Reflux Mechanisms in Gerd : Analysis of the role of transient lower esophageal sphincter relaxations

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SPHINCTOMETER RECORDING OF LES PRESSURE AND TRANSIENT LES RELAXATIONS IN PATIENTS WITH REFLUX DISEASE

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Acceptence for publication Neurogastroenterol Motil

ABSTRACT

Background: Investigate LES characteristics such as LES pressure and transient lower esophageal sphincter relaxations (TLESRs) in patients with gastroesophageal reflux disease (GERD) under physiological, ambulatory conditions.
Methods: Ambulatory 24 hr esophageal pH- and manometry by sphinctometer was performed in 15 GERD patients (5 females, age 26 - 75 yrs) and 10 healthy controls (5 females, age 19 - 55 yrs). Meal ingestion and supine period (sleep) were standardized.
Results: A circadian pattern was found for LES pressure with higher LES pressure supine (night) vs upright (day). At night but not at daytime, LES pressure was significantly ($p<0.01$) lower in patients vs controls. In patients the TLESR frequency was significantly ($p<0.01$) lower compared to controls, upright (3.2 ± 0.2 vs 2.2 ± 0.1 TLESR/h) but not supine (both 1.3 ± 0.1 TLESR/h). The percentage of TLESRs associated with reflux was significantly higher in GERD patients versus controls ($49 \pm 8\%$ vs $28 \pm 7\%$; $p<0.05$). TLESRs were the major reflux mechanism both in GERD patients (51%) and controls (71%).
Conclusions: A circadian pattern is observed for LES pressure and TLESR frequency. When upright, TLESR frequency in GERD patients is significantly lower versus controls. In GERD patients significantly more TLESRs are associated with reflux.

INTRODUCTION

In patients with gastroesophageal reflux disease (GERD), acid reflux mainly occurs during transient lower esophageal sphincter relaxations (TLESRs) or when lower esophageal sphincter (LES) pressure is low (1-3). TLESRs as reflux mechanisms have been studied previously during standardized protocols but only for a limited period of several hours. Studies on mechanisms of gastroesophageal reflux that employ ambulatory instead of stationary conditions may better reflect normal daily routine and physiology. Results from investigations using an ambulatory water-perfused sleeve have confirmed that in healthy volunteers and patients with GERD, TLESRs indeed are the major mechanism of reflux (4,5). However, other mechanisms such as a hiatus hernia, a low LES pressure or swallow induced LES relaxations may contribute to the excess reflux (6). It has previously been suggested that patients with GERD have an increased frequency of TLESRs compared to healthy subjects (2,7-9). However, other investigators reported that the frequency of TLESRs is not significantly different between patients with GERD and controls (4,5,10-13).

The sphinctometer is a solid-state catheter especially designed for recording sphincter characteristics. It contains an oil-filled cylinder where a pressure transducer is incorporated. In vitro studies have shown that the pressure output of the sphinctometer when recording sphincter pressure is lower compared to water-perfused sleeve manometry (14-16). Simultaneous recording with sphinctometer and water-perfused sleeve revealed that the sphinctometer reliably and accurately records spontaneous LES relaxations (15-17). However, when basal LES pressure is low as is frequently the case in GERD patients, adjustment of the criteria for TLESR is required in order to classify these spontaneous LES relaxations as TLESRs (16). Aim of the present study was to obtain information on diurnal

variation in TLESRs and other reflux mechanisms by performing ambulatory 24 h sphinctometer recording. Both patients with GERD and healthy volunteers were studied.

METHODS

Subjects

Fifteen patients with GERD (5 females; age range 26 - 75 years) and ten healthy subjects (5 females; age range 19 - 55 years) participated in the study. GERD was proven by endoscopy (esophagitis) and/or by 24 hour ambulatory pH-metry. Severity of esophagitis was graded endoscopically according to criteria of Savary and Miller. Endoscopy showed esophagitis grade 0 in 4 patients, grade I in 2 patients, grade II in 6 patients. A hiatal hernia was found in 4 patients. Reflux medication was stopped at least 5 days prior to the test. None of the healthy subjects had a history of gastro-intestinal disease or surgery or was on chronic medication. Informed consent was obtained from each individual. The study had been approved by the Ethics Committee of the Leiden University Medical Center.

Manometric and pH technique

In all subject esophageal water-perfused sleeve manometry was performed to determine the position of upper and lower esophageal sphincter. Solid-state ambulatory manometry (sphinctometer) was performed with an electronic catheter containing a 6 cm long sphinctometer and five solid state pressure transducers located at 30, 18, 8, 0 and –4 cm from the midpoint of the sphinctometer. These transducers were used for identification of swallow signals, esophageal body motility and intragastric pressure (11). The sphinctometer is an oil-filled silicone rubber cylinder around a solid state pressure microtransducer, 6 cm long with a diameter of 0.4 cm. The sphinctometer had been calibrated at pressures of 0 and 50 mmHg.

The sphinctometer catheter was introduced through the nose into the esophagus and positioned so that the sphinctometer straddled the LES. A glass pH electrode (Ingold LOT 440 continue glass reference electrode; Ingold Messtechnik AG, Urdorf, Germany) was positioned 5 cm above the upper margin of the LES. The pH electrode had been calibrated at pH 4.0 and 7.0. Sphinctometer and pH-catheter were connected to an ambulatory recorder (μdigitrapper Medtronic, Denmark) for continuous data recording. At the end of the test data were transferred to a personal computer system for later analysis.

Study protocol

The recordings were started at 12.30-13.00 p.m. Esophageal pH and motility were recorded simultaneously during 24 consecutive hours. After 15-30 min under basal, fasting conditions esophageal motility was measured for three hours after ingestion of the meal (time 0 to 180 min) with subjects sitting in a comfortable chair. Meals were ingested after the start of the test around 13.00 h, around 18.00 h and around 9.00 h the following day. The standardized liquid lunch consisted of 400 ml Nutridrink (Nutricia, Zoetermeer, The Netherlands) and contained 20 g protein, 26 g fat and 72 g carbohydrates (2520 kJ). Subjects were asked to consume the meal within 10 min. Breakfast consisted of bread with cheese or marmalade and dinner consisted of meat, vegetables and boiled potatoes. Intake of food and drinks with pH below 4 was restricted. Studies were undertaken under ambulatory conditions on outpatient basis and each person was encouraged to follow the daily routine during

registration. At home subjects were in supine position from 23.00 - 07.00 hour. The next day subjects returned to the hospital at the end of the registration period. During the study, periods of eating and drinking and supine position were noted in a diary.

Data analysis

Data was divided in two upright periods (13.00-23.00 hour and 07.00-13.00 hour) and a supine period (23.00-07.00 hour). LES tracings were analyzed for LES pressure and TLESR. The TLESR were defined according to Holloway et al (18). Based on a previous report from our group, the following adjustments in TLESR scoring were made. During low (< 5 mmHg) sphinctometer output registration of LES pressure, LESR with all characteristics of TLESR but not fulfilling the above criteria concerning rate of relaxation or absolute fall in LES pressure were also scored as TLESR when 1) an abrupt fall of LES pressure within 10 sec reached a pressure of ≤ 3 mmHg above intragastric pressure and 2) a relaxation rate ≥0.3 mmHg/s with respect to the all other criteria for TLESR (16). Gastroesophageal reflux episodes and mechanisms of reflux were scored using criteria described previously (3,18).

Statistical analysis

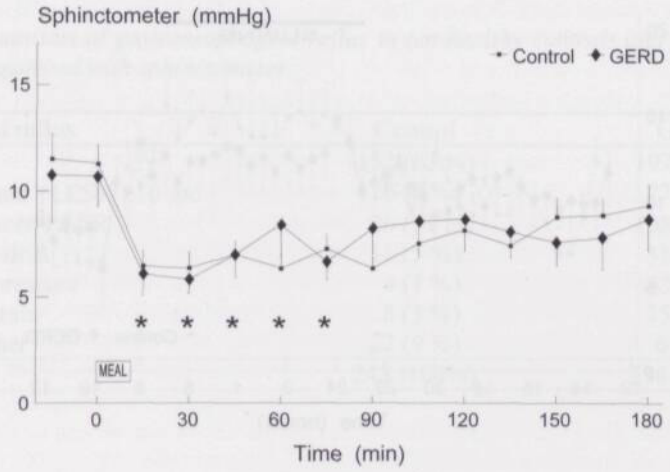
Data are expressed as mean ± SEM. LES pressure data were analyzed for statistical significance using (multiple) analysis of variance. The Mann Whitney U test for comparison of non-parametric data was used to compare results between patients and controls. A p value of <0.05 was considered significant.

RESULTS

Lower esophageal sphincter pressure

Fasting LES pressure (at 09.00 AM) was 12 ± 1 mmHg in controls and 11 ± 2 mmHg in patients with GERD. The meal significantly ($p<0.05$) decreased LES pressure in patients with GERD and controls up to 75 min after meal ingestion (Figure 1). LES pressure profiles during 24-hour sphinctometer registration showed LES pressure increments in the evening (Figure 2). In the control subjects LES pressure was significantly ($p<0.05$) higher during the supine period (14 ± 1 mmHg) compared to the upright period (10 ± 1 mmHg). In GERD patients LES pressure in the supine period (13 ± 2 mmHg) was higher compared to the upright period (11 ± 1 mmHg) although not significantly. In the supine period, but not in the upright period LES pressure was significantly ($p<0.01$) lower in GERD patients vs controls. In the second upright period, LES pressure again decreased to levels in the range of the previous day.

Figure 1. *Fasting and postprandial LES pressure in 15 patients with GERD (rhombs) and 10 healthy subjects (squares) *p<0.05 postprandial versus fasting.*



Transient lower esophageal sphincter relaxation

TLESR frequency profile during 24 hour sphinctometer registration is shown in Figure 3. Fasting TLESR frequency (at 09.00 AM) was 2.5 ± 0.8 TLESR/h in controls and 1.8 ± 0.5 TLESR/h in patients with GERD. Meal ingestion significantly ($p<0.05$) increased the frequency of TLESR (controls: 4.8 ± 0.9 and GERD: 2.9 ± 0.5 TLESR/h). The frequency of TLESR in the upright period was significantly ($p<0.05$) lower in patients with GERD (2.2 ± 0.1 TLESR/h) compared to controls (3.2 ± 0.2 TLESR/h). During the supine period the frequency of TLESR was not significantly different between GERD patients and controls: 1.3 ± 0.2 vs. 1.3 ± 0.1 TLESR/h respectively. Both in patients and controls the number of TLESRs was significantly ($p<0.05$) lower supine vs. upright. The frequency of TLESRs was not significantly different between the first and second upright period (Table 1). The percentage of TLESRs associated with acid reflux was significantly ($p<0.05$) higher in patients with GERD compared to in controls (49 ± 8% vs. 28 ± 7%).

Figure 2. *Twenty four hour continuous registration of LES pressure in 15 patients with GERD (rhombs) and 20 healthy subjects (squares).*

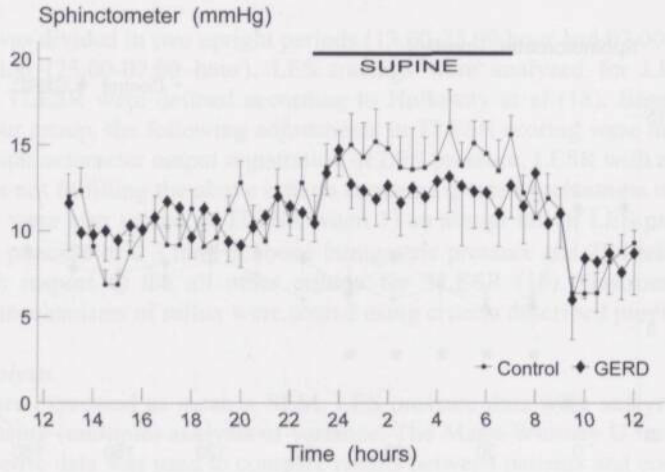


Table 1. *Diurnal frequency of TLESR (N/h) with comparison of upright periods and supine period in patients with GERD and controls. Asterisks denote significant ($p<0.05$) differences in the supine versus upright period. Dots denote significant ($p<0.05$) differences compared to controls.*

TLESR (N/h)	Control	GERD
13-23 hour	3.2 ± 0.2	2.2 ± 0.2•
23-07 hour	1.3 ± 0.2 *	1.3 ± 0.1*
07-13 hour	3.5 ± 0.2	1.9 ± 0.3•

Gastroesophageal reflux

The percentage of time with pH < 4 during 24 hr recording was significantly ($p<0.05$) higher in patients with GERD (7.0 ± 2.1 %) compared to controls (3.3 ± 0.9 %). This resulted both from a significantly higher number of reflux episodes in GERD patients vs controls (37 ± 5 vs 25 ± 5 per 24 hr) and from a significantly ($p<0.05$) longer duration of reflux episodes in patients with GERD versus controls (136 ± 12 sec vs 109 ± 11 sec).

Mechanisms of gastroesophageal reflux

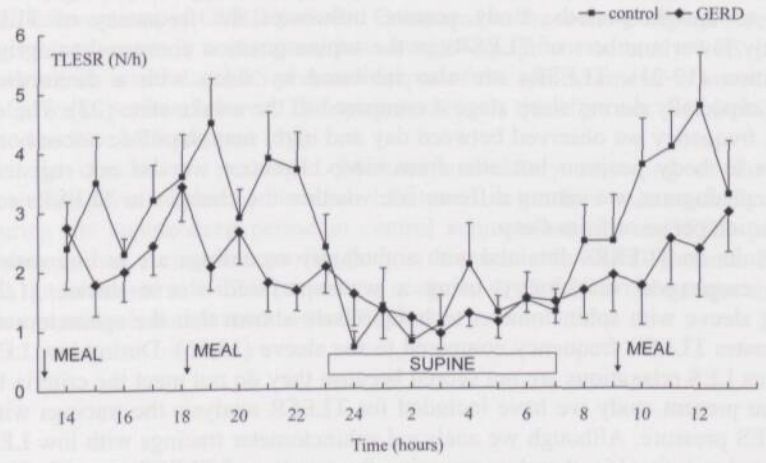
The mechanisms of reflux in patients and controls are listed in Table 2. TLESRs and swallow-related TLESRs are the main mechanism of reflux in control subjects (71%) and patients with GERD (51%). In patients with GERD about half of the reflux episodes occurred

during mechanisms of reflux other than TLESRs. Acid reflux episodes during swallow induced LES relaxation (20% vs. 11%), absent LES pressure (8% vs. 1%) and abdominal strain (14% vs. 3%) were increased compared to the control group. Twenty-eight episodes of acid reflux could not be explained by any of the mechanisms of reflux described above.

Table 2. *Mechanisms of gastroesophageal reflux in ten healthy controls and fifteen patients with GERD registered with sphinctometer.*

Mechanism of reflux	Control	GERD
TLESR	152 (63 %)	197 (37 %)
Swallow related TLESR ≥10 sec	20 (8 %)	77 (14 %)
Swallow induced LESR	26 (11 %)	108 (20 %)
LES pressure drift	11 (5 %)	31 (6 %)
Absent LES pressure	4 (1 %)	42 (8 %)
Abdominal strain	8 (3 %)	75 (14 %)
Unknown, other	22 (9 %)	6 (1 %)
Total	243 (100%)	536 (100%)

Figure 3. *Twenty four hour continuous registration of TLESR (n/h) in 15 patients with GERD (rhombs) and 10 control subjects (squares).*



DISCUSSION

Ambulatory 24 hour sphinctometer recording of LES pressure has shown diurnal variations with higher LES pressure during the supine period compared to upright periods both in controls and patients with GERD. In the upright periods the frequency of TLESRs was significantly lower in GERD patients compared to controls. This is the first report on prolonged ambulatory TLESR recording with the sphinctometer in controls and GERD patients. We confirm the results of others (4-6) using 24 hr ambulatory sleeve recording that TLESRs are the major mechanism of reflux in ambulatory healthy subjects and in patients with GERD.

LES pressure showed a diurnal pattern with increases during the evening resulting in higher LES pressure in the supine nighttime period compared to upright periods. Identical diurnal patterns have been described in studies with water-perfused sleeve manometry in recumbent asymptomatic subjects and patients with reflux esophagitis (1,2). LES pressure is influenced by body position. LES pressure was found to be higher in horizontal position compared to vertical position (19). However, other investigators did not observe an influence of body position on LES pressure (20,21). Sleep may also increase LES pressure, with pressure depending on the stage of sleep (22). Our twenty-four hour pressure profiles suggest a diurnal variation in LES pressure with elevated LES pressure during nighttime compared to daytime, although the influence of body position and sleep in our study cannot be separated. An elevated LES pressure at nighttime/supine position strengthens the barrier at the esophagogastric junction and therefore prohibits gastroesophageal reflux.

The frequency of TLESRs varied markedly during the day. Postprandially the number of TLESRs increased, resulting from gastric distention induced by the meal and from meal composition. During the supine period the frequency of TLESRs was significantly lower compared to upright periods. Body posture influences the frequency of TLESRs with significantly lower numbers of TLESRs in the supine position compared to upright/vertical body position (19-21). TLESRs are also inhibited by sleep with a diminished TLESR frequency especially during sleep stage 4 compared to the awake state (22). The differences in TLESR frequency we observed between day and night may therefore not only result from differences in body position but also from sleep. Because we did not register sleep by electroencephalogram, we cannot differentiate whether the changes in TLESRs results from supine position per se or from sleep.

Results on TLESRs obtained with ambulatory recordings are in line with data from stationary esophageal manometry using a water-perfused sleeve device (1,2). Studies comparing sleeve with sphinctometer technique have shown that the sphinctometer slightly underestimates TLESR frequency compared to the sleeve (15,16). During low LES pressure spontaneous LES relaxations are not scored because they do not meet the criteria for TLESR (13). In the present study we have included for TLESR analysis the tracings with low (<5 mmHg) LES pressure. Although we analyzed sphinctometer tracings with low LES pressure with adjusted criteria (16), thereby increasing the number of TLESRs scored, the frequency of TLESRs in reflux patients in our study (2.2 ± 0.1/h for GERD; 3.2 ± 0.2/h for controls) are in the same range as the data obtained with other ambulatory studies. We have previously shown during simultaneous measurement that sphinctometer and sleeve correlate very well with respect to TLESR detection (16). Therefore results from studies obtained with these techniques can be compared and were found to be in the same range.

TLESR account for about half of the acid reflux episodes in patients with GERD. We have shown that the contribution of "absent LES pressure", "abdominal straining" and "reflux during swallow-induced LES relaxations" as reflux mechanisms for acid reflux is increased in patients with GERD. Van Herwaarden et al (6) reported that excess reflux in GERD patients with hiatus hernia compared to those without hiatus hernia is caused by mechanisms other than TLESR such as low LES pressure, swallow-associated normal LES relaxation, deep inspiration and straining. In the present study four of the ten patients with GERD had a hiatal hernia. In patients with a hiatal hernia 39% of all reflux episodes occurred during TLESRs while in patients without a hiatal hernia TLESRs were responsible for a much higher percentage of 58% of all reflux episodes. Mechanism of reflux may differ according to the type of reflux patient. On the one end are subjects with a sufficient gastroesophageal (normal LES pressure) barrier who may have reflux predominantly through TLESRs versus on the other end subjects with low LES pressure and a hiatal hernia in whom gastroesophageal reflux predominantly occurs through non-TLESR mechanism.

Acid reflux is higher in patients with GERD due to several factors: increased number of reflux episodes, increased postprandial frequency of TLESRs, increased frequency of TLESR associated with acid reflux, and prolonged duration of reflux episodes. In the present study patients with GERD did not have an excess rate of TLESRs compared to controls. The duration of reflux episodes was only slightly increased compared to controls. However, a significantly higher percentage of TLESRs in the GERD patients was associated with reflux. In addition, mechanisms of reflux other than TLESRs accounted for the excess reflux in patients with GERD.

Simultaneous ambulatory esophageal (LES) manometry and pH recording may help to clarify mechanisms of acid reflux. Studies with the sphinctometer may improve our knowledge on pathophysiology of reflux, LES function and mechanisms of action of medical and surgical interventions in GERD patients. Compared to the water-perfused sleeve system (4,23), the sphinctometer is a compact, low weight equipment to study LES profiles. It should, however, be noted that LES pressure output of the sphinctometer is lower compared to output of a water-perfused sleeve. The sphinctometer is therefore not the ideal instrument to determine absolute LES pressure (16).

In conclusion: prolonged 24 hour ambulatory recording of the LES by sphinctometer has revealed that 1) circadian LES pressure profiles exist with elevated LES pressure during the supine/sleep period in control subjects but not in GERD patients. 2) TLESR frequency has a circadian profile both in controls and GERD patients. 3) TLESR frequency is not increased in GERD patients vs controls. 4) TLESR are the major mechanism of acid reflux in controls and patients with GERD.

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