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

Straathof, J.W.A.

2

TRANSIENT LOWER ESOPHAGEAL SPHINCTER RELAXATIONS AS REFLUX MECHANISM IN GASTROESOPHAGEAL REFLUX DISEASE: A QUANTITATIVE ANALYSIS.

J.W.A. Straathof, A.A.M. Masclee

Department of Gastroenterology-Hepatology
Leiden University Medical Center, The Netherlands

Submitted for publication

ABSTRACT

Background: Transient lower esophageal sphincter relaxations (TLESRs) are considered the major mechanism for gastroesophageal reflux but data from large scale studies on TLESRs and other reflux mechanisms in gastroesophageal reflux disease are still lacking.
Methods: Between 1995 and 2002 114 patients with documented GERD and 30 healthy controls underwent combined esophageal pH metry and sleeve manometry one hour before and 3 hours after ingestion of a mixed liquid meal (2520 kJ). TLESR frequency, gastroesophageal reflux and mechanisms of reflux were scored.
Results: Fasting TLESR frequency was not significantly different between GERD patients and controls 3.3 ± 0.3 vs 2.8 ± 0.4 per hour. Postprandial TLESR frequency was significantly ($p<0.05$) reduced in GERD patients vs. controls; first postprandial hour: 4.6 ± 0.3 vs. 6.1 ± 0.6 per hour. The percentage of TLESRs associated with reflux was significantly higher in GERD patients vs. controls: 42 ± 3 vs. 16 ± 3% ($p<0.001$). In GERD patients TLESRs accounted for 49% of reflux episodes versus 82% in controls ($p<0.05$). Neither the presence of a hiatal hernia nor degree of esophagitis affected the mechanism of reflux. However, reflux mechanisms were significantly related to fasting LES pressure.
Conclusions: In GERD patients the frequency of TLESRs is not increased over controls and postprandially the TLESR frequency is even significantly decreased. In GERD patients significantly more TLESRs are associated with acid reflux. Subgroups of GERD patients exist according to reflux type. Fasting LES pressure is an important predictor of reflux type and reflux mechanisms.

INTRODUCTION

Gastroesophageal reflux (GER) has a multifactorial origin. The esophagogastric junction functions as a barrier that only allows reflux of gastric content when lower esophageal sphincter (LES) pressure is low or during relaxations of the LES (1-3). The duration of a gastroesophageal reflux episode is dependent on esophageal factors that contribute to luminal clearance mechanisms such as peristalsis and buffering by saliva. Transient LES relaxations (TLESR) are spontaneous relaxations of the esophagogastric junction in the absence of a preceding swallowing event (3). TLESRs have been well recognized as an important mechanism of gastroesophageal reflux. Several reports have stated that in patients with gastroesophageal reflux disease (GERD) the number of TLESRs is significantly increased compared to healthy controls (2, 4-6). In healthy subjects TLESRs account for 80-100% of all reflux episodes but in patient with GERD a much smaller percentage of reflux episodes results from TLESRs (1-7). In GERD patients TLESR account only for about 50% of reflux episodes (1-9). The contribution of TLESRs to reflux in GERD patients is therefore less prominent as previously has been suggested. Several reports on TLESRs in reflux disease can be criticized either because of the small number of patients and controls included, or because different protocols to provoke TLESRs have been employed or because investigators did not take into account factors as the presence of a hiatal hernia or severity of reflux disease.

The present study was undertaken to expand our knowledge on the role of TLESRs as reflux mechanism in reflux disease and to correlate TLESRs and reflux mechanisms to LES

pressure, grade of esophagitis and presence of hiatus hernia. A large cohort of GERD patients was included. Of these patients data from endoscopy and 24 hour pH metry were available. TLESRs were evaluated according to a strict protocol and for comparison a large group of healthy controls was included.

METHODS

Subjects

A group of 114 patients with documented gastroesophageal reflux disease (55 male, 59 female; mean age 46 yr, range 21-73 yr) participated in the study. Between 1995 and 2002 reflux patients visiting the Department of Gastroenterology-Hepatology of the Leiden University Medical Center were asked to participate. All patients had symptoms of gastroesophageal reflux such as heartburn, regurgitation, retrosternal pain or dysphagia. GERD had been documented previously in all patients either by endoscopy showing erosive esophagitis and/or by ambulatory 24-hour pH monitoring demonstrating an increased esophageal exposure time to acid gastric content. As controls, 30 healthy volunteers were studied (11 male, 19 female; mean age 25 yr, range 19-54 yr). None of the controls had a history of gastro-intestinal disease or surgery or was on chronic medication. Informed consent was obtained from each individual and the protocol had been approved by the ethical committee of the Leiden University Medical Center.

Endoscopy data

Reports of previously performed endoscopies were reviewed. The severity of esophagitis had been graded endoscopically according to the criteria of Savary and Miller (10). In case multiple endoscopies had been performed the highest esophagitis score was taken for further analysis. Endoscopy in patients with GERD showed no esophagitis (endoscopy negative / grade 0) in 30 patients, mild esophagitis (grade I) in 29 patients, moderate esophagitis (grade II) in 40 patients, and severe esophagitis (grade III) in 15 patients.

24 hour pH metry data

Reports of previously performed 24 hour pH metry were reviewed. Twenty-four hour ambulatory intra-esophageal pH metry had been performed with the pH electrode positioned 5 cm above the LES. A portable recorder (μdigitrapper, Medtronic, Denmark) and a glass electrode with internal reference electrode (Ingold LOT 440 continue glassreference electrode; Ingold Messtechnik AG, Urdorf, Germany) were used. As reflux parameter we used the percentage of time with pH <4 for total recording time. Pathological reflux was defined as ≥4.0% of total time with esophageal pH below 4 (11).

Manometric and pH technique

The manometry catheter consisted of a multilumen silicone tube (outer diameter 5.0 mm) with seven side holes located at 29, 23, 18, 13, 8, 3 and -4 cm from the mid of the 6 cm long sleeve sensor (Dentsleeve Pty Ltd, Belair, South Australia). The catheter was continuously perfused with gas free distilled water by a low compliance pneumohydraulic capillary infusion system at a rate of 0.5 ml/min. The external pressures transducers (Medex

Inc., Ohio, U.S.A.) were connected via an analogue/digital converter (PC Polygraph HR, Medtronic, Denmark) to a personal computer system. The data were displayed continuously on a monitor and stored on the personal computer system (Polygram Upper GI 6.30, Gastrosoft Inc., Medtronic, Denmark).

The manometry catheter was introduced through the nose into the esophagus and positioned so that the sleeve sensor straddled the LES. The proximal side hole was positioned in the pharynx and was used for identification of swallow signals. The middle side holes registered esophageal body motility. The distal side hole was used as reference point for intragastric pressure. A glass pH electrode (Ingold, Urdorf, Germany) was passed through the nose and positioned 5 cm above the upper margin of the LES. The pH electrode had been calibrated at pH 4.0 and pH 7.0.

Study protocol

The experiment was started at 9.00 a.m. after an overnight fast. The subjects were studied in the upright position, sitting in a comfortable chair. They were not allowed to doze because of the effect of sleep on TLESR. The manometry and pH catheter were introduced into the esophagus and positioned as described above. Esophageal pH and motility were registered simultaneously during a 30 min fasting period and for 180 min after a standard breakfast consisting of 400 ml Nutridrink (Numico, Zoetermeer, The Netherlands) (20 g protein, 26 g fat and 72 g carbohydrates, 2520 kJ). Subjects were asked to consume the meal within 10 min.

Lower esophageal sphincter data analysis

Lower esophageal sphincter tracings were analyzed for LES resting pressure and LES relaxations (LESR). LES pressure was defined as mean end-expiratory LES pressure relative above intragastric pressure over a 2 min period. LESR's are divided in swallow induced LESR's and spontaneous LESR's. Swallow induced LESR are preceded by active swallows starting with a pharyngeal contraction. Residual LES pressure after wet swallows was defined as end-expiratory nadir LES pressure above intragastric pressure. Spontaneous LESR's, better known as transient LES relaxations (TLESRs) are divided in non-swallow related TLESRs, and swallow related TLESR. Spontaneous, non swallow related TLESR are defined as decreases in LES pressure of ≥ 5 mmHg with a rate of ≥ 1 mmHg/sec, within 10 sec reaching a pressure of ≤ 2 mmHg above intragastric pressure. No swallow signal occurs in the interval from 4 sec before to 2 sec after onset of LESR. Swallow related TLESRs are defined as spontaneous TLESRs, irrespective of the timing of LESR to swallowing when the duration of LESR is at least 10 sec (12).

pH analysis

Gastroesophageal reflux episodes are defined as a sudden fall (< 10 sec) of pH below 4.0 with a duration of at least 4 sec. The number and duration of reflux episodes were counted.

The mechanisms of each reflux episode were scored using the following criteria. Gastroesophageal reflux occurred during:

(1) TLESR (spontaneous LESR meeting the earlier mentioned criteria; swallow related LESR with the duration of LESR $\geq$ 10 sec).

(2) Swallow induced LESR (primary peristalsis or failed primary peristalsis with the duration of LESR ≤ 10 sec or multiple swallowing).
(3) LES pressure drift (a gradual loss of basal LES pressure).
(4) Absent LES pressure (less than 2 mmHg above intragastric pressure).
(5) Abdominal strain (an increase in abdominal pressure).

Statistical analysis

Data are expressed as mean values ± SEM. Data were analyzed for statistical significance using Chi-square test and analysis of variance (ANOVA). When this indicated a probability of less than 0.05 for the null hypothesis, Student-Newman-Keuls analyses were performed to determine which values between or within the experiments differed significantly. A p value of <0.05 was considered significant for all analyses. Additional analysis were performed to evaluate the effect on reflux characteristics and TLESRs of:
Non-erosive vs. erosive esophagitis and degree of esophagitis (Savary-Miller);
Presence/absence of a sliding hiatus hernia;
Basal LES pressure value in three subgroups: LESP < 10mmHg (low pressure), LESP between 10-20 mmHg (intermediate pressure) and LESP > 20 mmHg (normal pressure).

RESULTS

Patients: Age and reflux

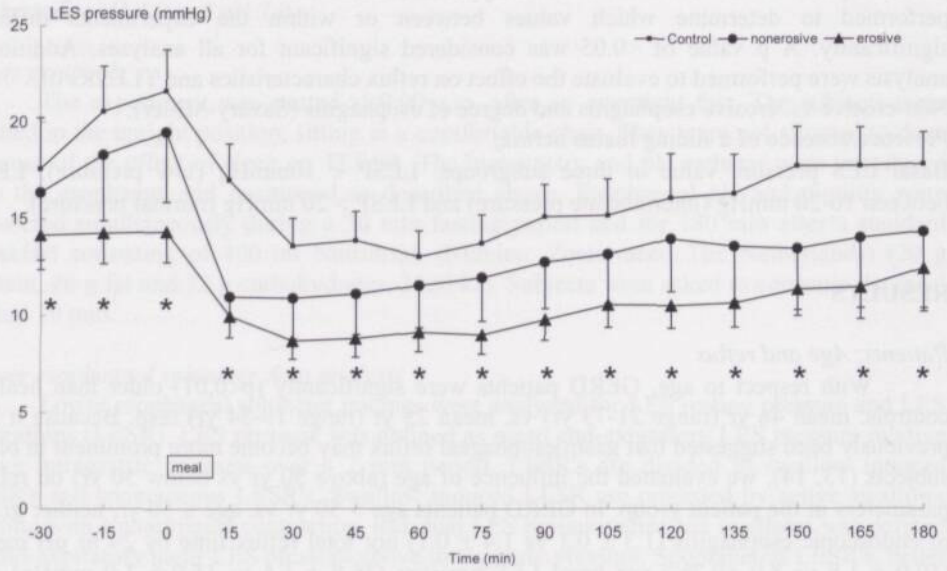
With respect to age, GERD patients were significantly ($p<0.01$) older than healthy controls: mean 46 yr (range 21-73 yr) vs. mean 25 yr (range 19-54 yr) resp. Because it has previously been suggested that gastroesophageal reflux may become more prominent in older subjects (13, 14), we evaluated the influence of age (above 50 yr vs below 50 yr) on reflux parameters in the patient group. In GERD patients age > 50 yr vs. age ≤ 50 yr, neither grade of endoscopic esophagitis (1.3 ± 0.1 vs 1.4 ± 0.1) nor total reflux time by 24 hr pH metry (10.0 ± 1.8 vs 8.9 ±0.7%) nor basal LES pressure (16.8 ± 1.5 vs 15.0 ± 1.0 mmHg) nor postprandial TLESR frequency (4.3 ± 0.4 vs 4.5 ± 0.3 per hour) were significantly different. Therefore differences in reflux characteristics between GERD patients and controls were considered not to be influenced by age.

Lower esophageal sphincter pressure

LES pressure in the basal period at time 0 min was significantly ($p<0.01$) lower in patients with GERD (16±1 mmHg) compared to healthy controls (22±2 mmHg). After ingestion of a meal LES pressure decreased significantly ($p<0.001$) compared to basal both in patients with GERD and in controls (Figure 1). Postprandial LES pressure was significantly ($p<0.01$) lower in patients with GERD compared to controls from meal ingestion until time 180 min. When reflux patients were separated into those with erosive and non-erosive reflux disease, LES pressure was not significantly different between endoscopy negative (non-erosive) GERD patients and controls: basal 19 ± 2 vs 22 ±2 mmHg and postprandially at 30 min: 11 ± 2 vs 13 ± 1 mmHg. However, the group of patients with erosive reflux disease had significantly lower basal and postprandial LES pressure compared to controls: basal 14 ± 1 vs 22 ± 2 mmHg ($p<0.01$) and postprandially at 30 min: 9 ± 1 vs 13 ± 1 mmHg ($p<0.01$). When

the patients with erosive esophagitis were further divided in subgroups based on grade of esophagitis, no significant differences in fasting or postprandial LES pressure were observed between patients with grade I, II and III esophagitis.

Figure 1. *Basal and postprandial LES pressure (mean ± SEM) in patients with erosive and non erosive reflux disease and in healthy controls. Asterisks denote significant differences between patients with erosive reflux disease vs. controls (*p<0.01).*



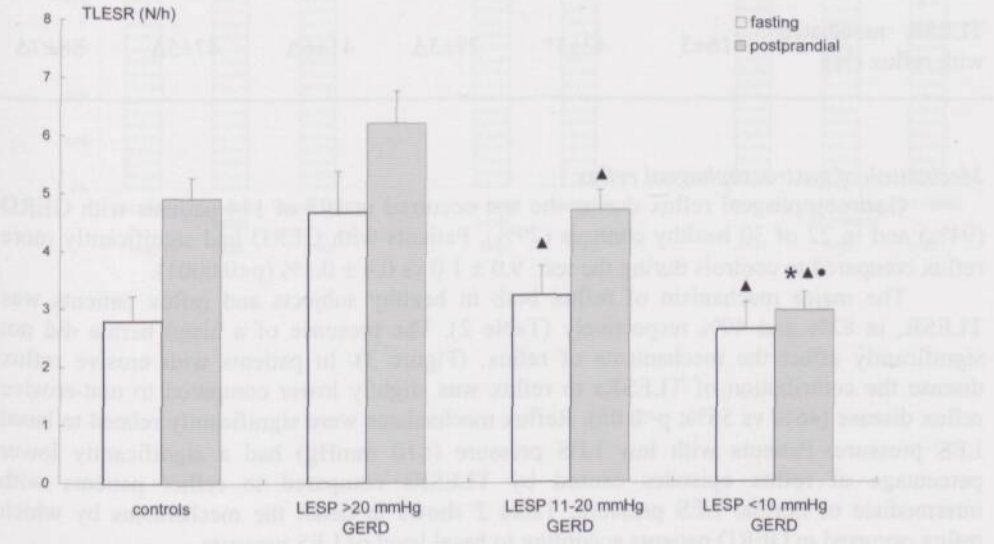
Transient lower esophageal sphincter relaxations

The frequency of TLESR in the fasting state did not significantly differ between GERD patients and controls: 3.3 ± 0.3 vs 2.8 ± 0.4 per hour. After ingestion of the meal the frequency of TLESRs increased in all groups (Table 1). For the subgroups, only in patients with grade I esophagitis was the rise in TLESR frequency over fasting statistically significant ($p<0.05$). In GERD patients postprandial TLESR frequency was significantly ($p<0.05$) lower compared to controls in the first postprandial hour. Concerning the reflux subgroups, only in patients with grade III was the difference with controls in the first postprandial hour significant ($p<0.05$). In the second and third postprandial hour no difference in TLESR frequency between patients and controls was found.

When reflux patients were divided in subgroups based on basal LES pressure, the basal TLESR frequency in GERD patients with normal LES pressure (>20 mmHg), intermediate LES pressure (10-20 mmHg) and low LES pressure (<10 mmHg) was not significantly different versus controls (Figure 2). In the intermediate and low LESP group,

basal TLESR frequency was significantly ($p<0.05$) lower compared to reflux patients with normal LESP. In the postprandial state GERD patients with low LES pressure had significantly less TLESRs compared to controls ($p<0.001$) and to GERD patients with intermediate and high LES pressure ($p<0.05$). The postprandial TLESR frequency correlated significantly ($r=0.39$; $p<0.001$) with basal LES pressure (low, intermediate, normal LES group).

Figure 2. *Frequency of transient lower esophageal sphincter relaxations (TLESR number/hour: mean±SEM) in 30 healthy controls and 114 patients with GERD. Patients are divided according to fasting LES pressure into three groups: low LES pressure (<10 mmHg); intermediate LES pressure (10-20 mmHg) and normal LES pressure (>20 mmHg). The asterisk denotes a significant difference vs. controls ($p<0.001$). Triangles denote significant differences between patient subgroups versus the patient group with normal LES pressure ($p<0.05$). The dot denotes a significant difference between patients with low vs. intermediate LES pressure ($p<0.05$).*



The endoscopic grade of esophagitis correlated significantly with the percentage of TLESRs associated with acid reflux (Table 1). TLESRs were accompanied by acid reflux in 29 ± 3% to 58 ± 7% in reflux patients. In healthy controls only 16 ± 3% of the TLESRs was associated with reflux.

Table 1. *Frequency of transient lower esophageal sphincter relaxations (TLESR; number/hour; mean±SEM) under fasting conditions and for 3 subsequent hours (I, II, III) after ingestion of a meal in 114 patients with GERD and 30 healthy controls. Dots denote significant differences between postprandial and fasting (p<0.05). The asterisks denote significant (p<0.05) differences compared to control. The triangles denote significant differences versus control (p<0.05-p<0.001)*

TLESR	Control n=30	GERD n=114	Grade 0 n=29	Grade I N=30	Grade II n=40	grade III n=15
Fasting	2.8±0.4	3.3±0.3	3.8±0.6	2.8±0.6	3.8±0.6	2.2±0.7
Postprandial I	6.1±0.6•	4.6±0.3•*	5.0±0.6	4.3±0.6•	5.0±0.5	3.3±0.6*
II	5.0±0.4•	4.1±0.3	4.2±0.6	3.5±0.5	4.7±0.5	3.5±1.1
III	3.7±0.5	3.2±0.3	3.0±0.5	3.0±0.5	3.5±0.5	3.0±1.0
TLESR associated with reflux (%)	16±3	42±3*	29±3Δ	41±6Δ	47±5Δ	58±7Δ

Mechanism of gastroesophageal reflux

Gastroesophageal reflux during the test occurred in 107 of 114 patients with GERD (94%) and in 22 of 30 healthy controls (79%). Patients with GERD had significantly more reflux compared to controls during the test: 9.0 ± 1.0 vs 0.4 ± 0.1% (p<0.0001).

The major mechanism of reflux both in healthy subjects and reflux patients was TLESR, in 82% and 49% respectively (Table 2). The presence of a hiatal hernia did not significantly affect the mechanisms of reflux. (Figure 3). In patients with erosive reflux disease the contribution of TLESRs to reflux was slightly lower compared to non-erosive reflux disease (46% vs 58%; p<0.05). Reflux mechanisms were significantly related to basal LES pressure. Patients with low LES pressure (≤10 mmHg) had a significantly lower percentage of reflux episodes caused by TLESRs compared to reflux patients with intermediate or normal LES pressure. Table 2 shows in detail the mechanisms by which reflux occurred in GERD patients according to basal level of LES pressure.

Figure 3. *Mechanisms of gastroesophageal reflux in healthy controls and patients with GERD. Patients are divided in subgroups according to presence of erosive GERD, presence of hiatal hernia and fasting LES pressure. Asterisks denote significant differences vs. controls ($p<0.001$). The fence denotes a significant difference between erosive vs. non-erosive GERD ($p<0.01$). The triangles denote significant differences vs. GERD subgroup with normal LESP ($p<0.001$). The dot denotes a significant difference between GERD subgroup with low LESP vs. intermediate LESP ($p<0.001$).*

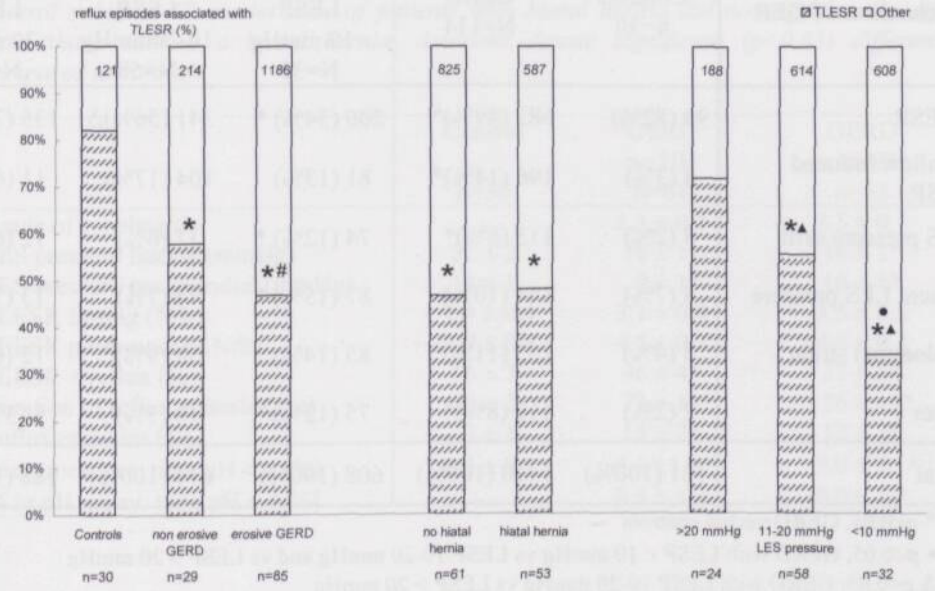


Table 1. *Frequency of transient lower esophageal sphincter relaxations (TLESR; number/hour; mean±SEM) under fasting conditions and for 3 subsequent hours (I, II, III) after ingestion of a meal in 114 patients with GERD and 30 healthy controls. Dots denote significant differences between postprandial and fasting (p<0.05). The asterisks denote significant (p<0.05) differences compared to control. The triangles denote significant differences versus control (p<0.05-p<0.001)*

TLESR	Control n=30	GERD n=114	Grade 0 n=29	Grade I N=30	Grade II n=40	grade III n=15
Fasting	2.8±0.4	3.3±0.3	3.8±0.6	2.8±0.6	3.8±0.6	2.2±0.7
Postprandial I	6.1±0.6•	4.6±0.3•*	5.0±0.6	4.3±0.6•	5.0±0.5	3.3±0.6*
II	5.0±0.4•	4.1±0.3	4.2±0.6	3.5±0.5	4.7±0.5	3.5±1.1
III	3.7±0.5	3.2±0.3	3.0±0.5	3.0±0.5	3.5±0.5	3.0±1.0
TLESR associated with reflux (%)	16±3	42±3*	29±3Δ	41±6Δ	47±5Δ	58±7Δ

Mechanism of gastroesophageal reflux

Gastroesophageal reflux during the test occurred in 107 of 114 patients with GERD (94%) and in 22 of 30 healthy controls (79%). Patients with GERD had significantly more reflux compared to controls during the test: 9.0 ± 1.0 vs 0.4 ± 0.1% (p<0.0001).

The major mechanism of reflux both in healthy subjects and reflux patients was TLESR, in 82% and 49% respectively (Table 2). The presence of a hiatal hernia did not significantly affect the mechanisms of reflux. (Figure 3). In patients with erosive reflux disease the contribution of TLESRs to reflux was slightly lower compared to non-erosive reflux disease (46% vs 58%; p<0.05). Reflux mechanisms were significantly related to basal LES pressure. Patients with low LES pressure (≤10 mmHg) had a significantly lower percentage of reflux episodes caused by TLESRs compared to reflux patients with intermediate or normal LES pressure. Table 2 shows in detail the mechanisms by which reflux occurred in GERD patients according to basal level of LES pressure.

Figure 3. *Mechanisms of gastroesophageal reflux in healthy controls and patients with GERD. Patients are divided in subgroups according to presence of erosive GERD, presence of hiatal hernia and fasting LES pressure. Asterisks denote significant differences vs. controls ($p<0.001$). The fence denotes a significant difference between erosive vs. non-erosive GERD ($p<0.01$). The triangles denote significant differences vs. GERD subgroup with normal LESP ($p<0.001$). The dot denotes a significant difference between GERD subgroup with low LESP vs. intermediate LESP ($p<0.001$).*

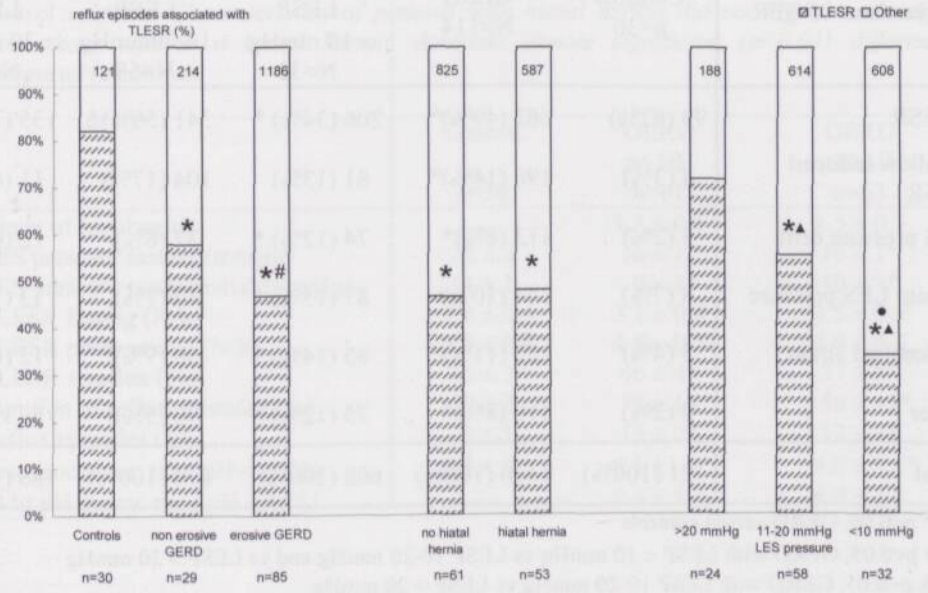


Table 2. *Mechanisms of gastroesophageal reflux for all reflux episodes observed during a total recording time of 474 hours in 30 healthy volunteers and 114 patients with gastroesophageal reflux disease. GERD patients were divided in 3 groups based on basal LES pressure: < 10 mmHg (low pressure), 10-20 mmHg (intermediate pressure) and > 20 mmHg (normal pressure).*

Mechanisms of GER	Controls n=30	GERD N=114	GERD		
			LESP <10 mmHg N=32	LESP 10-20mmHg N=58	LESP >20 mmHg N=24
TLESR	99 (82%)	682 (49%)*	206 (34%) •	341 (56%)Δ	135 (72%)
Swallow induced LESR	4 (3%)	196 (14%)*	81 (13%)	104 (17%)	11 (6%)
LES pressure drift	3 (2%)	113 (8%)*	74 (12%) •	37 (6%)	12 (6%)
Absent LES pressure	8 (7%)	144 (10%)	87 (15%) •	44 (7%)	13 (7%)
Abdominal strain	5 (4%)	155 (11%)*	85 (14%) •	58 (9%)	12 (6%)
Other	2 (2%)	110 (8%)*	75 (12%) •	30 (5%)	5 (3%)
Total	121 (100%)	1410 (100%)	608 (100%)	614 (100%)	188 (100%)

* $p<0.05$, GERD versus controls

• $p<0.05$, GERD with LESP < 10 mmHg vs LESP 10-20 mmHg and vs LESP > 20 mmHg

Δ $p<0.05$, GERD with LESP 10-20 mmHg vs LESP > 20 mmHg

Hiatal Hernia

Reflux mechanisms were not significantly different between reflux patients without and with a hiatal hernia (Table 3). In addition, neither were grade of esophagitis, LES pressure or TLESR frequency different between refluxers with and without a hiatal hernia.

Table 3. *Characteristics of GERD patients with or without hiatal hernia (HH) compared to control subjects. Characteristics of patients with hiatal hernia did not significantly differ from those without a hiatal hernia. Asterisks denote significant ($p<0.01$) differences compared to control.*

	Control n=30	GERD no HH n=61	GERD with HH n=53
Grade of esophagitis	-	1.3 ± 0.1	1.5 ± 0.1
LES pressure fasting (mmHg)	22 ± 2	16 ± 1*	16 ± 1*
LES pressure postprandial (mmHg)	14 ± 1	9 ± 1*	10 ± 1*
TLESR fasting (N/h)	2.8 ± 0.4	3.1 ± 0.4	3.5 ± 0.5
TLESR postprandial (N/h)	4.9 ± 0.4	4.5 ± 0.3	4.4 ± 0.4
TLESR + reflux (%)	16 ± 3	46 ± 4*	37 ± 5*
Duration of reflux episode (sec)	10 ± 2	73 ± 14*	56 ± 11*
Reflux episodes (N)	3 ± 1	15 ± 2*	12 ± 2*
Test procedure: time pH < 4 (%)	0.4 ± 0.1	9.1 ±1.8*	9.0 ± 2.1*
24 hr pH metry: time pH < 4(%)	—	9.8 ± 1.3	9.0 ± 1.2

DISCUSSION

We investigated the contribution of TLESRs to reflux in a large cohort of patients with GERD and healthy controls. In healthy controls, reflux to a small extent, is physiological and does not lead to symptoms. In the control subjects over 80% of the reflux episodes were provoked by TLESRs. Under postprandial conditions the frequency of TLESRs in healthy controls increases, however this increase in number of TLESRs does not greatly affect reflux time because only a small percentage of TLESRs was accompanied by reflux (16 ± 3%).

Patients with reflux disease did not have more TLESRs compared to controls as has been suggested previously (2-4, 6). TLESR frequency in reflux patients was not different from controls, as has been shown in several studies (7, 15-21). More precisely, in the first postprandial hour TLESR frequency even was significantly lower than in controls. TLESRs are a physiological phenomenon, especially in the postprandial period. During TLESRs venting of (excess) gas and/or liquid from the stomach is allowed. In the GERD patients the percentage of TLESRs associated with acid reflux was significantly higher compared to controls. Our data are in line with several studies on reflux and TLESRs, all reporting a

higher incidence of acid reflux during TLESRs in patients with GERD. Reflux of gas can be differentiated from liquid/acid reflux by electrical impedance measurement. As has been shown by Sifrim et al., many TLESRs are associated with liquid, non-acidic, reflux (19, 22).

Our data obtained in a large cohort of GERD patients settle account with the concept that reflux disease results from a disordered control of triggering of TLESRs. With increasing severity of endoscopic esophagitis more TLESR become associated with reflux. In patients with severe esophagitis even 58% of TLESR were accompanied by reflux.

The presence of a hiatal hernia did not influence reflux severity or reflux mechanism within the group of GERD patients. In patients with or without a hiatal hernia, about 50% of reflux episodes were associated with TLESRs and about 20% with low or absent LES pressure. Kahrilas et al. (23) studied GERD patients with and without a hiatal hernia by gastric distension with air and found a positive correlation between frequency of TLESRs and presence of a hiatal hernia. The separation of the lower esophageal sphincter from the diaphragm in case of hiatal hernia may facilitate TLESR triggering in the supine position. In upright position, hiatal hernia had no impact on TLESR frequency (9), an observation that is in line with our results. In an earlier report from the group of Kahrilas (24) a model on acid reflux was designed comprising data as LES pressure, size of hiatal hernia and reflux score. Both LES pressure and the length of a hiatus hernia were determinants of gastroesophageal junction incompetence. Van Herwaarden et al. (9) studied patients with or without a hiatal hernia by 24 hr ambulatory manometry of the LES and by pH metry. Patients with a hiatus hernia had more reflux but the excess of reflux in the patients with a hiatal hernia was not due to higher frequency of TLESR but due to other mechanisms of reflux such as low LES pressure, pointing to malfunction of the gastroesophageal barrier. The outcome of that study may have been affected by patient selection because only small numbers of reflux patients were investigated (9). In our large cohort of GERD patients the presence of a hiatal hernia did not influence the amount of acid reflux, nor reflux mechanisms nor LES motor characteristics. Hiatal hernia, however, prolonged the duration of reflux episodes. This may result not only from a higher acid volume load to the esophagus but also from impaired esophageal acid clearance.

The frequency of TLESRs was shown to be dependent on basal LES pressure. Patients with GERD with a normal LES pressure had significantly more TLESRs vs patients with low LES pressure. In the GERD patients with normal LES pressure 72% of reflux episodes were caused by TLESRs. In patients with low LES pressure TLESR frequency was reduced compared to controls and in that subset only 34% of reflux episodes occurred during TLESRs. The level of fasting LES pressure is therefore an important predictor of the reflux pattern in an individual GERD patient.

Our data suggest that different types of refluxers exist: patients with TLESR predominant reflux on the one hand and patients with esophagogastric junction incompetence on the other hand. In the later group, LES drift or absent pressure or abdominal strain (together causing 41% of reflux episodes) dominate over TLESRs (34% of reflux episodes).

Medical therapy of reflux disease is directed towards reducing the acidic component of the refluxate. This therapy is usually very effective but may fail in a small subset of patients (non responders) (25, 26). It is clinically relevant to determine the type of refluxer in the group of non responders because patients with low LES pressure and sphincter malfunction may require a treatment strategy that is different from patients with normal LES

pressure and TLESR predominant reflux. Future research should focus therefore more on quality than on quantity of TLESRs.

It is concluded that: 1) in GERD patients, frequency of TLESRs in the fasting state is not different form controls and postprandially the TLESR frequency even is significantly reduced. 2) in GERD patients significantly more TLESRs are associated with acid reflux. 3) in GERD patients TLESRs are the major mechanism of reflux but subtypes of refluxers exist (TLESR predominant vs LES incompetence). 4) LES pressure and not hiatal hernia or endoscopic grade of esophagitis determine the reflux mechanism.

REFERENCES

1. Dent J, Dodds WJ, Friedman RH, et al. Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects. J Clin Invest 1980;65:256-267.
2. Dodds WJ, Dent J, Hogan WJ, et al. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. N Engl J Med 1982;307:1547-1552.
3. Mittal RK, Holloway RH, Penagini R, et al. Transient lower esophageal sphincter relaxation. Gastroenterology 1995;109:601-610.
4. Holloway RH, Kocyan P, Dent J. Provocation of transient lower esophageal sphincter relaxations by meals in patients with symptomatic gastroesophageal reflux disease. Dig Dis Sci 1991;36:1034-1049.
5. Holloway RH, Lyrenas E, Ireland A. et al. Effect of intraduodenal fat on lower oesophageal sphincter function and gastro-oesophageal reflux. Gut 1997;40:449-453.
6. Penagini R, Bianchi PA. Effect of morphine on gastroesophageal reflux and transient lower esophageal sphincter relaxation. Gastroenterology 1997;113:409-414.
7. Schoeman MN, Tippett MD, Akkermans LM, et al. Mechanisms of gastroesophageal reflux in ambulant healthy human subjects. Gastroenterology 1995;108:83-91.
8. Dent J, Holloway RH, Toouli J, et al. Mechanisms of lower oesophageal sphincter incompetence in patients with symptomatic gastrooesophageal reflux. Gut 1988;29:1020-1028.
9. Van Herwaarden MA, Samson M, Smout AJ. Excess gastroesophageal reflux in patients with hiatus hernia is caused by mechanisms other than transient LES relaxations. Gastroenterology 2000;1119:1439-1446.
10. Savary M and Miller G. The esophagus. Handbook and Atlas of endoscopy. Solothurn, Switzerland: Gassmann AG, 1978:135-139.
11. Masclee AAM, de Best ACAM, de Graaf R, et al. Ambulatory 24 hr pH metry in the diagnosis of gastroesophageal reflux disease. Scand J Gastroenterol 1990;25:225-230.
12. Holloway RH, Penagini R, Ireland AC. Criteria for objective definition of transient lower esophageal sphincter relaxation. Am J Physiol 1995;268:G128-G133.
13. Smout AJ, Breedijk M, van der Zouw C, et al. Physiological gastroesophageal reflux and esophageal motor activity studied with a new system for 24-hour recording and automated analysis. Dig Dis Sci 1989;34:372-378.
14. Richter JE. Gastroesophageal reflux disease in the older patient: presentation, treatment, and complications. Am J Gastroenterol 2000;95:368-373.
15. Kahrilas PJ, Gupta RR. Mechanisms of acid reflux associated with cigarette smoking. Gut 1990;31:4-10.
16. Penagini R, Mangano M, Bianchi PA. Effect of increasing the fat content but not the energy load of a meal on gastro-oesophageal reflux and lower oesophageal sphincter motor function. Gut 1998;42:330-333.
17. Lidums I, Lehmann A, Checklin H, et al. Control of transient lower esophageal sphincter relaxations and reflux by the GABA(B) agonist baclofen in normal subjects. Gastroenterology 2000;118:7-13.
18. Holloway RH, Zhang Q. The GABA-B receptor agonist Baclofen inhibits transient lower oesophageal sphincter relaxations and gastro-oesophageal reflux in patients with reflux disease. Gut 2000;47:A24.
19. Sifrim D, Holloway R, Silny J, et al. Composition of the postprandial refluxate in patients with gastroesophageal reflux disease. Am J Gastroenterol 2001;96:647-755.
20. Trudgill NJ, Riley SA. Transient lower esophageal sphincter relaxations are no more frequent in patients with gastroesophageal reflux disease than in asymptomatic volunteers. Am J Gastroenterol 2001;96:2569-2574.

21. Wong WM, Lai KC, Hui WM, et al. Pahtophysiology of gastroesophageal reflux diseases in Chinese – Role of transient lower esophageal sphincter relaxation and esophageal motor dysfunction. Am J Gastroenterol 2004;99:2088-2093.
22. Sifrim D, Silny J, Holloway RH, et al. Patterns of gas and liquid reflux during transient lower esophageal sphincter relaxation. A study using intraluminal electrical impedance. Gut 1999;44:47-54.
23. Kahrilas PJ, Shi G, Manka M, et al. Increased frequency of transient lower esophageal sphincter relaxation induced by gastric distension in reflux patients with hiatal hernia. Gastroenterology 2000;118:688-695.
24. Sloan S, Rademaker AW, Kahrilas PJ. Determinants of gastroesophageal junction incompetence: hiatal hernia, lower esophageal sphincter, or both? Ann Int Med 1992;117:977-982.
25. Kahrilas PJ. Gastroesophageal reflux disease. JAMA 1996;276:983-988.
26. Chiba N, DeGara CJ, Wilkinson JM, et al. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. Gastroenterology 1997;112:1798-1810.