

Research Article

Transient Lower Esophageal Sphincter Relaxations and Mechanical Incompetence of the Lower Esophageal Sphincter – Is There a Relationship?

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Abstract

Introduction: The detailed process of a gastroesophageal reflux event is still under controversial discussion. Gastroenterologists have developed and favor the concept of Transient Lower esophageal Sphincter Relaxations (TLESR`s) as the major cause of gastroesophageal reflux episodes. TLESR`s are related with reflux episodes both in healthy individuals and patients with GERD. Another concept around the functional mechanism of the

antirefluxbarrier is a more mechanical interpretation of the Lower Esophageal Sphincter (LES), developed by surgeons.

The aim of this study is to investigate this relationship between TLESR`s and the mechanical failure of the LES by investigating these criteria in the same individuals.

Methods: In a referral center for esophageal and

gastric functional disease at the University Hospital in Würzburg, Germany, we investigated healthy volunteers and patients with proven GERD. The assessment of the LES consisted of the overall length, the intraabdominal length, and the end-expiratory pressure of the LES. The manometry was performed in a station-to-station-pull-through technique. The changing LES pressure and the TLESRs were measured with a sleeve catheter according to the protocol published by Dent and Schoeman. The presence of pathologic reflux in patients was evaluated by 24h pH monitoring.

Results: In total, 8 healthy volunteers were investigated (median age: 26 years (22-34)). In addition, 21 patients with GERD were evaluated (median age: 49 years (25-68)). The frequency of TLESR's was quite low in volunteers and patients with 0,4 TLESR's/h and 0,6 TLESR's/h respectively. While the frequency of TLESR's was not different between volunteers and GERD-patients, the percentage of reflux-associated TLESR's was significantly higher in GERD-patients with mechanically incompetent LES (20,8%), compared to the percentage in GERD-patients with intact LES (6,8%) and also compared to the percentage in healthy volunteers (7,8%) ($p < 0,001$).

Conclusion: The present analysis shows a relationship between a mechanically incompetent LES and an increased number of reflux-associated TLESR's, suggesting that the two mechanisms are not mutually exclusive, but may be instead different measurements of the same condition - a functionally and mechanically defective LES.

Keywords: Lower Esophageal Sphincter; LES; LES-incompetence; Transient Lower esophageal sphincter

relaxations; Transient Lower esophageal Sphincter Relaxations (TLESR's); Gastroesophageal Reflux Disease (GERD)

Introduction

The detailed process of a gastroesophageal reflux event is still under controversial discussion [1-10]. Gastroenterologists and surgeons differ substantially in their interpretation of reflux-related diagnostic studies regarding the actual reflux mechanism, leading to different explanations of the pathophysiologic findings [7-10]. It is understood that the pathophysiology of Gastroesophageal Reflux Disease (GERD) is determined by a multifactorial background [7-11]. This disease is associated with reflux mechanisms causing increased acid exposure in the esophageal lumen, which may lead to a variety of symptoms and esophagitis [7-11]. On the other hand, a limited number of gastroesophageal reflux episodes are physiologic [7-10].

Several factors were investigated and discussed as causes of gastroesophageal reflux such as transient Lower esophageal sphincter relaxations (TLESR's), the presence and severity of lower esophageal sphincter (LES) incompetence, the changes in anatomy such as a hiatal hernia, and associated motility disorders such as an impaired esophageal motility and/or associated gastric motility problems [7-11].

Gastroenterologists have developed and favor the concept of TLESR's as the major cause of gastroesophageal reflux episodes [3,4,7-9]. *Transient* TLESR's need to be separated from the swallow-induced relaxations of the LES, which are physiologic [7,9]. As shown in gastroenterologic literature, TLESR's are related with reflux episodes both in

healthy individuals and patients with GERD [4,7-9,12-15]. Some TLESR's are reflux associated and others are not [9,12-15]. In addition, a relationship between TLESR's and gastric distension has been published [14]. Gastric distension by air insufflation in patients with sliding hiatal hernias and a separation between squamocolumnar junction and hiatus resulted in an elevated frequency of TLESR's per hour [14]. It is anticipated that TLESR's are regulated by vagal reflex mechanisms, a triggering at the cardia and/or distention of the cardia and/or the fundus, leading to inhibition of the LES tonus [9,12-14]. TLESRs are frequently observed in the postprandial phase, which fits greatly in the the concept of increased TLESR's with increased gastric distension [14,15].

To some surprise, further investigations indicated that patients with GERD may not have more TLESRs than healthy controls [16-19]. If TLESR's are the major background of reflux events, one would expect a parallel increase of TLESR's with an increase in reflux episodes in more severe GERD. The latter opens several questions and stimulates the discussion about the background of TLESR's and their relations to different grades of severity in GERD.

Another concept of thinking around the functional mechanism of the antirefluxbarrier at the cardia is a more mechanical interpretation of the LES, developed by surgeons [1,2,5,6]. Starting with Allison, continued by Skinner, Belsey and Bombeck, the mechanical concept of the LES-competence was established [1,2,5,20-22]. The mechanical LES-incompetence was defined by a decreased overall length, altered intraabdominal position with decreased intraabdominal length and decreased pressure level of the LES, as propagated by DeMeester [1,2,5,10]. Many studies

show the relation between the mechanical deterioration of a LES and the increasing severity of GERD [5,6,10,11,22].

To the best of our knowledge we have not found any direct comparison of characteristic parameters the two major concepts in describing objectively the functional features of the LES. As a consequence, the aim of this study is to investigate this relationship between TLESR's and the mechanical failure of the LES by investigating these criteria in the same persons and patients in health and GERD.

Methods

Study individuals and investigations:

In a referral center for esophageal and gastric functional disease at the University Hospital in Würzburg, Germany, we investigated healthy volunteers and patients with proven GERD using functional assessment as established in clinical practice. The study was approved by the hospital institutional review board. All volunteers and patients gave informed consent for study evaluation and diagnostic work-up, and investigations followed a defined study protocol. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

The healthy volunteers were recruited among the students and employees of the hospital. They were screened for symptoms suggestive of any gastrointestinal (GI) disease, especially GERD or any other functional esophageal disorder. All received a history and physical examination. Those with positive findings were excluded from the study and further care

and diagnostic investigations regarding their symptoms and findings were suggested to the excluded volunteers.

All GERD-patients received a history and physical examination as well as an upper GI-endoscopy to verify the presence of an esophagitis and/or the presence of a hiatal hernia. All study-participants underwent standard esophageal manometry using a perfusion system (Mui, Motility systems, Canada and Sierra Scientific Instruments, USA) to determine the status of the LES as well as the esophageal peristaltic function as published earlier [5,6,23]. In all patients, medications known to affect gastrointestinal motility or gastrointestinal secretion were stopped three days, proton pump inhibitors one week prior to the study. A standard catheter assembly was used consisting of 5-fluid-filled polyethylene tubes (total outer diameter: 4,8mm) with sequential lateral openings of 0,8mm diameter, positioned at 5cm intervals from the distal end of the catheter radially oriented [5,23]. The rate of infusion was 0,6 ml per min. The assessment of the LES consisted of the overall length, the intraabdominal length as measured between the lower boarder of the LES and the Respiratory Inversion Point (RIP), and the end-expiratory pressure of the LES at the RIP. The manometry was performed in a station-to-station-pull-through technique (Medtronic, Minneapolis, USA). Criteria for a positive test for an incompetent LES were a sphincter pressure of 6mmHg or less, an overall length of 2cm or less, and an intraabdominal length or 1cm or less as published earlier [5,6,23].

The changing LES pressure and the TLESRs were measured with a sleeve catheter according to the protocol published by Dent and Schoeman (Technomatix Deutschland GmbH, Düsseldorf,

Germany) [3,4,12,13,24]. The sleeve was 6cm long and perfused with distilled water at a rate of 0,3 ml/min. In the beginning of each test a calibration of the system was performed. The sleeve catheter was placed in the LES and recording over hours was established. After an initial fasting period of 2 hours the patient received a standard test meal with semisolid joghurt and cheese-sandwich in the hospital, while this period was also recorded for assessing the postprandial phase of developing TLESR`s for 2 h. The total time of measurement was 21-24 hours for this ambulatory test. The individuals had another meal at home in the evening. Next morning, they returned to the laboratory to have the system removed. Afterwards the tracings were evaluated for frequency and duration of TLESR`s according to the published criteria [12,13,24]. These criteria were: 1. Absence of a pharyngeal swallow for 4 seconds before and 2 seconds after the relaxation episode; 2.a relaxation rate of ≥ 1 mmHg/sec; 3. time from onset to a complete relaxation of ≤ 10 seconds; 4. Nadir pressure of ≤ 2 mmHg.

The presence of pathologic reflux in patients was evaluated by 24h pH monitoring, utilizing the standard position of the pH probe 5 cm above the upper border of the LES. For analysis of gastroesophageal reflux, the DeMeester reflux score was used (score > 14.7 signified pathologic esophageal acid exposure) [2,5,25]. Probes were introduced together via a nasal orifice. Data collection devices were worn in a belt on the patient`s waist. Registration lasted for at least 22 h. Patients recorded the time of food or fluid consumption and posture changes on a diary card. They were instructed to stay upright during the daytime.

Study analysis:

As a control group, healthy volunteers were recruited among the students and employees of the hospital. Care was taken to identify their intact esophageal motility and physiologic LES function by standard manometry. The patient group consisted of individuals with proven GERD by 24-esophageal pH-monitoring and by the presence of esophagitis on endoscopy. The group of GERD patients were separated in those with a mechanical incompetent LES and those with a competent LES to show the relationship between those functional factors and the character of the assessed TLESR`s. The TLESR-data of these 3 groups, healthy volunteers, GERD-patients with and those without LES-incompetence were determined and compared. Total acid exposure was analysed as well as a separate analysis of the acid exposure during the first 2h postprandially to be able to determine the postprandial percentage of reflux associated TLESR`s.

Statistical analysis:

All data are presented as median. Statistical evaluations were done using Fisher`s exact test, and non-parametric tests (Mann-Whitney-U-test, Kruskal-Wallis) with SAS software (SAS Institute, Cary, NC). *P*-Values < 0.05 were considered to be significant.

Results:

In total, 8 healthy volunteers were investigated with a median age of 26 years [22-34]. There were 4 females and 4 males. All individuals tolerated the measurements well without any adverse events. In addition, 21 patients with GERD were evaluated with a median age of 49 years (25-68). There were 12 female and 9 male patients. The frequency of TLESR`s was quite low in volunteers and patients with 0,4 TLESR`s/h and 0,6 TLESR`s/h respectively. This was not statistically significantly different.

Table 1 shows an overview on the results of the measurements. While the frequency of TLESR`s was not different between volunteers and GERD-patients, the percentage of reflux-associated TLESR`s was significantly higher in GERD-patients with mechanically incompetent LES (20,8%), compared to the percentage in GERD-patients with intact LES (6,8%) and also compared to the percentage in healthy volunteers (7,8%) ($p < 0,001$). This was true for the analysis during the total measurement as well as for the postprandial evaluation time (Table 1).

The duration of the TLESR`s was in median 15 sec in the healthy volunteers, 16,9 sec in GERD-patients with normal LES and 16,3 sec in GERD-patients with incompetent LES, which showed no significant difference.

The results show that the findings with reflux-associated TLESR`s correlated with the patients with mechanical defective LES. This underlines that both concepts are not necessary in controversy, but emphasize the role of the LES, both as a mechanical and functional antireflux barrier.

Groups	Total assessment time		Postprandial period (2 h)	
	Number of TLESR`s per hour	% TLESR`s reflux-associated	Number of TLESR`s per hour	% TLESR`s reflux-associated
Healthy volunteers (n=8)	0,4 (0,2-0,8)	7,8 (0-33)	0,3 (0-1)	9,4 (0-75)
Patients with GERD and mechanical LES-incompetence	0,7 (0,2-1,5)	6,8 (0-20)	0,8 (0-2)	7,7 (0-33)
Patients with GERD without mechanical LES-incompetence	0,5 (0,2-1,1)	20,8 * (0-47)	0,6 (0-2)	40,5 * (0-100)

Table 1: Overview on comparative results of manometric studies in healthy volunteers and GERD-patients assessing mechanical parameters of LES- incompetence and characteristics of Transient Lower esophageal Sphincter Relaxations

Discussion

Patients with GERD can present with a wide variety of clinical symptoms [26-28]. The classic and most typical symptoms are heartburn and/or regurgitation. However, patients may demonstrate with atypical symptoms such as nausea, epigastric pain, cough, hoarseness, and thoracic pain [26,28].

GERD is a highly prevalent, benign disorder in North America and Europe [8-11,26]. It`s multifactorial pathophysiology has been studied extensively with new diagnostic technology [8-11,29-34].

It is widely accepted that the antireflux barrier at the esophago-gastric junction plays a major role in the prevention of excessive gastroesophageal reflux and its failure can cause pathologic reflux. Several anatomical and functional structures such as the distal esophageal muscular wall, the diaphragm, the phrenoesophageal ligament and the neural network are involved. As mentioned above, there are some controversial issues

regarding the details of functional mechanisms and dysfunction [1-10]. These mechanisms determine the detailed process of a reflux event [7-10].

The mechanical interpretation of the LES, established by surgeons describe the incompetence of the LES with a shortened intraabdominal length, an overall shortening of LES-length, and/or decreased LES pressure, which has been demonstrated in patients with severe GERD [1,5,10,22,23,35-38]. It must be emphasized that LES-incompetence is not just a pressure weakness, but also a structural insufficiency in length and position of the sphincter with regards to the diaphragm [10,22,23]. The surgical argument of a structural deficit of the antireflux-barrier is supported by the results of several analysis, in which nearly 90% of a large GERD population show a mechanically incompetent antireflux barrier, indicating the major role of this criterion as the underlying cause of this disease [8,10,11].

On the other hand, the etiology emphasized by gastroenterologists determines TLESRs as the major cause of pathologic gastroesophageal reflux events [3,4,7-9,12-15]. Functional investigations showed that reflux episodes occurred almost exclusively during TLESRs [7-9,12-15,39-41]. TLESRs are frequently observed in the postprandial phase [8,15]. Dent and Dodds described a spontaneous opening of the LES as the most important mechanism for the development of gastroesophageal reflux [3,4]. This occurs in healthy persons and also in patients with GERD and was considered a physiologic mechanism to evacuate ingested air from the gastric lumen [7,8,12-17]. However, if the LES is open during such relaxations, acid reflux can occur. Transient lower esophageal sphincter relaxations (TLESR`s) develop without previous swallowing, and may be increased in pathologic reflux. In contrast, LES-relaxations are triggered in the process of swallowing. In TLESR`s, a vagal reflex is caused by stimulation at the cardia and by fundic distension [3,4,7-9,12-17,24]. This signal reaches via afferent vagal lines the central nervous system and further causes an inhibition of the LES and diaphragm, leading to a TLESR [7,12-17,24,39-41]. The relaxation develops with a pressure drop of > 1 mmHg/sec and continues for approximately 10sec [7,12-17,39-41]. TLESR`s were detected and recorded by a special manometric device, a sleeve catheter that is inserted in the high pressure zone and assesses the complete length of the sphincter [3,4,7,24]. The sleeve catheter is able to characterize the intraluminal and integral pressure changes over the complete length of the high pressure zone.

TLESR`s are reported to be related to gastric distension [8,9,12-17]. Further investigations indicated that patients with GERD do not have more TLESR`s

than healthy controls [18,42].

The latter raises the question, how the TLESR-concept may fit in the setting of severe GERD, in which the frequency TLESR`s does not increase [7,8,15,18]. One explanation suggests that distension of the gastric fundus during a meal, or air distension of the proximal stomach cause temporary shortening of the LES, which could be recorded as decreased LES-pressure, when the mechanism is in fact a transient shortening [10,43-45]. The current study shows some explanation, since those patients with GERD and a mechanical incompetent LES show more TLESR`s to be reflux-associated.

In addition, several studies showed that a worsening mechanical function of the LES correlates with an increased rate of grossly visible esophageal damage noted on endoscopy [10,11,35-38].

Both concepts of describing and assessing the background of reflux events can also be applied in the current discussion about GERD and excessive overeating in western societies with subsequent obesity [8,10,46-47]. The process of repetitive overeating in our daily life will cause mechanical and functional alterations in the upper G.I.-tract [8,10,47-49]. When a person is eating a large meal, the ability of the stomach and especially the fundus allows for an enlargement of the gastric lumen to ingest the complete meal by fundic accommodation. Fundic enlargement by accommodation will cause mechanical strain on the LES, since the strong pull of the gastric wall on the LES at the angle of His will shorten eventually the sphincter area and its lower segment, while at the same time the physiologic sphincter function needs to keep the high pressure zone closed to

prevent excessive postprandial reflux. If this process is repeated on a daily basis and an individual is wearing out the LES, it is not surprising that the strain on the tissue weakens these structures. In addition, there is evidence that during and shortly after a meal the acid secretion is massively stimulated by several mechanisms and newly secreted acid collects in the subcardial region creating an „acid-pocket“ [8-10]. This acid-pocket is directly located below the LES, being under strain by shortening through fundic accommodation. Thus, reflux can occur easily after large meals. The progression from physiologic amounts of reflux to excessive and pathologic gastroesophageal acid reflux is well understood [8-10]. Again, if this process is maintained over several decades, the mechanical and functional abilities of the esophagogastric junction are fading and the progression towards functional, histologic and anatomical changes are possible.

Manometric studies have shown that in the postprandial phase an effacement of the LES and the cardia occurs and at the same time a shortening of the LES can be detected due to the fundic accommodation as described above [10]. Since physiologic LES-function depends on its intra-abdominal segment, both in pressure and intra-abdominal length, a spontaneous shortening of the sphincter in the postprandial phase will create a temporary incompetency, leading to a temporary spontaneous opening of the sphincter. The latter could fully explain the manometric observations of a TLESR in the postprandial phase [7-10]. This would explain, why TLESR's are increased in the postprandial phase.

In conclusion: The present analysis shows a relationship between a mechanically incompetent LES

and an increased number of reflux-associated TLESR's, suggesting that the two mechanisms are not mutually exclusive, but may be instead different measurements of the same condition - a functionally and mechanically defective LES.

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