disorder, and lend support to further attempts to treat the disorder with behaviour therapy. Behaviour therapy has been shown to be effective in other functional gastrointestinal disorders such as the irritable bowel disorder.[10,11] In order to investigate the presence of a possible carry-over effect, we compared the total number of supragastric belches in the first and second half of each 30-min recording period. The results show that differences in (supragastric) belch rate between the first and second half were small, which indicates that the presence of an important carry-over effect is unlikely.

Recently, we have shown that patients with aerophagia did not differ from controls with respect to air swallowing rate, intragastric air bubble size or frequency of gastric belches.[3] Instead, patients with aerophagia showed a distinct air transport pattern that was characterized by a sudden increase in impedance moving in distal direction, followed by a rapid decrease in impedance moving in retrograde direction again (supragastric belch). Simultaneous recording of pressures showed that patients either sucked air into the esophagus by means of creating a negative thoracic pressure or injected air in the esophagus by means of pharyngeal contraction. Air was expulsed in retrograde direction by an abdominal strain. The results of this study confirm those findings. Air suction was found in 7 patients, 1 patient exhibited pharyngeal air injection and 1 patient used both mechanisms to fill his esophagus with air.

The mechanisms used by patients for supragastric belches are similar to the mechanisms that laryngectomized patients use for esophageal speech.[12] Speech therapists teach patients to suck air into the esophagus by using a reverse Valsalva manoeuvre or push air into the esophagus by means of pharyngeal contraction. After the esophagus is filled, the air is expulsed in retrograde direction and sounds are created by leading the air along the neoglottis, a pharyngeal fold. Patients with aerophagia thus exhibit similar air movement patterns as the laryngectomized patients. We hypothesize that they learned this behaviour in the past and somehow lost control over it. It is not unlikely that a speech therapist can make the patient conscious of his behaviour, by showing him what actions result in supragastric belching. Measurement of esophageal impedance and pressures during belching could be useful to determine whether the patient sucks air or injects air into the esophagus. In a more primitive form, this is already done by those gastroenterologists who show their patients that they can belch themselves as well, in order to make clear to their patients that they suffer from a learned behaviour.[13] It is important that the speech therapist realizes that these patients do not swallow air in abnormal quantities and that therefore treatment should not focus on changing their swallowing behaviour. Good communication between gastroenterologist and speech therapist concerning management of these patients is advisable.

In conclusion, we have shown that distraction and attention have a large effect on the frequency of belching in patients with aerophagia. This suggests that psychological factors are important in this disorder. Based on these observations, behaviour therapy may hold promise in these patients.

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Relationships between air swallowing, intragastric air, belching and gastro-oesophageal reflux

A.J. Bredenoord
B.L.A.M. Weusten
R. Timmer
L.M.A. Akkermans
A.J.P.M. Smout

Dept. of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands
Gastrointestinal Research Unit, University Medical Center, Utrecht, The Netherlands

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Abstract

Background: With each swallow a certain amount of air is transported to the stomach. The stomach protects itself against excessive distention by swallowed air through belching (gas reflux). The mechanism of belching (transient lower oesophageal sphincter relaxation) is also one of the mechanisms underlying gastro-oesophageal reflux. Aim: To investigate whether swallowing of air leads to an increase in size of the intragastric air bubble and to gastro-oesophageal reflux. Methods: Multichannel intraluminal impedance measurement was used to quantify the incidence of swallowing of air in 20 healthy volunteers before and after a meal. Radiography was used to measure the size of the intragastric air bubble. Gastro-oesophageal reflux was assessed by concurrent impedance and pH measurement. Results: The rate of air swallowing was correlated to the size of the intragastric air bubble postprandially and to the rate of gaseous gastro-oesophageal reflux. The number of air swallows and the size of the intragastric air bubble did not correlate with the number of liquid acid and non-acid reflux episodes. Conclusions: In healthy subjects, air swallowing promotes belching but does not facilitate acid reflux.

Introduction

Belching, the passage of gaseous material from the stomach to the mouth, is a physiological phenomenon. A study using ultra-fast computer tomography showed that with each liquid swallow a certain volume of air was ingested simultaneously.[1] Several studies have shown that distention of the proximal stomach induced by inflation with air triggers transient relaxations of the lower oesophageal sphincter (TLOSRs).[2-5] By means of these TLOSRs ingested air can be vented. It has been shown that TLOSRs are also the most important mechanism through which non-gaseous gastric contents can enter the oesophagus.[6,7] The mechanisms enabling belching (gas reflux) are of particular interest since they bear great resemblance to the mechanisms underlying gastro-oesophageal reflux.[8] Almost 50 % of patients with gastro-oesophageal reflux disease (GORD) complain of a certain degree of excessive belching and belching is also common in patients with functional dyspepsia.[9,10] Recently, multiple intraluminal electrical impedance monitoring was introduced as a novel technique for investigation of bolus transport in luminal organs.[11] This technique makes it possible to distinguish movements of even small volumes of gas through the oesophagus in oral and in aboral direction.[12] Using impedance monitoring we aimed to investigate whether swallowing of air leads to an increase in size of the intragastric air bubble and whether it promotes gastro-oesophageal reflux.

Methods

Subjects

We studied 20 healthy volunteers (14 males and six females: mean age 28 years, range 19–46 years). Subjects were free of gastrointestinal symptoms and were not taking any medication. Written informed consent was obtained from all subjects and the protocol was approved by the Medical Ethics Committee of the University Medical Center Utrecht. This study was carried out according to the standards set by the declaration of Helsinki.

Validation study

In three healthy subjects determination of air swallowing was assessed on both fluoroscopy and impedance monitoring. This validation study was performed on another day as the other part of the study. After insertion of the impedance catheter, 10 20-mL swallows of a fluid barium suspension were monitored with

concurrent fluoroscopy and impedance. Framing speed for fluoroscopic pictures was 10/s.[1] For each swallow, the amount of swallowed air was determined on the fluoroscopic picture using millimeter blocked paper. For this measurement, the picture was used that was taken when the bolus head reached the radio-opaque electrodes of impedance channel 5 on the impedance catheter (see below). On the impedance tracings, the maximum amplitude caused by the swallowed air was determined with respect to baseline impedance.

Study protocol

After an overnight fast radiographic images of the upper abdomen were obtained in anteroposterior and lateral direction with the subject in upright position (Figure 1). Thereafter, routine oesophageal manometry was performed to determine the distance from the nostrils to the lower oesophageal sphincter (LOS). The impedance catheter and the pH catheter were introduced transnasally and positioned based on the manometric findings (see below). After an adaptation period of at least 10 min recording was started and subjects were asked to minimize head movements and to breathe normally. After 45 min of continuous recording the subjects took a standardized meal consisting of one hamburger (McDonald's Quarter Pounder), 20 g of fresh onions, 44 g of potato chips and 475 mL of orange juice (in total 967 kCal). This meal was used to provoke reflux in a previous study by our group.[13] The meal had to be finished in 30 min. Immediately after ingestion of the meal, recording was continued for another 90 min. Forty-five min after the meal radiographic images in anteroposterior and lateral position were obtained. Subjects remained seated for the duration of the study.

			10 min	45 min	30 min	45 min		45 min
x-ray	manometry	insertion pH and imp catheters	adaptation	recording	meal	recording	x-ray	recording

Figure 1. Study protocol

Impedance and pH monitoring

For impedance monitoring a 7-channel impedance catheter was used (Aachen University of Technology, FEMU, Aachen, Germany). This catheter (outer diameter 2.3 mm) enabled recording from seven segments, each recording segment being 2 cm long. The recording segments were located with electrodes at 0–2, 2–4, 4–6, 8–10, 10–12, 14–16 and 17–19 cm above the upper border of the

manometrically localized LOS (Figure 2). Impedance signals were stored in a digital system (Aachen University of Technology, FEMU) using a sample frequency of 1000 Hz. Intraluminal pH monitoring was performed with a catheter with a glass pH electrode (Ingold A.G., Urdorf, Switzerland) and data were stored in a digital datalogger (Orion, MMS, Enschede, The Netherlands) using a sampling frequency of 2 Hz. A cable connects the pH datalogger with the impedance datalogger. pH data are thus stored on both dataloggers and can be visualized together with the impedance tracings. The pH glass catheter was positioned 5 cm above the manometrically upper border of the LOS.

Data analysis

The size of the gastric air bubble projection was measured from the anteroposterior and lateral radiographic images using transparent millimetre blocked paper. The projection of the impedance catheter was used as a reference for actual size. Previously established criteria were used to identify swallows, gas reflux, liquid reflux and mixed gas–liquid reflux in the impedance signals.[14-16] We also identified air-containing swallows (air swallows) as swallows that were preceded by an impedance peak of more than 1000 Ω above baseline that was recognizable in the most distal impedance segment.[17] We chose a threshold of 1000 Ω because this was found to be well above the amplitude of baseline noise. Furthermore, using the pH tracings, liquid reflux, mixed gas-liquid reflux and gas reflux events were classified as acidic or non-acidic, using a threshold of pH < 4. Total acid reflux events and percentage of time with pH < 4 were also assessed. In the analysis, the period of meal consumption was disregarded.

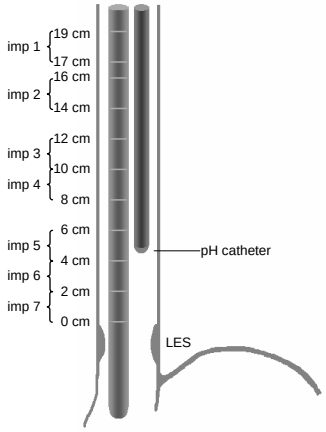

Figure 2. Schematic representation of positioning of the recording catheters. The impedance catheter included seven measuring segments. The numbers indicate the distance above the manometric upper border of the LOS. Impedance was measured between the electrodes at 0 and 2, 2 and 4, 4 and 6, 8 and 10, 10 and 12, 14 and 16, and 17 and 19 cm above the upper border of the LOS.

Statistical analysis and presentation of data
Pearson's correlation coefficient was calculated to explore the relation between gastric air bubble size before and after the meal and the relation between gastric air bubble size in anteroposterior and lateral direction. Spearman's correlation calculations were performed for all other data. Repeated measures ANOVA and Friedman's test were used to perform comparisons for repeated measures of parametric and non-parametric data, respectively. Analysis of the data is performed on per subject values. Significance level was set to 0.05. Throughout the manuscript data are presented as mean ± SEM.

Results

In the validation study a strong and statistically significant correlation ($p<0.01$) was found between the amplitude of the air-induced increase in impedance on the tracings and the size of the swallowed air as assessed with fluoroscopy for each of the three subjects, with the Spearman correlation coefficients varying between 0.78 and 0.89 (Figure 3). Often the air bolus moved in front of the barium but not infrequently a vertical air–fluid interface was observed in the distal oesophagus.
In the main study gastric air bubble size measured radiographically in anterior and lateral projection correlated extremely well, both before ($r=0.978$, $p<0.001$) and after the meal ($r=0.856$, $p<0.001$). No significant correlation was found between pre- and postprandial gastric bubble size in anterior ($r=0.388$, $p=0.12$) and lateral projections ($r=0.351$, $p=0.15$).

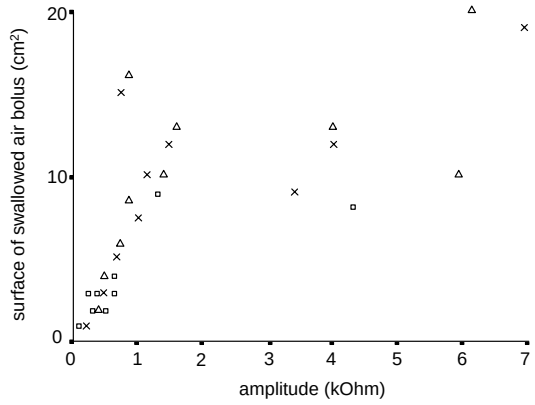

Figure 3. Relationship between the surface of swallowed air bolus determined with radiography and the peak in impedance caused by the passage of the bolus in the in the validation study. Different markers are used for the three healthy subjects.

Table 1. Gastric air bubble size, swallows, air swallows, and reflux parameters

	Preprandial period	First 45-min period postprandial	Second 45- min period postprandial	p-value
Gastric air bubble size AP (cm^2)	11.3 ± 1.4	12.0 ± 1.6		NS
Gastric air bubble size L (cm^2)	9.8 ± 3.5	11.0 ± 1.4		NS
Swallows / hour	79.4 ± 8.6	68.5 ± 5.5	62.1 ± 5.9	NS
Air swallows / hour	21.3 ± 3.7	26.1 ± 2.3	23.6 ± 3.5	NS
Liquid reflux events / hour	0.6 ± 0.6	2.1 ± 0.5	1.4 ± 0.4	p≤0.05
Gas reflux events / hour	4.6 ± 1.0	3.4 ± 0.9	3.3 ± 0.4	NS
Mixed reflux events / hour	0.5 ± 0.2	3.9 ± 0.6	3.9 ± 0.4	p≤0.05
Acid reflux events / hour	0.5 ± 0.1	3.0 ± 1.4	4.2 ± 1.2	p≤0.05
% time with pH < 4	0.8 ± 0.5	3.9 ± 1.4	8.1 ± 2.2	p≤0.05

AP, anteroposterior; L, lateral projections. Repeated measures ANOVA was used to perform comparisons for repeated measures of % of time with pH < 4, Friedman's test was used for comparison of all other data.

The hourly rate of swallows, air swallows, or gas reflux episodes did not differ significantly between the pre- and postprandial recording period. In contrast, the incidence of liquid and mixed reflux increased significantly immediately after the meal (Table 1). Postprandially, liquid and mixed reflux events were acidic in 66.7 and 49.2 %, respectively, while gas reflux was never acidic (Figure 4).

A statistically significant correlation was found between the number of air swallows and the number of gas reflux events, both before ($r=0.40$, $p<0.05$) and after ($r=0.48$, $p<0.05$, first 45 min, $r=0.54$, $p<0.05$, second 45 min) the meal (Figure 5), whereas the total number of swallows did not correlate significantly with the occurrence of gas reflux events. Correlation of air swallowing with liquid or mixed reflux events was not statistically significant, nor was the correlation of air swallows with the time with pH < 4 or the total number of acid reflux events. Correlation between the number of air swallows after the meal in the period before the radiograph and the size of the postprandial gastric air bubble was significant for both anterior ($r=0.61$, $p<0.05$) (Figure 6) and lateral projections ($r=0.60$, $p<0.05$) but correlation between the total number of swallows and postprandial gastric air bubble size was not. In addition, no significant correlation was found between the size of the gastric air bubble and the occurrence of reflux of any kind (gas, liquid or mixed). There was no relation between the size of the gastric air bubble and the time with pH < 4 or the total number of acid reflux episodes.

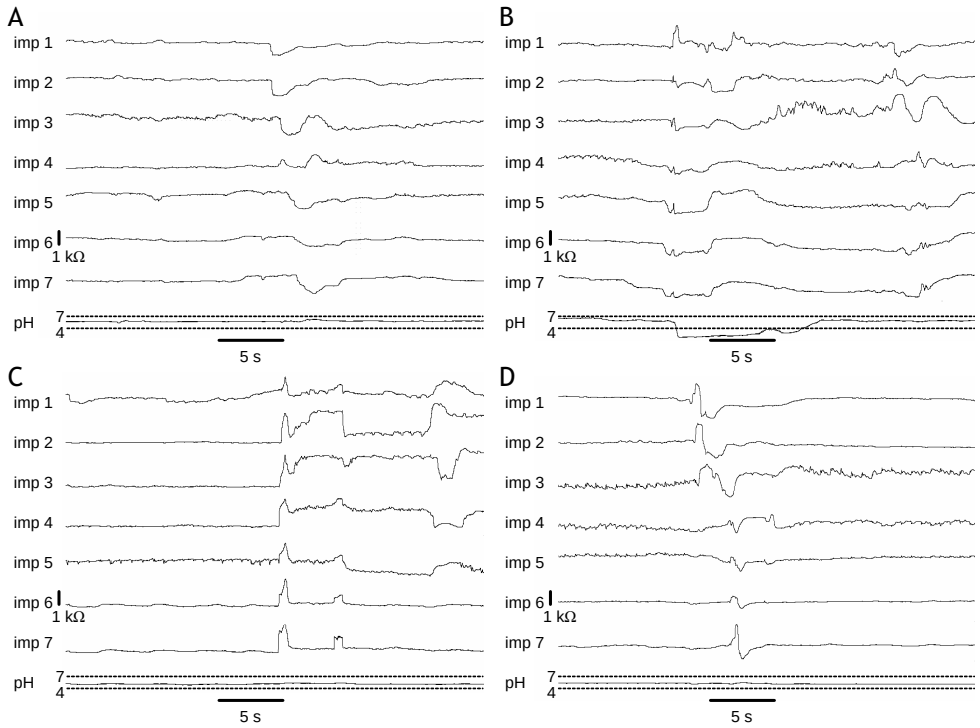

Figure 4. Oesophageal impedance and pH signals. (A) Regular dry swallow. The decrease in impedance during "dry" swallows is most likely due to swallowed saliva (B) Mixed gas-liquid reflux. After the initial decrease in impedance, indicating liquid reflux, a rapid increase in impedance occurs. pH falls below 4. (C) Gas reflux without change in pH. (D) Air swallow. An increase in impedance followed by a decrease moving in aboral direction, representing air being pushed forward in front of a liquid bolus.

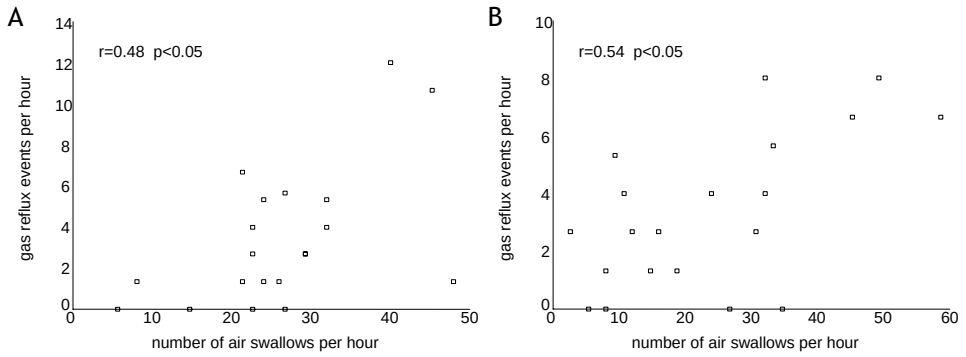

Figure 5. Relationship between frequency of air swallows and gas reflux events in the first 45 min after the meal (A) and the second 45 min after the meal (B).

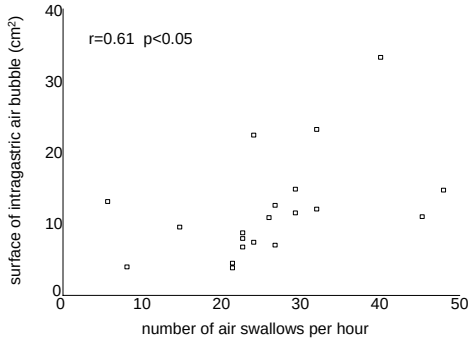

Figure 6. Relationship between frequency of air swallows in the first postprandial 45 min and surface of the intragastric air bubble on radiography after the meal.

Discussion

Previous studies have shown that the presence of a large volume of air in the proximal stomach triggers stretch receptors in the gastric cardia and leads to an increase in the rate of TLOSRs.[2,5,8,18,19] These TLOSRs are the most important mechanisms through which acidic gastro-oesophageal reflux can occur.[6,7] It was, therefore, hypothesized that an increase of intragastric air volume, for example after swallowing of air, would lead to acid reflux.[3,4] However, thus far the relation between swallowing of air, gastric air volume and acid reflux had remained uninvestigated.

Multiple intraluminal impedance monitoring makes it possible to detect transport of air and liquids in the oesophagus, both in oral and in aboral direction. Reflux of air and liquids and swallowing of liquids have already been investigated using impedance monitoring but this is the first study that uses impedance monitoring for the quantification of air swallowing. Our validation study shows that the increase in impedance that precedes the decrease in impedance caused by swallowed liquids is dependent on the amount of air swallowed and the correlation between impedance amplitude and size of the air swallow was better for smaller air swallows than for larger air swallows. We thus quantified air swallowing in this study using a threshold for the amplitude of air swallows of 1000 Ω above baseline impedance.

Thus far, swallowing of air was only studied using radiography and computerized tomography. The exposure of subjects to radiation restricts the duration of the period during which air swallowing is monitored with these techniques. We show that impedance is also capable of monitoring air swallowing. This will create opportunities to study air swallowing in conditions where swallowed gastric air is

believed to play a role such as the gas-bloat syndrome after fundoplication, GORD and functional dyspepsia. In aerophagia, repetitive belching does not originate from regular air swallowing and gas reflux as described in this paper, but instead a different air transport pattern is seen as can be observed with impedance monitoring.[17] With the use of impedance monitoring and radiography, we were able to show that the size of the gastric air bubble is related to the frequency with which air is swallowed. We also found a significant correlation between gas reflux and air swallowing. Air swallowing did not provoke reflux of liquid or mixed gas–liquid gastric contents in these healthy volunteers. Apparently venting decreases the volume of swallowed air in the gastric fundus, without affecting gastro-oesophageal sphincter continence for acid and non-acid liquids. A study in dogs showed that filling of the stomach with liquid leads to a distention of the cardia that is different from that resulting from filling of the stomach with both liquid and gas.[20] Perhaps the gastric receptors that are triggered by gaseous distention differ from those that are triggered by distention by liquid, resulting in the ability of the stomach to differentiate between gaseous and liquid filling and to react differently. The concept that intragastric air does not facilitate the reflux of liquids is supported by a study by Sifrim et al. showing that in mixed reflux events liquid often precedes gas reflux.[12] They furthermore observed that in only a minority of acid reflux episodes, gas occurred as the primary event. Their conclusion was that belching can precipitate acid reflux, but that most acid reflux occurs as a primary event. Another finding of our study was that after a meal both liquid and mixed reflux increased considerably, but gas reflux did not. This observation supports the hypothesis that gas and liquid reflux are provoked by different mechanisms.

In the current study no relation was found between the size of the gastric air bubble and the different reflux parameters, while other studies showed that distention of the stomach with a barostat balloon increases the rate of TLOSRs. It should be noted however, that although TLOSRs are the most important mechanisms by which reflux occurs, other mechanisms also play a role. Furthermore, not every TLOSR is followed by reflux. Another explanation for the seemingly discrepant results of our study as compared with the studies using barostat and manometry is that distention of the stomach with an balloon filled with air is quite a different stimulus than the physiological distention of the stomach by ingested air.

A possible limitation of this study is the short measurement period during which recordings were made. Impedance and pH were monitored during a short pre- and postprandial period. Twenty-four hour data would possible render more

information. However, reproducibility of reflux monitoring with impedance monitoring of even a short postprandial period was found to be very acceptable and intrasubject variability was considered much smaller than intersubject variability.[21]

The relations found in this study between postprandial air swallowing and gas reflux were statistically significant but not very strong with calculated r values of 0.480 and 0.539. The same can be said for the relation between air swallowing and the size of the gastric air bubble (r=0.611 for anterior images and r=0.603 for lateral images). In part, this can be attributed to the fact that the events air swallowing and gas reflux were scored as either present or absent, while volumes of air transport associated with air swallows and gas reflux episodes were not measured. Other factors such as duodenal gas escape may play a role. However, studies in normal subjects in whom gas was inflated into the stomach have shown that only moderate amounts of gas leave the stomach via the duodenum and most of the gas escapes by belching.[2,22] Our observation that a correlation between air swallowing and gastric air bubble size is absent before the meal but appears to be present postprandially suggests that in the fed state air escapes the stomach through the duodenum less easily and is stored in the fundus instead. It is known that a meal rich in lipids, as used in this study, slows intestinal gas transit and provokes gastric distention.[23,24]

It is important to stress that this study was performed in healthy subjects and that the conclusions drawn from it are, therefore, not necessarily applicable to patients with GORD. It would be most interesting to investigate whether the mechanisms that enable venting of gas without occurrence of acid reflux are preserved in patients with GORD. It has been shown that GORD patients have an abnormal intragastric distribution of acid after a meal.[25,26] It is possible that this abnormality compromises the competence of the stomach to vent gas without the occurrence of liquid reflux.

In conclusion, we showed that multiple intraluminal impedance monitoring is a useful tool to study gas transport in the human oesophagus. In healthy subjects, liquid and mixed gastro-oesophageal reflux events are largely related to feeding, but gas reflux is related to air swallowing. Swallowing of air and accumulation of air in the stomach do not lead to acid reflux in healthy volunteers.

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Air swallowing, belching, and reflux in patients with gastroesophageal reflux disease

A.J. Bredenoord
B.L.A.M. Weusten
R. Timmer
A.J.P.M. Smout

Dept. of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands
Gastrointestinal Research Unit, University Medical Center, Utrecht, The Netherlands

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Abstract

Belching and gastroesophageal reflux share a common physiological mechanism. The aim of this study was to investigate whether air swallowing leads to both belching and reflux. Methods: Esophageal impedance, pH, and pressure were measured during two 20-min recording periods in 12 controls and 12 patients with gastroesophageal reflux disease (GERD), before and after intragastric inflation of 600 mL of air. This was repeated after a meal. Subsequently, ambulatory 24-hour impedance-pH measurement was performed. Results: During the 24-h study, patients showed a higher incidence of air swallows (287 ± 45 vs 176 ± 24, $p<0.05$), belches (52.4 ± 6.6 vs 32.7, $p<0.01$) and acid reflux (42.3 ± 7.6 vs 19.1 ± 2.8, $p<0.01$) than controls. After air infusion the incidence of gas reflux episodes was increased, both in patients (0.58 ± 0.36 vs 3.50 ± 0.61, $p<0.01$) and in controls (0.75 ± 0.67 vs 4.08 ± 0.59, $p<0.01$). In contrast, the incidence of acid and weakly acidic reflux episodes was not increased after air infusion, neither in patients (acid: 1.25 ± 0.37 vs 1.20 ± 0.33, weakly acidic: 1.08 ± 0.40 vs 0.80 ± 0.23) nor in controls (acid: 0.72 ± 0.34 vs 0.50 ± 0.23, weakly acidic: 0.80 ± 0.35 vs 0.33 ± 0.19). Air infusion increased transient lower esophageal sphincter relaxations (TLESR) frequency in patients and controls, but this was entirely because of an increase in gas reflux-associated TLESRs. Conclusions: Patients with GERD swallow air more frequently and belch more frequently than healthy subjects. However, air swallowing is not the cause of their increase in reflux.

Introduction

With swallowing, air can be ingested and transported to the stomach[1]. Several studies have shown that gastric distention induced by inflation of the stomach with air may trigger transient lower esophageal sphincter relaxations (TLESRs).[2-4] These TLESRs allow ingested air to be vented and this serves as a physiological protection against dilatation of the stomach. However, TLESRs are also the most important mechanism through which liquid gastric contents can reflux into the esophagus.[5] Belching and gastroesophageal reflux thus share the same mechanism. Almost 50 % of patients with gastroesophageal reflux disease (GERD) complain of excessive belching.[6,7] Already in 1961, Tuttle et al. reported that in patients with GERD heartburn often occurred during belching.[8] In a study in dogs, 58 % of the gastroesophageal reflux episodes were accompanied by audible belching.[9] Furthermore, antireflux surgery not only reduces gastroesophageal reflux of acid but also seems to reduce belching.[10,11] However, the exact relationship between air swallowing, intragastric air, belching, and gastroesophageal reflux has remained unclear.

The aim of this study was to further explore the role of air ingestion and eructation in the pathogenesis of GERD. More specifically,we wished to investigate whether (a) gastric air infusion leads to an increase in acid and weakly acidic reflux, and (b) patients with GERD swallow air and belch more frequently than healthy subjects.

Methods

Subjects

We studied 12 healthy volunteers (5 males: mean age 33 yr, range 23–56 yr) and 12 patients with GERD (7 males: mean age 38 yr, range 26–64 yr). Subjects received remuneration for participation into this study. All patients had symptoms of heartburn and/or regurgitation and a pathological esophageal acid exposure (time with pH < 4 greater than 6.0 %). A hiatal hernia of approximately 3 cm was present in five patients. Mild esophagitis was observed in six patients (five patients Los Angeles grade A, one patient Los Angeles grade B). Written informed consent was obtained from all subjects and the protocol was approved by the medical ethical committee of the University Medical Center Utrecht.

Study protocol

This study consisted of two parts, a stationary part in which the effect of air inflation on the occurrence of gaseous and liquid gastroesophageal reflux was investigated and an ambulatory part in which air swallowing, belching and gastroesophageal reflux were monitored for almost 24 hour (Figure 1).

The use of gastric acid-inhibitory drugs and drugs that influence gastrointestinal motility was discontinued 5 days before the study. After an overnight fast the manometry catheter was introduced transnasally. After positioning the manometry catheter, the impedance and the pH catheter were introduced transnasally and positioned based on the manometric findings (see below). Subjects were in an upright position and after an adaptation period of at least 10 min the experiment was started. Patients were asked to minimize head movements in order to avoid axial displacement of the catheters. After 20 min of measurement of impedance, pH and pressure 600 mL of air was inflated manually in the stomach over 5 min through a channel in the manometry catheter, using a syringe (Figure 1).

	stationary part: air infusion								ambulatory part	
	20 min	5 min	20 min		90 min	20 min	5 min	20 min	2 hr	22 hr
insertion catheters	rec	600 mL air	rec	meal		rec	600 mL air	rec		ambulatory study

Figure 1. Protocol of the study. Rec indicates recording of impedance, pH, and pressure.

After another 20 min of recording in the fasting state, the subjects consumed a standardized meal consisting of a hamburger (McDonald's Quarter Pounder consisting of a bun, sauce, meat, pickle, and cheese), 20 g of fresh onions, 44 g of potato chips, and 475 mL of orange juice (in total 967 kcal). The meal had to be finished in 30 min. Ninety minutes after ingestion of the meal, recording was continued. After 20 min of recording, another 600 mL of air was inflated in the above described fashion. After the air was insufflated, recording was continued for another 20 min. Thereafter the manometry catheter was removed and a 24-hour ambulatory impedance-pH measurement was carried out. The first 2 hours of the 24-hour recording were excluded from the analysis in order to minimize the effect of the previously inflated air.

Manometric technique

A water-perfused silicone rubber catheter (outer diameter 4.0 mm, length 75 cm, channel diameter 0.4 mm) was used for manometric recording. The proximal

part of the assembly incorporated five sideholes at 1-cm intervals. Of these, the sidehole most clearly showing pharyngeal contractions was selected for recording swallows. After selection of this sidehole, perfusion of the other four pharyngeal sideholes was discontinued because it has been suggested that pharyngeal stimulation with water may trigger TLESRs.[12] There were four esophageal sideholes at 5-cm intervals. The distal end of the catheter incorporated a 6-cm long reverse perfused sleeve sensor and a gastric sidehole. All sideholes were perfused at a rate of 0.08 mL/min using a pneumohydraulic perfusion system (Dentsleeve Pty Ltd,Wayville, South Australia). The sleeve sensor was perfused at a rate of 0.30 mL/min.
Pressures were measured with external pressure transducers (Abbott, Sligo, Ireland). Pressure data were stored in digital format in two 12-channel dataloggers (Medical Measurement Systems, 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.

Intraluminal impedance and pH monitoring
For intraluminal impedance monitoring a 7-channel impedance catheter was used (Aachen University of Technology, FEMU, Aachen, Germany). This catheter (outer diameter 2.3 mm) enabled recording from seven segments, each recording segment being 2-cm long. The 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 localized LES. Impedance signals were stored in a digital system (Aachen University of Technology, FEMU, Aachen, Germany) using a sample frequency of 50 Hz.[13] Intraluminal pH monitoring was performed with a glass pH electrode (Ingold A.G., Urdorf, Switzerland) and data were stored in a digital datalogger (Orion, MMS, Enschede, The Netherlands) using a sampling frequency of 2 Hz. The pH glass catheter was positioned 5 cm above the upper border of the LES. Using a cable that connected the pH datalogger with the impedance datalogger the pH signals were stored on both dataloggers to enable synchronization.

Data analysis
In the analysis of the impedance tracings, gas reflux was defined as a rapid (>3000 Ω/s) and pronounced rise in impedance that moved in retrograde direction over at least two consecutive impedance sites.[14] Liquid reflux was defined as a fall in impedance of ≥ 40 % of baseline impedance that moved in retrograde direction over the two distal impedance sites. Mixed liquid-gas reflux was defined as gas reflux occurring during or immediately preceding liquid

reflux. Liquid and mixed reflux episodes were classified as acidic when the pH dropped below 4; reflux episodes were classified as weakly acidic when nadir pH was between 7 and 4.[15] Belches were defined as pure gas and mixed reflux episodes in which the gas component reached the most proximal impedance segment and the liquid component (in mixed reflux episodes) did not. The percentage of time with pH below 4 was calculated for four 20-min periods.
In the impedance tracings, all liquid transit sequences presumably induced by dry swallows were identified. These were referred to in the manuscript as "swallows". Air-containing swallows (air swallows) were defined as swallows that were preceded by an impedance peak of more than 1000 Ω above baseline, measured in the most distal impedance segment. Detection of air swallows with impedance monitoring was validated previously and has been shown to be reproducible.[16,17]
End-expiratory LES pressure, recorded with the sleeve sensor, was calculated using the intragastric pressure as reference. TLESRs were identified using the criteria developed by Holloway et al.[18]
In the analysis, the periods of meal consumption were disregarded.

Statistical analysis and presentation of data
Analysis was performed on a per subject basis. Comparisons before and after air infusion were performed using the Wilcoxon signed rank test. Comparisons between patients and controls were performed using the Wilcoxon rank sum test. Relationships between parameters were expressed using the Spearman correlation coefficient. Differences were considered statistically significant when $p \leq 0.05$. Throughout the manuscript data are presented as mean ± SEM.

Results

Twenty-four hour impedance-pH study
During the 24-hour impedance pH studies, the patients had significantly more mixed gas-liquid reflux episodes, more reflux episodes with a gas component (gas and mixed gasliquid) and more belches (Table 1). The proportion of liquid and mixed reflux episodes was not different between healthy subjects (45.8 % liquid and 54.2 % mixed) and patients with GERD (47.2 % liquid and 52.8 % mixed). The number of pure liquid and pure gas reflux episodes was not significantly different between the two groups (Table 1). More acid reflux episodes were found in the patients compared with the controls, but the number of weakly acidic reflux

episodes was not different. Similar total numbers of swallows without air were identified in the two groups but air swallows occurred significantly more often in the patients than the healthy subjects (Table 1).

There was a statistically significant relationship between the number of air swallows and the number of belches in patients ($r=0.59$, $p<0.05$) and in controls ($r=0.63$, $p<0.05$).

Table 1. Characteristics of reflux events and swallows observed during 24-hour monitoring in controls and patients with GERD

	Controls	Patients	p
Gas reflux	15.7 ± 2.5	22.9 ± 6.1	0.5
Liquid reflux	15.4 ± 2.1	29.8 ± 7.8	0.3
Mixed reflux	18.2 ± 2.1	33.4 ± 3.3	**<0.01**
Acid reflux	19.1 ± 2.8	42.3 ± 7.6	**<0.01**
Weakly acidic reflux	14.5 ± 1.1	21.0 ± 5.3	0.9
Swallows (no air)	818.2 ± 57.3	782.1 ± 89.3	0.4
Air swallows	175.8 ± 24.3	287.4 ± 45.1	**0.04**
Belches	32.7 ± 2.9	52.4 ± 6.6	**<0.01**

All values represent mean ± SEM per 24 h

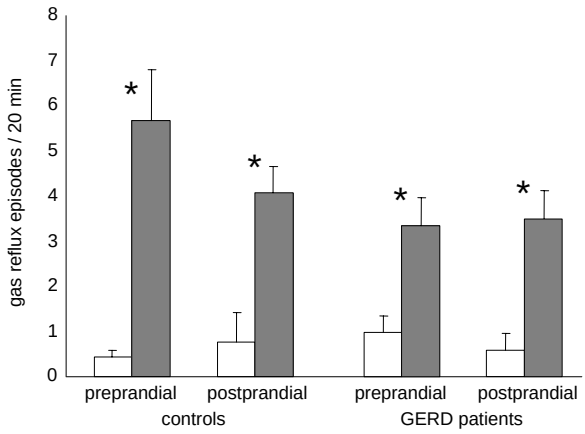

Figure 2. Gas reflux episodes before (open bars) and after (grey bars) infusion of 600 mL of air in controls and in patients with GERD. *:$p<0.05$

Air infusion study

After intragastric air infusion, therewas a significant increase in gas reflux episodes in patients and in controls, both in the pre- and postprandial state (Figure 2). In contrast, there was no difference in the number of liquid or mixed liquid-gas reflux episodes before and after air inflation, although the air inflation tended to decrease the number of pure liquid reflux episodes both in controls and in patients with GERD (Tables 2 and 3). In both groups, air infusion did not have an effect on the incidence of acid or weakly acidic reflux events in the 20-min period before and after consumption of a meal (Tables 2 and 3). Furthermore, esophageal acid exposure was not significantly affected by air infusion neither before nor after the meal.

Most gas reflux occurred in the first half of the 20-min measurement period after air infusion before (82.3 %) and after (74.4 %) the meal in patients and before (73.1 %) and after (86.0 %) the meal in controls. In contrast, the incidence of liquid-containing reflux episodes (pure liquid and mixed) was evenly distributed as approximately half of the mixed and liquid reflux episodes occurred in the first half of the 20-min period before (40.2 %) and after (54.6 %) the meal in patients and before (50.0 %) and after (44.0 %) the meal in controls. In both groups the number of TLESRs increased significantly after air infusion, both in preprandial and postprandial condition (Figure 3). This increase in TLESRs was gas reflux-associated but not liquid or mixed liquid-gas reflux associated.

Table 2. Effect of air infusion on reflux types in healthy controls

	Preprandial			Postprandial		
	Before air	After air	p-value	Before air	After air	p-value
Gas reflux	0.42 ± 0.15	5.67 ± 1.14	**<0.01**	0.75 ± 0.67	4.08 ± 0.59	**<0.01**
Liquid reflux	0.08 ± 0.08	0.0 ± 0.0	0.3	0.83 ± 0.27	0.0 ± 0.0	0.1
Mixed reflux	0.17 ± 0.11	0.41 ± 0.26	0.4	0.68 ± 0.34	0.83 ± 0.24	0.4
Acid reflux	0.08 ± 0.08	0.0 ± 0.0	0.3	0.72 ± 0.34	0.50 ± 0.23	0.2
Weakly acid reflux	0.17 ± 0.11	0.42 ± 0.26	0.3	0.82 ± 0.35	0.33 ± 0.19	0.1
Acid exposure time (%)	0.04 ± 0.04	0.0 ± 0.0	0.7	1.80 ± 1.22	1.03 ± 0.60	0.6

All values represent mean ± SEM per 20-min period except acid exposure time which is presented as percentage of time.

Table 3. Effect of air infusion on reflux types in patients with GERD

	Preprandial			Postprandial		
	Before air	After air	p-value	Before air	After air	p-value
Gas reflux	1.00 ± 0.35	3.33 ± 0.65	**0.02**	0.58 ± 0.36	3.50 ± 0.61	**<0.01**
Liquid reflux	0.0 ± 0.0	0.0 ± 0.0	1.0	0.83 ± 0.247	0.25 ± 0.13	0.1
Mixed reflux	0.75 ± 0.13	0.58 ± 0.23	0.5	1.50 ± 0.40	1.74 ± 0.30	1.0
Acid reflux	0.25 ± 0.13	0.25 ± 0.13	1.0	1.25 ± 0.37	1.20 ± 0.33	0.8
Weakly acid reflux	0.50 ± 0.15	0.33 ± 0.19	0.6	1.08 ± 0.40	0.80 ± 0.23	0.2
Acid exposure time (%)	0.33 ± 0.27	0.14 ± 0.07	0.8	9.64 ± 4.89	7.46 ± 3.47	0.9

All values represent mean ± SEM per 20-min period except acid exposure time which is presented as percentage of time.

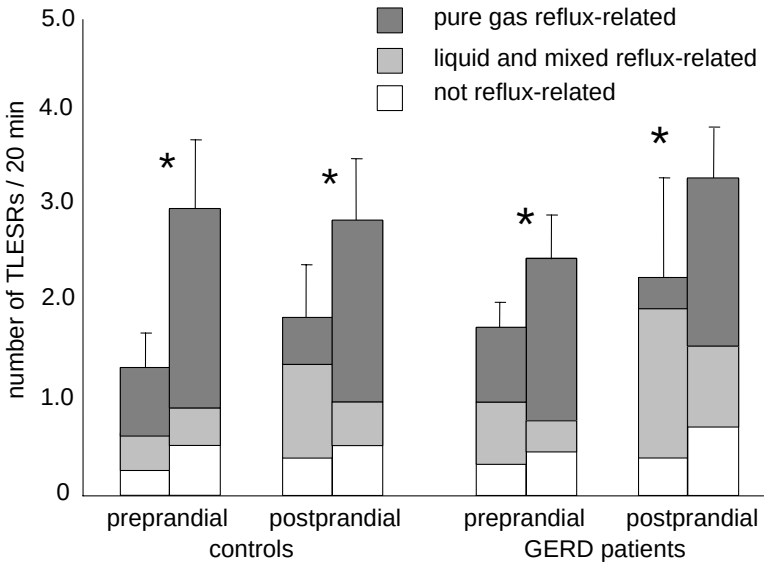

Figure 3. Number of TLESRs before and after infusion of 600 mL of air in controls and in patients with GERD. The total number of TLESRs and the number of TLESRs with gas reflux are increased after air infusion. *:p<0.05

Discussion

Belching is a symptom that is commonly reported by patients with GERD.[7,19] It has been shown that most belches occur during TLESRs.[9] TLESRs play an important role in the pathogenesis of gastroesophageal reflux.[20] During TLESRs both liquid and gaseous material can enter the esophagus and it has been suggested that acid reflux may be a variant of the belch reflex.[6] When the gas component of a reflux episode passes the upper esophageal sphincter and the liquid component does not, this is perceived as a belch.

This study has shown that in patients with GERD the rate of belching is approximately 60 % higher than in healthy subjects. This is the first study that confirms the widespread belief that belching is more common in patients with GERD. As most of the gastric gas enters the stomach with swallowing, one would expect that the GERD patients exhibit a higher number of air swallows. Indeed, the patients investigated in our study had approximately 65 % more air swallows compared with controls. Furthermore, a positive relationship was found between the rate of air swallowing and belching. In patients with GERD, higher frequencies of mixed reflux episodes and acid reflux episodes were observed as well.

These findings do not answer the question whether excessive air swallowing leads to increased gastroesophageal reflux. In order to study the effect of excessive gastric air accumulation on reflux we infused 600 mL of air in the stomach of patients with GERD and healthy controls. The results show that, although there was a significant increase in the incidence of TLESRs and gas reflux episodes in both groups, acid and weakly acidic reflux episodes did not increase after air infusion. Esophageal acid exposure was not increased either after air infusion. A similar result was found after consumption of a meal. It thus seems that the high frequencies of air swallowing and belching found in patients with GERD are not directly related to pathological gastroesophageal reflux. During a TLESR, swallowed air may escape from the stomach as pure gas reflux or in the company of liquid material, which results in mixed gas-liquid reflux. Thus gas reflux does not seem to promote the occurrence of reflux of liquid material. In contrary, although not statistically significant gas inflation seems to reduce the number of pure liquid episodes. It could be possible that the large gas volume in the proximal stomach would displace any liquid contents, thereby reducing the number of liquid reflux episodes. Another possibility is that the large volume of gas in the stomach converts liquid reflux into mixed reflux episodes.

Our observation that belching is not causing acid and weakly acidic reflux is supported by the results obtained in a study by Sifrim et al. in which the sequence of occurrence of the gas and liquid component in mixed reflux episodes was investigated.[14] The authors found that in the majority of acid reflux episodes, the liquid component was not preceded by gas but occurred as primary event. We have previously shown in healthy subjects that air swallowing and the size of the intragastric air bubble were not related to the occurrence of liquid gastroesophageal reflux.[17] However, Barham et al. reported that most acid reflux episodes in healthy subjects and patients with GERD were induced by belching.[21] In that study, belch-induced acid reflux episodes were defined as acid reflux episodes occurring during a TLESR with the presence of a common cavity. However, the possibility that belching was the result of gas reflux following liquid reflux was not mentioned. Furthermore, the assumption was made that common cavities were a reliable marker of gas reflux. Recent studies using impedance monitoring have shown that this is not the case.[14,22]

The question remains why patients swallow more air than healthy subjects. Differences in salivary secretion between patients and controls could play a role.[23] It is unlikely that differences in oropharyngeal anatomy account for these findings but it could well be that more air is captured in the pharyngeal chamber when patients initiate a swallow as a response to a retrosternal burning sensation. It has been shown that the amplitude of peristaltic contractions can be controlled voluntarily. In the study by Valori et al. big gulps resulted in larger peristaltic waves than little swallows.[24] It is not unlikely that with big gulps more air is transported as well.

In this study,we used a slightly different definition of belching than previously published definitions. Belching was defined by both pure gas and mixed liquid-gas reflux episodes in which the gas component reached the proximal esophagus and the liquid component did not. The rationale behind this was the observation that patients not only belch during gas reflux episodes but also during mixed reflux episodes.[8]

One might argue that a 20-min period is too short to measure the effect of air infusion on the incidence of gastroesophageal reflux. However, most of the gas reflux episodes occur in the first minutes after air infusion. Between 70 % and 80 % of the gas reflux episodes that were observed in this 20-min period occurred within the first 10 min. In contrast, liquid-containing reflux episodes were distributed evenly over the 20-min recording periods and approximately 50 % occurred in the second half of the recording period. Thus, the 20-min period used

in this study appears to be sufficiently long to study the possible reflux-eliciting effect of intragastric air.
Another possible limitation of this study is the fact that impedance monitoring is very useful to investigate patterns of air transport but it is not an ideal tool to perform quantitative assessments of esophageal contents. Contact of the electrodes with the mucosa can blur an impedance increase caused by the passage of air and on the other hand a small volume of liquid can go undetected when its passage coincides with a large volume of gas.
In conclusion, in patients with GERD the frequency of air swallows, acid reflux, and belches is higher than in healthy subjects. However, it is unlikely that increased air swallowing is the cause of increased acid and weakly acidic reflux in GERD patients.

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Summary

Chapter 1, the general introduction, offers a description of the important role of transient lower oesophageal sphincter relaxations (TLOSRs) and hiatal hernias in the pathophysiology of gastro-oesophageal reflux disease. The complex relationship between reflux symptoms and the occurrence of gastro-oesophageal reflux episodes is discussed. Furthermore, the potential for oesophageal application of new investigational techniques such as intraluminal impedance monitoring and high-resolution manometry is made clear. Finally we discuss what is known about pathophysiology and presentation of aerophagia, a rare disorder in which patients complain of excessive belching. At the end of chapter 1 the nine questions are formulated that were addressed during our studies.

In **chapter 2** the minimal sample frequency required to evaluate oesophageal transit and gastro-oesophageal reflux using impedance monitoring is investigated. In all systems for impedance monitoring signals are stored in digital format after analog-to-digital (A/D) conversion at a predefined rate, the sample frequency. In healthy subjects and patients with reflux disease impedance signals were acquired during a postprandial period, using a sample frequency of 1000 Hz. Additionally, 10 liquid swallows were recorded in the healthy subjects. Dedicated software was used to derive, from the original 1000-Hz files, series of new data files with sample frequencies of 500, 200, 100, 50, 20, 10, 8, 5 and 4 Hz. In all these files, liquid and gas reflux events were identified. In the analysis of the swallows, bolus head advance time and total bolus transit time were measured. Reflux events were detectable down to a sample frequency of 50 Hz. In transit analysis errors for bolus head advance time at frequencies below 8 Hz exceeded 2.5 %. Therefore, in impedance monitoring the minimal sample frequency is 50 Hz for the detection of reflux and 8 Hz for the evaluation of oesophageal transit.

The reproducibility of gastro-oesophageal reflux detection using impedance monitoring was studied in **chapter 3**. Oesophageal impedance and pH signals were recorded in 20 healthy volunteers during 90-min postprandial periods on two separate days. Hourly rates of gas, liquid and mixed gas-liquid reflux episodes were measured in each recording period as well as the percentage of time with pH < 4 and the rate at which acid reflux episodes occurred. As a quantitative description of inter- and intra-individual variation for each variable, the mean % of covariation was calculated. As a second measure for reproducibility, Kendall's coefficients of concordance (W values) were calculated. For all variables, inter-individual % of covariation was at least 50 % higher than intra-individual % of covariation. Statistically significant

concordances between the two days were found for gas reflux and mixed reflux episodes while concordance for liquid reflux episodes tended to be significant. Comparable concordances were found for the reflux episodes measured with impedance and the number of acid reflux episodes and % of time with pH < 4. Therefore we are confident that postprandial reflux data assessed with impedance monitoring are as reproducible as assessed with pH monitoring.

In **chapter 4** a study of the pressure inversion point (PIP) is described. The PIP is defined as the point at which, during stationary pull-through manometry of the oesophago-gastric junction, the polarity of the respiratory-associated pressure variations changes. Traditionally, the PIP is ascribed to transition of the pressure sensor from the abdominal to the thoracic cavity. We used high-resolution manometry to investigate the validity of this concept in healthy volunteers and in patients with a sliding hiatus hernia. In the analysis of the manometric tracings, the position of the PIP was identified. When there was a second, more distal PIP, its position was also noted. The amplitude of the respiratory-associated pressure variations, defined as the difference between end-expiratory and end-inspiratory pressure, was also measured. We found that double PIPs were found both in healthy controls (23 % of time) and in patients with a hernia (38 % of time). Amplitudes of the respiratory-associated pressure variations were significantly higher at the proximal and distal border of the PIP than in the oesophageal body and stomach. We also observed a relationship between the localization of the highest end-expiratory pressure and the position of the PIP. During TLOSRs the amplitude of the respiratory pressure variations at the proximal and distal border of the PIP decreased, approximating respiratory pressure variations in the oesophagus and stomach. We conclude that the PIP is caused by sliding of the high-pressure zone along pressure sensors rather than by the transition from the thoracic to the abdominal compartment. A double PIP is likely to result from sliding of the catheter along two high-pressure zones: the lower oesophageal sphincter (LOS) and the diaphragm.

Another study with high-resolution manometry is described in **Chapter 5**. The anti-reflux barrier at the oesophago-gastric junction consists of the intrinsic LOS and the diaphragmatic sphincter. In patients with a hiatal hernia these constituents are separated. We performed high-resolution manometry of the oesophago-gastric junction in healthy controls, patients with a small hernia and patients with a large hernia. Prevalence of a double high-pressure zone profile of the oesophago-gastric junction was noted and pressures and distance between

the pressure zones were assessed. Patients with a large hernia showed a significantly higher prevalence of the double pressure zone profile with inspiration than patients with a small hiatal hernia and controls. The distance between the two high-pressure zones was also larger in patients with a large hernia. In conclusion, high-resolution manometry makes it possible to distinguish the diaphragmatic pressure component from the LOS. Two high-pressure zones can not only be found in subjects with a hiatal hernia but also in healthy volunteers.

In **chapter 6** we investigate whether high-resolution manometry is as reliable for the detection of TLOSRs as sleeve sensor manometry. In order to study this, we performed prolonged oesophageal manometry using a catheter incorporating both a sleeve sensor and closely spaced sideholes straddling the oesophago-gastric junction. TLOSRs detected with either one or both techniques were scored. Reflux during TLOSRs was detected using manometry (common cavity), intraluminal impedance and pH monitoring. A similar number of TLOSRs was detected using both techniques. There was no difference in the proportion of TLOSRs accompanied by reflux between TLOSRs detected with high-resolution and TLOSRs detected with sleeve sensor manometry. We conclude that high-resolution manometry is as accurate as sleeve sensor manometry for the detection of TLOSRs.

In **chapter 7** we studied patients with a small hiatal hernia. As observed in the study presented in chapter 5, intermittent complete reduction of a hiatal hernia can be observed with high-resolution manometry as a transition from a double high-pressure zone profile (hernia) to a single (reduced) high-pressure zone profile. In this chapter we investigated whether intermittent separation of diaphragm and LOS favours the occurrence of gastro-oesophageal reflux. In patients with a small hiatal hernia prolonged high-resolution manometry was performed. Combined pH-impedance monitoring was used to detect acid and weakly acidic reflux episodes. We found that the single high-pressure zone profile (reduced hernia) was present for 56.5 % of the total time and the double high-pressure zone profile (unreduced hernia) was present for 43.5 % of the total time. In all patients both pressure profiles were observed. The reflux rate was almost doubled when the LOS and diaphragm were separated versus the reflux rate in the reduced hernia state. In the two-pressure-zone state there was an increase in all reflux mechanisms except TLOSRs. Based on this data we conclude

that spatial separation of the diaphragm and LOS results in a two-fold increase in acidic and weakly acidic reflux, due to reflux mechanisms other than TLOSRs.
In **chapter 8** we describe a study in which we investigated why some TLOSRs are accompanied by gastro-oesophageal reflux and others are not. In 12 healthy subjects prolonged high-resolution manometry was performed and reflux was detected using pH-impedance monitoring. A total of 219 TLOSRs were detected. No differences were observed between the duration of TLOSRs with liquid-containing reflux, gas reflux and no reflux. The trans-sphincteric pressure gradient was similar in TLOSRs with liquid reflux, gas reflux and no reflux. Prevalence, duration and amplitude of oesophageal pre-contractions and sphincteric after-contractions were not different for TLOSRs with and without reflux. The total number of TLOSRs decreased significantly from 8.2±0.8 in the first to 5.7±0.5 in the second and 4.4±0.6 in the third 70-min recording period. The number of TLOSRs accompanied by liquid-containing reflux decreased from the first to the third 70-min period while the number of TLOSRs with gas reflux remained unchanged. These data suggest that factors other than TLOSR characteristics determine whether or not gastro-oesophageal reflux occurs during the TLOSR.

An overview on the literature on symptom association analysis is provided in **chapter 9**. Reflux of gastric contents may lead to symptoms and mucosal inflammation. While the latter can be detected endoscopically, symptom-reflux association analysis is the only method that can adequately identify reflux as the cause of short-lived symptoms with sudden onset such as heartburn, regurgitation, chest pain and cough. Such analysis should therefore be included in every 24-hour pH study evaluating these complaints. We conclude that indices that express the strength of the symptom-reflux association numerically, such as the symptom index (SI), symptom sensitivity index (SSI) and the symptom association probability (SAP), constitute the most important information that can be obtained from a 24-hour pH study.

In **chapter 10** we describe a study in which the yield of symptom-reflux association analysis of combined oesophageal pH-impedance data is compared to the yield of analysis of pH data alone. In 60 patients with symptoms of heartburn and regurgitation combined 24-hour pH-impedance monitoring was performed. Acid-suppressive medication was stopped in advance. Patients were instructed to note the time of occurrence and nature of each of their symptoms. Eleven types of reflux episodes were defined, based on combinations of magnitude of the pH

drop, nadir pH and nature of the refluxate (gas, liquid) on impedance tracings. Symptom association analysis using the SI, SSI and SAP was performed for each definition of reflux. We found that the proportion of patients with a positive SAP varied, depending on the definition of reflux episodes. When both pH and impedance parameters were used to identify reflux a higher proportion of patients had a positive SAP than with pH alone. Symptom association analysis for acidic and weakly acidic reflux separately did not result in a higher yield than analysis with all reflux episodes pooled, regardless of pH. The conclusion of this study is therefore that in patients off proton pump inhibitors the addition of impedance monitoring to oesophageal pH monitoring leads to an increase in the proportion of patients in whom an association between reflux episodes and symptoms can be identified.

Chapter 11 describes a case of a 72-year old female patient presenting with heartburn. During pH monitoring not a single acid reflux episode was detected and achlorhydria was suspected. Upper endoscopy revealed atrophic gastritis and antibodies against parietal cells and intrinsic factor were found. The diagnosis of autoimmune atrophic gastritis was made and 24-hour impedance pH monitoring was performed. Again no acid reflux was observed, but weakly acidic and weakly alkaline reflux episodes were observed. A positive temporal relationship between weakly acidic reflux episodes and the onset of heartburn episodes was found, demonstrating that in this achlorhydric patient heartburn resulted from gastro-oesophageal reflux of weakly acidic material. We conclude that impedance monitoring provides important information as to whether or not symptoms are related to reflux episodes, even in patients with achlorhydria.

In **chapter 12** we investigated the enigma why some reflux episodes evoke symptoms and others do not. In patients with symptoms suggestive of gastro-oesophageal reflux, characteristics of symptomatic and asymptomatic reflux episodes were compared. Compared to asymptomatic episodes, symptomatic episodes were associated with a larger pH drop, lower nadir pH and higher proximal extent. Symptomatic reflux episodes also had a longer volume and acid clearance time and symptomatic episodes were preceded by a higher oesophageal cumulative acid exposure time. The proximal extent of episodes preceding regurgitation was larger than that of those preceding heartburn. Only 15 % of the symptomatic reflux episodes were weakly acidic. Some pure gas reflux episodes were symptomatic. These symptomatic pure gas reflux episodes were more frequently accompanied by a pH drop than asymptomatic gas reflux

episodes. These findings indicate that heartburn and regurgitation are more likely to be evoked when the pH drop is large, the proximal extent of the refluxate is high and volume and acid clearance are delayed. Sensitization of the oesophagus occurs by preceding acid exposure. Furthermore, weakly acidic reflux is responsible for only a minority of symptoms in patients off therapy. Pure gas reflux associated with a pH drop ("acid vapour") can also be perceived as heartburn and regurgitation.

Besides acidity other factors such as proximal extent may determine whether a reflux episode is perceived or not. In **chapter 13** we aimed to investigate the reflux profile of GORD patients with a physiological acid exposure and an association between reflux episodes and symptoms. Twenty-four hour impedance-pH monitoring was performed in 14 GORD patients with excessive acid exposure (pH+), 14 GORD patients with physiological acid exposure (pH-) and 14 controls. All patients had a positive symptom-reflux association during 24-hour monitoring (SAP+). We found that the incidence of acid reflux episodes in pH- SAP+ patients and controls was comparable but lower than in pH+ SAP+ patients. No differences in number of weakly acidic reflux episodes were observed between pH- SAP+ patients, pH+ SAP+ patients and controls. The proportion of reflux episodes that reached the proximal oesophagus was significantly higher in the pH+ SAP+ (33.5 %) and pH- SAP+ (36.0 %) patients than in the controls (19.5 %). These findings lend further support to the concept that proximal extent of the refluxate is an important factor in the generation of reflux symptoms.

In **chapter 14** patients with aerophagia are studied. These patients are believed to have excessive belching due to air swallowing. In order to investigate this, we measured oesophageal pH and impedance before and after a meal in patients with excessive belching and healthy controls and identified patterns of air transport through the oesophagus. The size of the gastric air bubble was measured radiographically. We observed that in all subjects air is propelled in front of about a third of the swallow-induced peristaltic waves (air swallows). Two types of retrograde gas flow through the oesophagus (belch) were observed. In the first type air flowed from the stomach through the oesophagus in oral direction ("gastric belch"). In the second type air entered the oesophagus rapidly from proximal and was expulsed almost immediately in oral direction ("supragastric belch"). Surprisingly, the incidence of air-containing swallows and gastric belches were similar in patients and controls but supragastric belches occurred exclusively in patients. The conclusion that can be drawn from this

study is therefore that in patients with excessive belching the incidence of gaseous reflux from the stomach to the oesophagus is similar to that in healthy subjects. Their excessive belching activity follows a distinct pattern, characterized by rapid antegrade and retrograde flow of air in the oesophagus that does not reach the stomach.

In **chapter 15** the effects of attention and distraction on the frequency of belching in patients with aerophagia are described. A study was performed in which combined oesophageal manometry and impedance monitoring was performed for 2 hours, divided into 4 30-min recording periods. Period I: patient unaware that recording had commenced. Period II: patient informed of recording in progress. Period III: distraction by filling in questionnaires. Period IV: no distraction. A total of 1258 belches was measured, 51 of which were the result of air that escaped from the stomach (gastric belches). 1207 belches (96 %) were events during which air was expelled in oral direction almost immediately after entering the oesophagus from proximally (supragastric belches). Gastric belches were distributed equally over the four recording periods. In contrast, the incidence of supragastric belches increased significantly from period I to period II, after patients were told that recording was started. During period III (questionnaires) the incidence of supragastric belches decreased while period IV the incidence of supragastric belches increased again. Thus, when patients with excessive belching are unaware that they are being studied or when they are distracted the incidence of belching is significantly reduced. These findings underline the importance of psychological factors and provide rationale for behavioural therapy in this disorder.

Chapter 16 describes the relationships between air swallowing, intragastric air, belching and gastro-oesophageal reflux in healthy subjects. During swallowing air can be transported to the stomach. The stomach protects itself against excessive distention by swallowed air through belching (gas reflux). As mentioned, the mechanism of belching (TLOSR) is also one of the mechanisms underlying gastro-oesophageal reflux. Aim of this study was to investigate whether swallowing of air leads to an increase in size of the intragastric air bubble and to gastro-oesophageal reflux. Multichannel intraluminal impedance measurement was used to quantify the incidence of swallowing of air in healthy volunteers before and after a meal. Radiography was used to measure the size of the intragastric air bubble. Gastro-oesophageal reflux was assessed by concurrent impedance and pH measurement. We observed that the rate of air swallowing was correlated to the

size of the intragastric air bubble after the meal and to the rate of gaseous gastro-oesophageal reflux. The number of air swallows and the size of the intragastric air bubble did not correlate with the number of liquid acid and non-acid reflux episodes. We thus conclude that in healthy subjects, air swallowing promotes belching but does not facilitate acid reflux.

Belching and gastro-oesophageal reflux share a common physiological mechanism. In **chapter 17** we describe a study in which we investigated whether air swallowing leads to both belching and reflux. Oesophageal impedance, pH and pressure were measured during two 20-min recording periods in 12 controls and 12 patients with GORD, before and after intragastric inflation of 600 mL of air. This was repeated after consumption of a meal. Subsequently, ambulatory 24-hour impedance-pH measurement was performed. During the 24-hour study, patients showed a higher incidence of air swallows, belches and acid reflux than controls. After air infusion the incidence of gas reflux episodes was increased, both in patients and in controls. In contrast, the incidence of acid and weakly acidic reflux episodes was not increased after air infusion, neither in patients, nor in controls. Air infusion increased TLOSR frequency in patients and controls, but this was entirely due to an increase in gas reflux-associated TLOSRs. We conclude that patients with GORD swallow air more frequently and belch more frequently than healthy subjects. However, air swallowing is not the cause of their increase in reflux.

The questions that were formulated at the end of chapter 1 can be answered as follows:

1 The minimal sample frequency for gastro-oesophageal reflux monitoring using impedance monitoring is 50 Hz and the minimum sample frequency for transit testing is 8 Hz.
2 Detection of gastro-oesophageal reflux with intraluminal impedance monitoring is as reproducible as reflux detection using pH monitoring.
3 High-resolution manometry can be used to study the two components of the oesophago-gastric junction and is as accurate as sleeve sensor manometry for the detection of TLOSRs.
4 Spatial separation of the diaphragm and LOS as a consequence of a hiatal hernia results in a two-fold increase in acidic and weakly acidic reflux, due to reflux mechanisms other than TLOSRs.
5 The magnitude of the pH drop, proximal extent of the refluxate, volume and acid clearance time and preceding acid exposure determine whether a reflux episode is perceived or not.
6 In patients off proton pump inhibitors the addition of impedance monitoring to oesophageal pH monitoring leads to an increase in the proportion of patients in whom a positive association between reflux episodes and symptoms can be identified.
7 Patients with aerophagia exhibit air swallowing and gastric belches in similar frequencies as healthy subjects. Their excessive belching activity follows a distinct pattern, characterized by rapid antegrade and retrograde flow of air in the oesophagus that does not reach the stomach, which we describe as supragastric belching.
8 During distraction a pronounced decrease in frequency of belching is observed in patients with aerophagia, while an increase in belching occurs when the patient’s attention is focussed on belching.
9 Intra-gastric air injection and air swallowing lead to gastro-oesophageal reflux of gas but not of liquids.

Nederlandse samenvatting

Hoofdstuk 1 vormt de algemene inleiding. Hierin wordt de rol van "transient lower oesophageal sphincter relaxations" (TLOSRs) en hiatus-hernia in de pathofysiologie van gastro-oesofageale refluxziekte beschreven. De complexe relatie tussen refluxsymptomen en het vóórkomen van reflux wordt behandeld. Tevens worden twee nieuwe technieken beschreven waarmee de functie van de slokdarm kan worden onderzocht, te weten intraluminale impedantiemeting en "high-resolution" manometrie. Tenslotte wordt samengevat wat bekend is van de pathofysiologie en presentatie van aerofagie, een relatief zeldzame aandoening waarbij de patiënt klaagt over overmatig boeren.

In **hoofdstuk 2** wordt een onderzoek beschreven naar de minimale bemonsteringsfrequentie ("sample frequentie") die vereist is voor impedantiemetingen van de slokdarm. Hierbij werd onderscheid gemaakt tussen toepassing van de techniek voor onderzoek van slokdarmpassage en onderzoek van gastro-oesofageale reflux. Bij gezonde proefpersonen en bij patiënten met refluxziekte werden na het nuttigen van een maaltijd impedantiemetingen gedaan waarbij de signalen werden opgeslagen met een frequentie van 1000 Hz. Tevens werden impedantiesignalen geregistreerd tijdens het slikken van een kleine hoeveelheid water. Met behulp van speciaal ontworpen software werden de 1000 Hz bestanden omgezet in bestanden met een sample frequentie van 500, 200, 100, 50, 20, 10, 8, 5 en 4 Hz. In deze bestanden werden alle vloeibare en gasvormige reflux-episoden geïdentificeerd. Voor de analyse van de slokdarmpassage werden "bolus head advance time" en "total bolus transit time" gemeten. Verlaging van de sample frequentie had geen effect op de detectie en kwantificering van reflux tot een sample frequentie van 50 Hz. In de analyse van de slokdarmpassage (waterslokken) werd de afwijking ten opzichte van het 1000 Hz origineel groter dan 2.5 % wanneer de sample frequentie lager was dan 8 Hz. Daarom concluderen wij dat 50 Hz de minimale sample frequentie is voor refluxdetectie en 8 Hz de minimale sample frequentie voor analyse van slokdarmpassage.

In het in **hoofdstuk 3** beschreven onderzoek werd de reproduceerbaarheid van impedantie- en pH-signalen onderzocht. Twintig gezonde vrijwilligers ondergingen een impedantie- en pH-meting op 2 verschillende dagen. De gasvormige, vloeibare en gemengde (gas-vloeistof) reflux-episoden werden geregistreerd, alsook het percentage van de tijd met de pH onder de 4 en het aantal zure reflux-episoden. Als maat voor de inter- en intra-individuele variatie van elke parameter werd het gemiddelde co-variatie-percentage berekend.

Tevens werd de Kendall's coefficient of concordance (W-waarde) berekend voor iedere variabele. Voor alle variabelen gold dat het inter-individuele co-variatie-percentage tenminste 50 % hoger lag dan het intra-individuele co-variatie-percentage. Statistisch significante concordantie tussen de twee dagen werd gevonden voor gasvormige en gemengde reflux-episoden terwijl de concordantie voor vloeibare reflux een duidelijke trend in de richting van significantie vertoonde. Een vergelijkbare concordantie werd gevonden voor de reflux-episoden gemeten met impedantie en voor de pH-metrische parameters percentage van de tijd onder de pH 4 en het aantal zure reflux-episoden. De conclusie is dat refluxdetectie uitgevoerd met impedantiemeting een reproduceerbaarheid heeft die vergelijkbaar is met die van refluxdetectie met pH-metrie.

Hoofdstuk 4 beschrijft een onderzoek naar het "pressure inversion point" (PIP). Het PIP wordt omschreven als het punt waarop tijdens een "pull-through" manometrie van het sfinctercomplex de polariteit van de ademhaling-gerelateerde drukvariaties omkeert. Doorgaans wordt de oorsprong van het PIP toegeschreven aan de overgang van het abdominale compartiment naar het thoracale compartiment. Wij besloten dit concept te onderzoeken door middel van high-resolution manometrie bij gezonde vrijwilligers en bij patiënten met een hiatus-hernia. Tijdens de analyse werd de positie van het PIP geïdentificeerd. Wanneer er tevens een tweede, meer distaal gelegen PIP te zien was, werd de positie van dit PIP ook genoteerd. De amplitude van de respiratoire drukvariaties, gedefinieerd als het verschil tussen eind-expiratoire en eind-inspiratoire druk, werd ook gemeten. We vonden dubbele PIPs zowel bij gezonde vrijwilligers (23 % van de totale tijd) als bij patiënten met een hernia (38 % van de totale tijd). De amplitudes van de ademhaling-gerelateerde drukvariaties waren significant hoger rond het PIP dan elders in de slokdarm en in de maag. Er werd een verband gevonden tussen de lokalisatie van de hoogste eind-expiratoire druk en de positie van het PIP. Tijdens TLOSRs verminderde de amplitude van de ademhaling-gerelateerde drukvariaties rond het PIP en benaderde deze de grootte van drukvariaties in de slokdarm en maag. We concluderen dan ook dat het PIP wordt veroorzaakt door het op-en-neer bewegen van de hoge-drukzone langs druksensoren op de catheter en niet wordt veroorzaakt door de overgang van het thoracale naar het abdominale compartiment. Een dubbel PIP wordt waarschijnlijk veroorzaakt door het op-en-neer bewegen van twee hoge-drukzones: de onderste slokdarm sfincter (LOS) en het diafragma.

Een volgend onderzoek met high-resolution manometrie wordt beschreven in **hoofdstuk 5**. De anti-reflux-barrière op de overgang van slokdarm naar maag bestaat uit de LOS en een deel van het diafragma dat fungeert als sfincter. Bij patiënten met een hiatus-hernia liggen deze twee delen uit elkaar. High-resolution manometrie werd uitgevoerd bij gezonde vrijwilligers, bij patiënten met een kleine hiatus-hernia en bij patiënten met een grote hiatus- hernia. Het vóórkomen van een dubbele hoge-drukzone op de slokdarm-maag overgang werd bestudeerd en de druk in en de afstand tussen de twee hoge-drukzones werd gemeten. Bij patiënten met een grote hernia kwam een dubbele hoge-drukzone significant vaker voor dan bij patiënten met een kleine hiatus-hernia en gezonde vrijwilligers. De afstand tussen de twee hoge-drukzones was tevens groter bij de patiënten met een grote hernia. Concluderend stellen we dat high-resolution manometrie het mogelijk maakt om het aandeel van het diafragma en de LOS afzonderlijk te bestuderen. Verder worden twee hoge-drukzones niet alleen gevonden bij patiënten met een hiatus-hernia maar ook bij gezonde vrijwilligers.

In **hoofdstuk 6** wordt een onderzoek beschreven waarin werd geëvalueerd of high-resolution manometrie even geschikt is voor de detectie van TLOSRs als de huidige gouden standaard techniek, namelijk manometrie met behulp van een zogeheten sleeve sensor. Er werd gebruik gemaakt van een katheter met zowel een sleeve sensor als met een high-resolution deel ter hoogte van de slokdarm-maag-overgang. We analyseerden het aantal TLOSRs dat werd gedetecteerd met een of beide technieken. Reflux tijdens TLOSRs werd gedetecteerd door middel van manometrie (“common cavity” fenomeen), impedantie-registratie en pH-metrie. Er werden gelijkaardige aantallen TLOSRs gedetecteerd met sleeve sensor manometrie als met high-resolution manometrie. Er werd geen verschil gevonden tussen beide technieken in het percentage TLOSRs dat gepaard ging met reflux. We concluderen dan ook dat high-resolution manometrie even accuraat is voor TLOSR detectie als sleeve sensor manometrie.

In **hoofdstuk 7** wordt een onderzoek met high-resolution manometrie beschreven waarin het effect van tijdelijke spontane reductie van een kleine hiatus-hernia op gastro-oesofageale reflux werd geëvalueerd. Zoals beschreven in hoofdstuk 5 kan tijdelijke complete reductie van een hiatus-hernia worden waargenomen met high-resolution manometrie als de overgang van twee hoge-drukzones (LOS en diafragma gescheiden: hernia) naar één hoge-drukzone (LOS en diafragma vallen samen: gereduceerde status). Tot anderhalf uur na een maaltijd werden intraluminale drukken geregistreerd met behulp van high-resolution manometie

en werd gecombineerde pH-impedantie meting gebruikt voor de detectie van zure en zwak-zure reflux-episoden. De hernia was gereduceerd (één hoge-drukzone) gedurende 56.5 % van de totale tijd en aanwezig (twee hoge-drukzones) gedurende 43.5 % van de totale tijd. Zowel het herniaprofiel als het gereduceerde profiel werd bij alle patiënten aangetroffen. Wanneer de LOS en het diafragma gescheiden waren, verdubbelde het vóórkomen van reflux. Alle refluxmechanismen behalve TLOSRs waren hiervoor verantwoordelijk. We concluderen dat spatiële scheiding van diafragma en LOS leidt tot een verdubbeling van zure en zwak-zure reflux. Deze verdubbeling is het gevolg van een toename van andere refluxmechanismen dan TLOSRs.

In **hoofdstuk 8** beschrijven we een onderzoek waarin werd nagegaan waarom sommige TLOSRs wel met gastro-oesofageale reflux gepaard gaan en andere niet. High-resolution manometrie werd verricht bij 12 gezonde vrijwilligers en reflux werd gedetecteerd middels pH-impedantie meting. In totaal werden er 219 TLOSRs gedetecteerd. Er werden geen verschillen aangetoond in de duur van de TLOSRs die gepaard gingen met reflux van vloeistoffen, TLOSRs gepaard met gas reflux en TLOSRs zonder reflux. De drukgradiënt over de LOS was eveneens niet verschillend tussen deze TLOSRs. Het vóórkomen, de duur en de amplitude van oesofageale contracties voor TLOSRs en sfincterische contracties na TLOSRs was niet verschillend tussen TLOSRs met en zonder reflux. Er was een significante afname van het totaal aantal TLOSRs van 8.2±0.8 in de eerste postprandiale meetperiode tot 5.7±0.5 in de tweede en 4.4±0.6 in de derde meetperiode van 70 minuten. Het aantal TLOSRs met vloeibare reflux nam af van de eerste naar de derde 70-minuten periode terwijl het aantal TLOSRs met gasvormige reflux onveranderd bleef. Deze gegevens suggereren dat niet de karakteristieken van TLOSRs maar andere factoren bepalen of TLOSRs worden vergezeld van gastro-oesofageale reflux.

In **hoofdstuk 9** wordt een overzicht gegeven van de literatuur over de analyse van de associatie tussen refluxsymptomen en reflux. Gastro-oesofageale refluxziekte (GORZ) wordt gedefineerd als mucosale schade en/of symptomen als gevolg van het terugstromen van maaginhoud in de slokdarm. Schade aan de slokdarmmucosa kan men detecteren door middel van endoscopie maar symptoom-associatie-analyse is de enige methode die op een betrouwbare wijze reflux als oorzaak van symptomen als zuurbranden, oprispingen, retrosternale pijn en hoest kan identificeren. Een pathologische zuur-expositietijd van de slokdarm bewijst namelijk niet dat de symptomen van de patiënt het gevolg zijn

van zure reflux. Het is daarom aangewezen om symptoom-associatie-analyse uit te voeren bij elke 24-uurs pH-metrie die wordt verricht voor dergelijke klachten. We concluderen dat indices die de relatie tussen symptomen en reflux episoden numeriek uitdrukken, zoals de symptom index (SI), symptom sensitivity index (SSI) en de symptom association probability (SAP), belangrijke informatie verschaffen.

In **hoofdstuk 10** wordt een onderzoek beschreven waarin de diagnostische opbrengst van analyse van de correlatie tussen symptomen en reflux-episoden ("symptoom-associatie-analyse") in gecombineerde pH- en impedantiemetingen werd vergeleken met die van pH-metingen alleen. Zestig patiënten met klachten van zuurbranden en oprispingen ondergingen een 24-uurs pH- en impedantiemeting. De zuurremmende medicatie werd een week voor de meting gestaakt. We instrueerden de patiënten om het tijdstip en de aard van hun klachten te noteren. Elf verschillende definities van reflux episoden werden gehanteerd, gebaseerd op combinaties van grootte van de pH-daling, laagst gemeten pH en de aard van de reflux-episode (gas, vloeibaar). Symptoomanalyse werd voor elke definitie afzonderlijk uitgevoerd. Dit resulteerde erin dat het percentage van de patiënten met een positieve SAP varieerde, afhankelijk van de definitie die werd gebruikt. De diagnostische opbrengst was hoger bij reflux-definities die zowel pH- als impedantie-parameters gebruikten. Aparte symptoom-analyse voor zure en zwak-zure reflux episoden resulteerde niet in een hogere opbrengst dan symptoom-analyse waarbij alle reflux-episoden samen werden genomen, onafhankelijk van de pH. De conclusie van dit onderzoek is dan ook dat bij patiënten die hun medicatie hebben gestaakt voor de meting de combinatie van pH- en impedantie-meting reflux vaker kan identificeren als oorzaak van de klachten dan pH-metrie alleen.

In **hoofdstuk 11** beschrijven we de casus van een 72 jarige vrouw die zich presenteerde met klachten van zuurbranden. Tijdens de pH-meting werd echter geen enkele zure reflux-episode gemeten en het vermoeden van achloorhydrie rees. Tijdens de endoscopie werd een atrofische gastritis aangetroffen. Het serum van onze patiënte was positief voor antilichamen tegen pariëtale cellen en intrinsic factor. De diagnose atrofische gastritis op auto-immune basis werd gesteld. Vervolgens werd 24-uurs pH- en impedantie-meting uitgevoerd om de oorzaak van het zuurbranden op te sporen. Wederom kwamen er geen zure reflux-episoden voor, maar zwak-zure en zwak-alkalische reflux-episoden werden wel gemeten. De relatie tussen reflux-episoden en symptomen bleek positief,

hetgeen aantoonde dat gastro-oesofageale reflux de oorzaak was van haar zuurbrandklachten. We concluderen dat een impedantie-meting belangrijke informatie kan verschaffen over of symptomen wel of niet gerelateerd zijn aan reflux-episoden, zelfs bij patiënten met achloorhydrie.

Hoofdstuk 12 wordt een studie beschreven waarin wordt onderzocht waarom sommige reflux-episoden wel waargenomen worden (met andere woorden symptomatisch zijn) en andere niet. De karakteristieken van symptomatische en asymptomatische reflux-episoden werden vergeleken in patiënten met symptomen die suggestief zijn voor reflux. Vergeleken met asymptomatische reflux-episoden hadden symptomatische reflux-episoden een grotere pH-daling, een lagere minimale pH en reikten tot hoger in de slokdarm. Verder duurde de volume- en zuur-klaring van symptomatische reflux-episoden langer en werden symptomatische reflux episoden voorafgegaan door een grotere cumulatieve oesofageale zuur-expositie dan asymptomatische reflux-episoden. Reflux-episoden die gepaard gingen met het symptoom regurgitatie (oprisping) kwamen hoger in de slokdarm dan reflux-episoden die zuurbranden uitlokten. Slechts 15 % van de symptomatische reflux-episoden werd veroorzaakt door zwak-zure reflux-episoden. Enkele puur gasvormige reflux-episoden waren symptomatisch, deze gingen frequenter gepaard met een pH-daling dan asymptomatische gasvormige reflux-episoden. Deze gegevens suggereren dat reflux-episoden eerder zuurbranden en regurgitatie veroorzaken wanneer zij gepaard gaan met een diepe pH-daling, tot hoog in de slokdarm reiken en een trage zuur- en volumeklaring hebben. De slokdarm wordt gesensitiseerd door voorafgaande expositie aan zuur. Verder zijn zwak-zure reflux-episoden verantwoordelijk voor slechts een klein deel van de symptomen bij patiënten die hun medicatie hebben gestaakt. Puur gasvormige reflux geassocieerd met een pH-daling (“zure damp”) kan gepaard gaan met zuurbranden en regurgitatie.

Het al dan niet symptomatisch zijn van reflux episodes wordt door bepaald door de zuurgraad en andere factoren zoals de proximale uitbreiding van een reflux episode. In **hoofdstuk 13** onderzochten we het reflux profiel van GORZ patiënten met een fysiologische blootstelling van de slokdarm aan maagzuur die een associatie hebben tussen het vóórkomen van reflux episoden en reflux symptomen. Vierentwintig-uurs impedantie-pH metingen werden uitgevoerd bij 14 GORZ-patiënten met een overmatige blootstelling van de slokdarm aan zuur (pH+), 14 GORZ-patiënten met een fysiologische blootstelling van de slokdarm aan zuur (pH-) en 14 gezonde vrijwilligers. Alle patiënten hadden een positieve

symptoom-reflux associatie tijdens de 24-uurs meting (SAP+). Het vóórkomen van zure reflux-episoden in de pH- SAP+ patiënten en de gezonde vrijwilligers was gelijkaardig en lager dan dat bij pH+ SAP+ patiënten. Er werden geen verschillen tussen de 3 groepen gevonden in het vóórkomen van zwak zure reflux-episoden (pH tussen 4 en 7). De fractie van reflux episoden die de proximale slokdarm bereikte was bij de pH- SAP+ reflux-patiënten (36.0 %) en bij de pH+ SAP+ reflux patiënten (33.5 %) hoger dan de gezonde vrijwilligers (19.5%). Deze bevindingen ondersteunen het concept dat de proximale uitbreiding van het refluxaat een belangrijke factor is bij het totstandkomen van reflux-symptomen.

Hoofdstuk 14 handelt over patiënten met aerofagie, een afwijking die gekenmerkt wordt door overmatig boeren. Onder artsen heerst de gedachte dat deze patiënten overmatig boeren doordat zij te veel of te frequent lucht slikken. Patiënten zijn er dikwijls van overtuigd dat overmatige intragastrische gasvorming de oorzaak is van hun symptomen. We onderzochten dit door voor en na een maaltijd pH en impedantie te meten in de slokdarm van patiënten met aerofagie en gezonde vrijwilligers en de patronen van luchttransport door de slokdarm te analyseren. De grootte van de intragastrische luchtbel werd beoordeeld op Röntgen-opnamen.
Bij alle personen namen we waar dat lucht werd voortgestuwd tijdens één op de drie slik-geïnduceerde peristaltische golven (luchtslikken). Twee typen van gastransport in retrograde richting (boeren) werden geïdentificeerd. In het eerste type boer ontsnapte lucht vanuit de maag in proximale richting ("gastrische boer"). Het tweede type boer kenmerkte zich door een snelle influx van lucht vanuit proximale richting dat bijna onmiddellijk werd uitgedreven in proximale richting ("supra-gastrische boer"). De frequentie van luchtslikken en gastrisch boeren was niet verschillend tussen patiënten en vrijwilligers, maar supra-gastrische boeren kwamen uitsluitend voor bij de patiënten.
We kunnen concluderen dat bij patiënten met overmatig boeren de frequentie van gasvormige reflux van maag naar slokdarm niet hoger is dan die bij gezonde vrijwilligers. Het overmatige boeren waar deze patiënten over klagen ontstaat door een ander mechanisme dat wordt gekenmerkt door een snelle antegrade influx van lucht gevolgd door het uitstoten van deze lucht in retrograde richting. Deze lucht bereikt de maag dus niet.

In **hoofdstuk 15** worden de effecten van aandacht en afleiding op de frequentie van boeren bij patiënten met aerofagie beschreven. Er werd een onderzoek uitgevoerd waarbij gedurende 2 uur de drukken en impedantie in de slokdarm

werd gemeten. Deze meetperiode werd verdeeld in 4 periodes van elk 30 minuten. Periode I: patiënt is zich niet bewust dat hij wordt gemeten. Periode II: patiënt wordt medegedeeld dat er wordt gemeten. Periode III: patiënt wordt afgeleid middels het invullen van vragenlijsten. Periode IV: patiënt wordt gemeten zonder afleiding. In totaal werden er 1258 boeren geregistreerd, waarvan 51 het resultaat waren van lucht die ontsnapte uit de maag (maagboeren). 1207 boeren (96 %) waren het resultaat van lucht die werd uitgestoten in orale richting bijna onmiddellijk nadat het de slokdarm binnenkwam uit proximale richting (supragastrische boeren). De maagboeren kwamen even vaak voor in elk van de 4 meetperiodes. Echter, er was een duidelijke toename van supragastrische boeren van periode I naar periode II, nadat de patiënten was verteld dat zij werden gemeten. Tijdens periode III (vragenlijsten) nam de frequentie van supragastrische boeren weer af terwijl deze weer toenam in periode IV. Concluderend, wanneer patiënten zich niet bewust zijn van de meting en wanneer zij worden afgeleid is de frequentie van boeren in belangrijke mate gereduceerd. Deze bevindingen onderstrepen het belang van psychologische factoren en leveren onderbouwing voor het aanwenden van gedragstherapie voor aerofagie.

Hoofdstuk 16 beschrijft de relatie tussen luchtslikken, de grootte van de intragastrische luchtbel, boeren en gastro-oesofageale reflux. Tijdens slikken wordt lucht getransporteerd naar de maag. De maag wordt beschermd tegen extreme dilatatie ten gevolge van ingeslikte lucht door boeren (gasvormige reflux). Zoals eerder genoemd is de TLOSR het mechanisme waardoor zowel boeren als gastro-oesofageale reflux ontstaan. Doel van deze studie was om te onderzoeken of luchtslikken leidt tot een toename in de grootte van de intragastrische luchtbel en tot gastro-oesofageale reflux. Bij gezonde vrijwilligers werd het aantal luchtslikken gekwantificeerd met impedantie-meting. De grootte van de luchtbel in de maag werd gemeten op Röntgen-opnamen. Gastro-oesofageale reflux werd gedetecteerd met pH- en impedantie-metingen. De grootte van de luchtbel in de maag was gerelateerd aan het aantal luchtslikken. Het aantal luchtslikken en de grootte van de intragastrische luchtbel waren niet gerelateerd aan het aantal vloeibare zure en zwak-zure reflux-episoden. Deze bevindingen suggereren dat, bij gezonde vrijwilligers, luchtslikken leidt tot boeren, maar niet tot zure reflux.

Er is een gemeenschappelijk fysiologisch mechanisme voor boeren en gastro-oesofageale reflux. In **hoofdstuk 17** beschrijven we een onderzoek waarin we

kijken naar het effect van luchtslikken op het vóórkomen van boeren en reflux. Intra-oesofageale drukken, pH en impedantie werd gemeten bij 12 patiënten met refluxziekte en 12 gezonde vrijwilligers tijdens twee meetperioden van 20 minuten, voor en na inflatie van 600 mL lucht in de maag. Dit werd herhaald na het nuttigen van een maaltijd. Vervolgens werd een 24-uurs impedantie-pH meting uitgevoerd. Tijdens de 24-uurs meting vertoonden de patiënten een hogere incidentie van luchtslikken, boeren en zure reflux. Na luchtinflatie nam zowel bij de patiënten als bij de gezonde vrijwilligers de incidentie van gasvormige reflux toe. De incidentie van zure en zwak-zure reflux was niet toegenomen na luchtinflatie. Het inblazen van lucht verhoogde de frequentie van TLOSRs in beide groepen, maar dit was volledig te wijten aan een toename van TLOSRs die gepaard gingen met gasvormige reflux. We concluderen dat patiënten met refluxziekte een hogere frequentie hebben van luchtslikken en meer boeren dan gezonde vrijwilligers. Luchtslikken veroorzaakt echter niet gastro-oesofageale reflux.

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Curriculum Vitae

Albert Jan (Arjan) Bredenoord werd geboren op 9 november 1977 in Utrecht. Na het behalen van het middelbare schooldiploma in 1996 begon hij met de studie Geneeskunde aan de Universiteit Antwerpen. Tijdens de laatste jaren van zijn studie verrichte hij dierexperimenteel onderzoek naar de pathogenese van gastrointestinale motiliteitsstoornissen tijdens sepsis in het Laboratorium voor Gastroenterology van de Universiteit Antwerpen (Prof. P.A. Pelckmans). In juli 2001 werd een wetenschappelijke stage gelopen op de Gastrointestinal Research Unit van het UMC Utrecht bij Prof. A.J.P.M. Smout. Hier maakte hij kennis met het klinisch wetenschappelijk onderzoek op het gebied van de pathofysiologie van gastro-oesofageale refluxziekte. In de zomer van 2002 deed hij een keuze co-schap op de afdeling Gastroenterology van de Mayo Clinic Rochester onder begeleiding van Prof. M. Camilleri. Op 20 juni 2003 studeerde hij met de vermelding “grote onderscheiding” af aan de Universiteit Antwerpen. Aansluitend werd hij aangesteld als arts-onderzoeker in het Sint Antonius Ziekenhuis Nieuwegein onder begeleiding van Dr. B.L.A.M. Weusten, Dr. R. Timmer en Prof. A.J.P.M. Smout. In 2005 ontving hij de Rustgi Award van de American Gastroenterology Association en in 2006 de Young Investigator Award van de Functional Brain-Gut Research Group. Op 1 april 2006 is hij gestart met zijn vooropleiding interne geneeskunde in het St. Antonius Ziekenhuis te Nieuwegein (opleider: Dr. D.H. Biesma).