



# Pathophysiology of gastroesophageal reflux disease— which factors are important?

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**Background:** Pathophysiology of gastroesophageal reflux disease (GERD) shows a multifactorial background. Different anatomical and functional alterations can be determined such as weakness of the lower esophageal sphincter (LES), changes in anatomy by a hiatal hernia (HH), an impaired esophageal motility (IEM), and/or an associated gastric motility problem with either duodeno-gastro-esophageal reflux (DGER) or delayed gastric emptying (DGE). The purpose of this study is to assess a large GERD-patient population to quantitatively determine different pathophysiologic factors contributing to the disease.

**Methods:** For this analysis only patients with documented GERD (pathologic esophageal acid exposure) were selected from a prospectively maintained databank. Investigations: history and physical, body mass index, endoscopy, esophageal manometry, 24 h-pH-monitoring, 24 h-bilirubin-monitoring, radiographic-gastric-emptying or scintigraphy, gastrointestinal quality of life index (GIQLI).

**Results:** In total, 728 patients (420 males; 308 females) were selected for this analysis. Mean age: 49.9 years; mean BMI: 27.2 kg/m<sup>2</sup> (range, 20–45 kg/m<sup>2</sup>); mean GIQLI of 91 (range: 43–138; normal level: 121); no esophagitis: 30.6%; minor esophagitis (Savary-Miller type 1 or Los Angeles Grade A): 22.4%; esophagitis [2–4]/B–D: 36.2%; Barrett's esophagus 10%. Presence of pathophysiologic factors: HH 95.4%; LES-incompetence 88%, DGER 55%, obesity 25.6%, IEM 8.8%, DGE 6.8%.

**Conclusions:** In our evaluation of GERD patients, the most important pathophysiologic components are anatomical alterations (HH), LES-incompetence and DGER.

**Keywords:** Gastroesophageal reflux disease (GERD); pathophysiology of GERD; lower esophageal sphincter (LES); hiatal hernia; duodeno-gastro-esophageal reflux (DGER)

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## Introduction

Numerous publications on the pathophysiology of gastroesophageal reflux disease (GERD) demonstrate the multifactorial background of this benign disorder, highly prevalent in the western industrialized countries of

North America and Europe (1–7). Understanding of the pathophysiology of reflux has expanded in recent decades with the advent of new diagnostic technology (8–15). The disease is associated with reflux of gastric contents into the esophagus causing mainly increased acid exposure in the esophageal lumen and/or esophagitis (5,14). GERD often

has an inconsistent clinical picture, with many variables contributing to the disease process. Patients present with a wide variety of initial symptoms; the classic manifestations of GERD are heartburn and/or regurgitation. However, patients may demonstrate atypical symptoms as well, presenting with cough, laryngitis, and asthma (5,6).

Morphological and functional investigations may demonstrate the presence of different anatomical and functional alterations such as a weakness of the lower esophageal sphincter (LES), an altered frequency of transient LES relaxations (TLESRs), changes in anatomy i.e. the presence and size of a hiatal hernia (HH), and associated motility disorders such as an impaired esophageal motility (IEM) and/or the possible involvement of associated gastric motility problems (4-19). Most reports are more focused on one or the other background cause of the disease (10-20). Prior reports on the pathophysiology of GERD often neglect to include a quantitative assessment of a large population, instead focusing on a qualitative overview of pathophysiological factors (5-7). The importance of the individual involvement of pathophysiologic components of GERD may be elucidated by analysing a large population of GERD-patients, thus permitting a broad assessment of the presence of factors contributing to the development of GERD. This opportunity was provided by documenting these factors over years in a tertiary referral center for patients with benign upper gastrointestinal disorders.

Based on publications on the pathophysiology of GERD, in conjunction with several published guidelines from Europe and North America, a list of the critical factors and mechanisms contributing to GERD was compiled (4-7,13-23). These include hiatal anatomic changes, i.e., hiatal hernia, LES incompetence, TLESRs, esophageal acid exposure, insufficient esophageal motility (IEM), delayed gastric emptying (DGE), duodeno-gastro-esophageal reflux (DGER) and obesity.

The purpose of this study is to assess a large GERD patient population to achieve a quantitative determination of the different pathophysiologic factors contributing to the disease.

## Methods

Our group managed and investigated patients with GERD at a tertiary referral center in Frankfurt/Germany for benign esophageal and gastric disorders. All patients with foregut symptoms, referred for establishment of a precise diagnosis and potential surgical treatment, underwent a

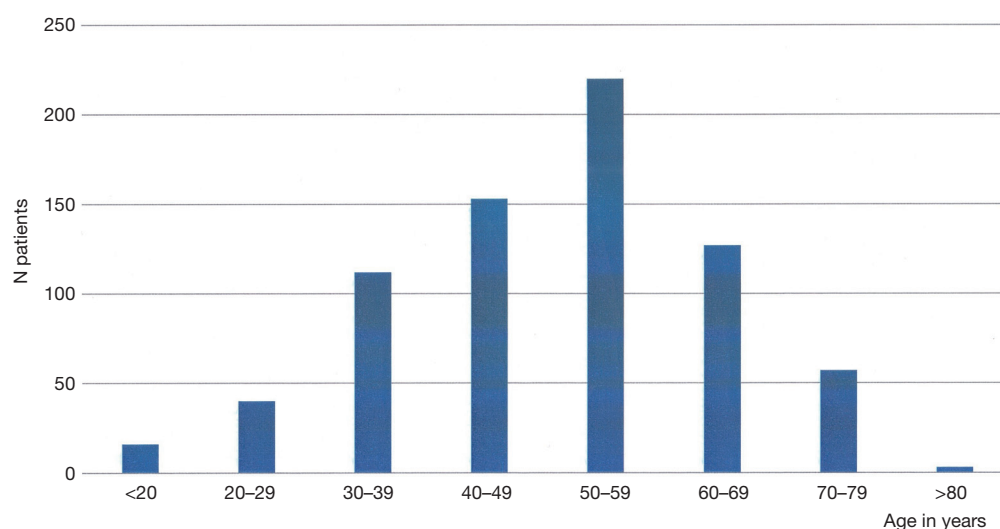
history and physical examination, as well as standardized symptom questionnaires since 2003. In addition, all patients were evaluated in a surgical diagnostic gastrointestinal-function laboratory.

For this analysis only patients with documented GERD by proven pathologic esophageal acid exposure were selected from a prospectively maintained databank for all investigated patients, who were all under PPI-therapy prior to the initial office visit. We excluded data from patients with prior anti-reflux operations, as well as patients with other esophageal disorders (i.e., achalasia, dysmotility), focusing on patients with a primary diagnosis of GERD without any previous interventions, as documented by positive 24 h-pH monitoring test (1,14). The study was approved by the hospital institutional review board (MKF-010/2010). All 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.

Management of patients was performed by the same team over the complete study period. The patients were first evaluated by an experienced, board-certified surgeon to perform the clinical assessment and determine a diagnostic plan. Symptoms were evaluated with a standardized questionnaire measuring also symptom intensity with an analog scale from 0 (no symptoms) – 5 (maximum intensity). All patients had a measurement of their body mass index (BMI). All patients underwent an upper gastrointestinal endoscopy. Initially lesions detected in the esophagus were classified according to Savary and Miller, later this was revised to classification according to the Los Angeles classification system (5,23,24). Hiatal hernia size was measured by vertical length, from the beginning of the gastric folds representing the cardia to the level of the crura as detected during endoscopy. Care was taken to perform these measurements at the beginning of the investigation prior to major air-insufflation of the stomach.

Quality of Life was evaluated in this study population by the Gastrointestinal Quality of Life Index (GIQLI), a well-established metric that is validated in several languages (25). The GIQLI carries five different components addressing quality of life, including core GI symptoms, psychological, physical, and social factors, disease-specific items, and influence of administered therapy with a maximum index points of 144, evaluated by 36 questions.

All patients underwent esophageal manometry initially



**Figure 1** Age distribution among 728 patients with proven GERD as documented by pathologic esophageal acid exposure by 24 h-pH-monitoring. GERD, gastroesophageal reflux disease.

by perfusion manometry, since 2010 by high resolution manometry (HRM) to determine LES incompetence and the presence or absence of an esophageal motility disorder (3,11,12,15,18,26).

The presence of pathologic reflux was evaluated by 24-h-pH-monitoring. In recent years impedance pH-monitoring utilizing the standard position of the pH probe 5 cm above the upper border of the LES was used (1,3,4). Impedance-pH-monitoring was performed using standard technique for analysis of the DeMeester score (8-10,26). A DeMeester score above 14.7 signified pathologic esophageal acid exposure. The results of this investigation determined also the selection of the patients for this analysis. Seven days prior to the examination, all medications affecting motility and acid suppression were stopped. Bilirubin exposure as marker for DGER was measured with a photoptic assessment system (Bilitec™) and evaluated as published previously (10,27).

Our goal was to investigate a representative population of GERD patients. Initially all patients with symptoms indicating a GERD presence were seen and investigated. For the analysis we focused on patients with documented GERD by positive pathologic acid exposure on 24-h pH monitoring. The intensity of symptoms was compared to the functional status of the patients such as incompetence of the LES and the extent of the esophageal acid exposure.

Statistical comparison with a t-test for unpaired samples

was used for the comparison of data from the different samples. A Chi-square test was used for comparison of group data.

## Results

### *Patient characteristics*

More than 1,800 patients had been documented in the foregut database between 2003 and 2017. In total, 728 patients (420 males; 308 females) were selected for this analysis based on a documented presence of GERD by positive pathologic 24-h-pH-monitoring regarding the presence of pathophysiologic components of GERD and the availability of the data. Mean age was 49.9 years (range, 18–101 years). *Figure 1* shows the age distribution in these patients. *Table 1* provides an overview on the characteristics of the selected patients. The mean BMI in this GERD-patient population is 27.2 kg/m<sup>2</sup> (range, 20–45 kg/m<sup>2</sup>). *Figure 2* shows the distribution of BMI in the patient population, indicating that 26.6% of these patients have been obese.

Quality of Life as measured with the GIQLI is demonstrated in *Figure 3*. Different dimensions of the GIQLI such as gastrointestinal symptoms, emotional status, physical status, social status and influence of therapy are demonstrated. The values of the GERD study population are related to the maximal possible index values for the 5

different dimensions, showing a mean overall GIQLI of 91 (range, 43–138; normal level: 121). Notably, Quality of Life of GERD patients in the study population was substantially decreased to normal patient metrics.

The presence of esophagitis is demonstrated in *Figure 4*. A substantial part (30.6%) of these GERD patients did not show any evidence of esophagitis, however these patients were all under PPI-therapy. Minor esophagitis (Savary-Miller type 1 or Los Angeles Grade A) was documented in 22.4% of patients. More severe mucosal damage and/or alterations were seen in almost 50% of GERD-patients

in this population (*Figure 4*). In 10% an endoscopic and histologic evidence of Barrett's esophagus was documented.

### Results of pathophysiologic factors

The analysis of 728 patients with primary GERD in a tertiary surgical referral unit shows as pathophysiologic factors and contributors of the disease the presence of hiatal hernias (HH), the LES-incompetence, an IEM, delayed gastric emptying (DGE) and the presence of DGER. *Figure 5* demonstrates an overview of the frequency of these different pathophysiologic components of GERD in our study population.

Most frequent factors are the presence of a hiatal hernia (95.4%) as major anatomic alteration and the LES-incompetence (too weak and/or too short LES) (88%). The majority of GERD patients have a hiatal hernia measuring between 2–5 cm vertical length.

Another important factor is DGER, present in 55% of these GERD patients, in patients with histologic and endoscopic evidence of Barrett's esophagus even 89%.

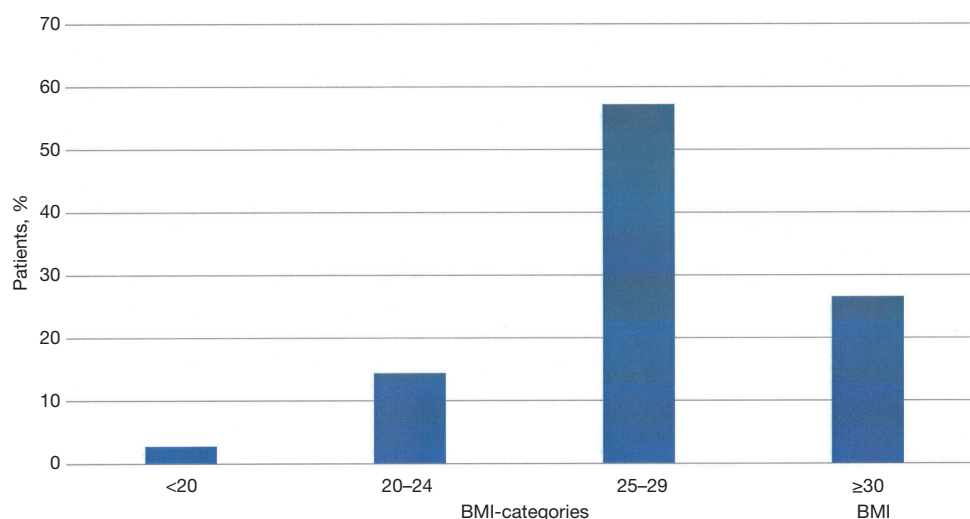
DGE could be measured by Barium-Sandwich emptying radiography and/or gastric emptying scintigraphy in 6.8% of these patients. IEM was found in 8.8% of the patients, based on esophageal manometry.

*Table 2* demonstrates the relationship between objective functional test results and the intensity of symptoms. The intensity of heartburn has been significantly different

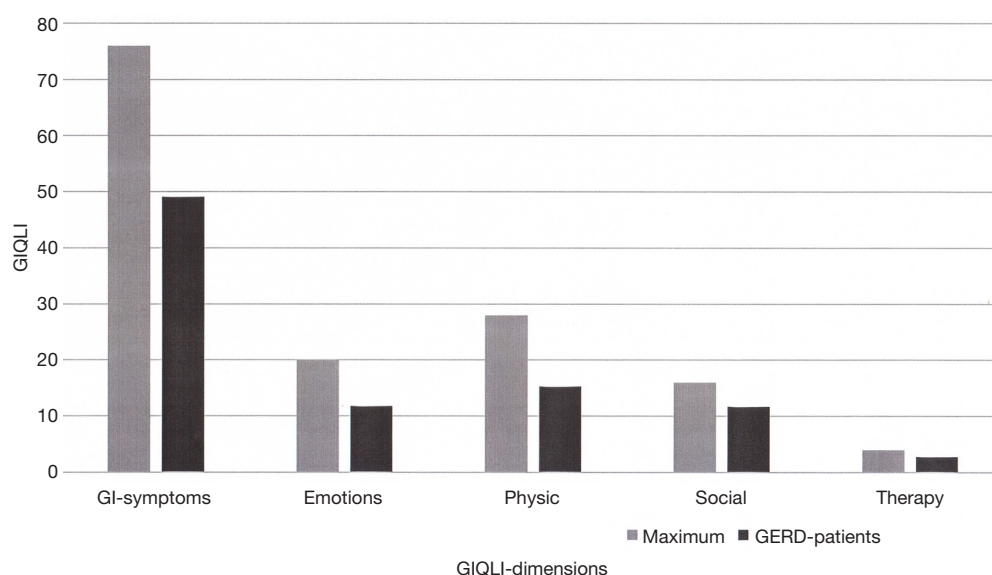
**Table 1** Overview on the patients' characteristics

| Variables                     | GERD-data |
|-------------------------------|-----------|
| N                             | 728       |
| Age (years), mean             | 49.9      |
| BMI mean                      | 27.2      |
| Esophagitis (% presence)      | 69.4      |
| Hiatal hernia (% presence)    | 95.4      |
| GIQLI mean (normal: 121)      | 92.9      |
| LES incompetence (% presence) | 88.0      |
| Esophageal acid exposure      |           |
| Mean (normal: <14.7)          | 53.9      |
| % presence                    | 100       |

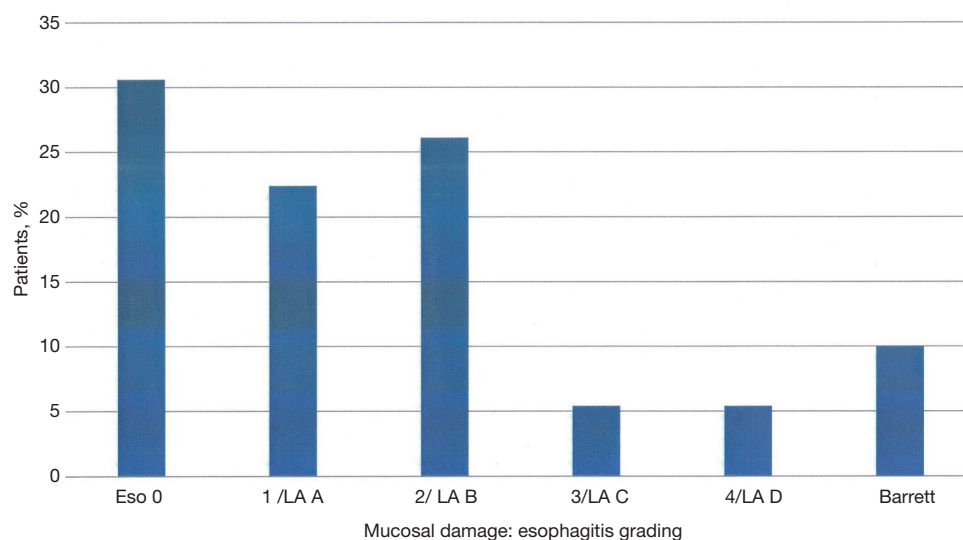
GIQLI, gastrointestinal quality of life index.



**Figure 2** Distribution of body mass index assessment as marker of obesity in 728 GERD-patients in Frankfurt am Main, Germany. GERD, gastroesophageal reflux disease.



**Figure 3** Distribution of quality of life, assessed in GERD-patients by GIQLI. Note the importance of gastrointestinal symptoms as well as physical sign among the different dimensions of the GIQLI. The GIQLI is substantially reduced in GERD-patients compared to values of a healthy control group. GERD, gastroesophageal reflux disease; GIQLI, gastrointestinal quality of life index.



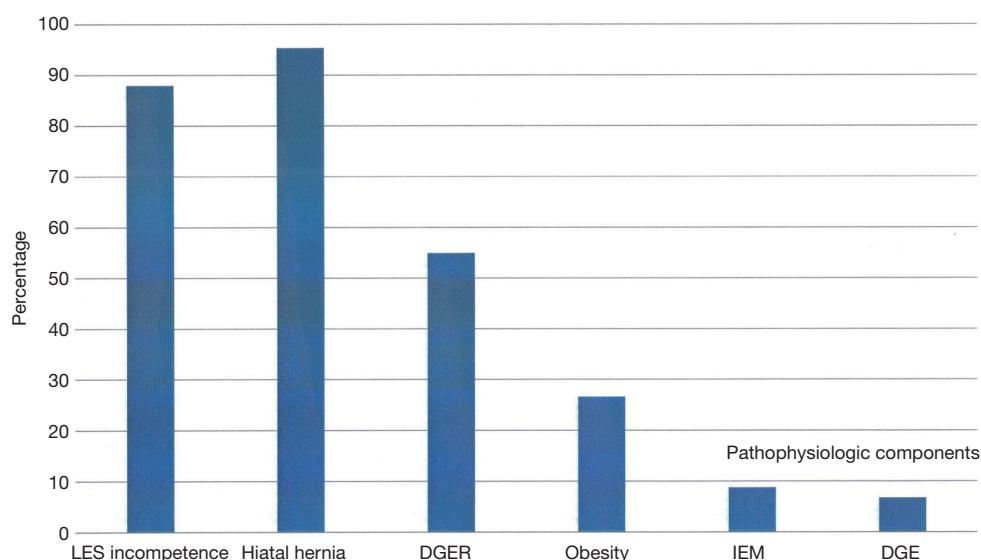
**Figure 4** Distribution of the presence of esophagitis in 728 GERD-patients determined either by Savary-Miller classification [1–4] or by Los Angeles grading (A–D). Ten percent of patients do have endoscopic and histologic evidence of Barrett’s esophagus. GERD, gastroesophageal reflux disease.

between patients with and those without LES incompetence (LES-I). The intensity scores are elevated for patients with incompetent sphincter (3.4 in patients with LES-I; 1.8 in patients without LES-I;  $P < 0.0006$ ). The differences in symptom intensity are also significant for regurgitation,

however all other symptoms have no remarkable differences detected for changes in objective functional status.

In summary, presence of hiatal hernia, a mechanically incompetent LES and the presence of duodenal juice contents in the esophageal lumen are the most frequent





**Figure 5** Overview on the presence of different pathophysiologic factors in this cohort of 728 GERD-patients as determined by extensive diagnostic investigations. HH 95.4%; LES-incompetence 88%, DGER 55%, obesity 25.6%, IEM 8.8%, DGE 6.8%. GERD, gastroesophageal reflux disease; HH, hiatal hernia; LES, lower esophageal sphincter; DGER, duodeno-gastro-esophageal reflux; IEM, impaired esophageal motility; DGE, delayed gastric emptying.

**Table 2** Relation between symptom intensity [measured on analog scale from 0 (none) – 5 (maximum) and LES-incompetence]

| Symptom              | LES competent | LES incompetent | P      |
|----------------------|---------------|-----------------|--------|
| Heartburn            | 1.8           | 3.4             | 0.0006 |
| Regurgitation        | 1.4           | 2.7             | 0.003  |
| Retrosternal pain    | 0.6           | 0.5             | ns     |
| Respiratory symptoms | 1.9           | 1.8             | ns     |
| Dysphagia            | 0.8           | 0.9             | ns     |
| Epigastric pain      | 2.1           | 2.2             | ns     |
| Nausea/vomiting      | 0.5           | 1.2             | ns     |
| Fullness             | 2.2           | 2.5             | ns     |
| Gas-related symptoms | 2.2           | 2.4             | ns     |

LES, lower esophageal sphincter.

pathologic changes in GERD, followed by less frequent factors such as obesity, IEM, and DGE.

## Discussion

The characteristics of our study population reflect a typical picture of GERD patients, with average age around the 4th and 5th decade of life, as previously reported in the literature (5-7). Patients with GERD exhibit a

substantial reduction in their quality of life (28-32). When examining the contributing factors to overall quality of life, gastrointestinal symptoms and physical changes are the main drivers reducing quality of life, reflected in the GIQLI-data (25,28,32). These two factors can influence the emotional component, which can further reduce the GIQLI score. This supports previous literature indicating that patients seek definitive interventional treatment after undergoing long-term medical management (28,29,33,34).

**Table 3** Overview on the presence (percentage) of pathophysiologic factors in GERD in literature

| Author, year       | LES  | TLESR                 | HH | DGER | DGE     | IEM              | Obesity |
|--------------------|------|-----------------------|----|------|---------|------------------|---------|
| DeMeester, 1992    | 91   | –                     | 82 | –    | 33      | 16               | 15      |
| Fuchs, 1995        | 87   | –                     | 80 | 6    | 5       | 14               | –       |
| Boeckxstaens, 2007 | 90   | 33                    | 75 | –    | 10–33   | 25–48            | –       |
| Herbella, 2010     | High | 40                    | 54 | –    | –       | 40–50, severe 20 | –       |
| Herregods, 2015    | High | Association with acid | –  | 12   | Related | OR: 1,87         | 31      |

LES, lower esophageal sphincter; TLESR, transient LES relaxation; HH, hiatal hernia; GERD, gastroesophageal reflux disease; DGE, delayed gastric emptying; IEM, impaired esophageal motility.

In addition to reduction in quality of life, psychological ability of patients to cope with the symptoms plays a significant role in their well-being (31,35,36). GERD patients have a wide variety of symptoms along with substantial overlap with other disorders, thus symptomatology alone is difficult to use for diagnostic discrimination and/or patient selection for therapy (5,31,37–39).

Various pathophysiologic factors may contribute to both severity and the trajectory of reflux (2–7). GERD has been determined to be a multifactorial disorder (2–7). Prior publications highlight the different components, usually either providing an overview or focusing on a few detailed aspects of the pathophysiologic background of the disease (5–13,16–21). *Table 3* demonstrates an insight regarding the main publications with overviews on the pathophysiologic background of GERD (3,4,6,7,13). In the current analysis, we assessed a population of 728 GERD patients, permitting evaluation of all possible contributing factors in one population, thus allowing for comparison of the presence of different pathophysiologic components. Our results show that anatomical changes and malfunction of the cardia as the natural antireflux barrier are the most frequent functional defects detected.

The anatomic changes after pathologic deterioration of cardia fixation in the hiatal aperture by the phrenoesophageal membrane, with subsequent development of hiatal hernia are frequent, if not critical in precipitating the development of GERD (5,6,14,20,23,26). Our study shows that most hernias measure in the 2–5 cm range of vertical extension between the cardia and crura; this dimension may reflect the time period from initial symptoms to diagnostic work-up in recent years.

The weakness of the natural antireflux barrier at the cardia obviously plays an important role in the pathophysiology of GERD (2–7,14,26). As published in multiple studies, LES-incompetence either via decreased intraabdominal

length, overall shortening of LES-length, and/or decreased LES-pressure, has been demonstrated in severe GERD (2–7,13,14,18–20). In our analysis, LES incompetence is present in 88% of the investigated patients and is therefore a major component. Other reports have analysed transient LES-relaxations as major factor of pathologic reflux, which is discussed controversially between surgeons and gastroenterologists (6,14,17–19,40–47). Fact is, that the malfunction of the anatomical and functional components of the antireflux barrier plays a major role in allowing for pathologic gastroesophageal reflux (6,14,40–42).

Another controversial discussion has developed around reflux of duodenal and enteric contents into the esophagus. Duodenal refluxate can be quite harmful to the esophageal mucosa (3,4,10,14,27,48–52). Studies of patients diagnosed with Barrett's esophagus indicated that the refluxate is composed of duodenal contents, highlighting both the presence and effect of DGER (10,14,48–52). We investigated this subset of subjects with the Bilitec™ bilirubin monitoring device. Our findings support the contribution of DGER to the pathophysiology of GERD, particularly in Barrett patients (10,14,48–52). The implications may play a role in the progression of GERD and Barrett's esophagus (50–52).

IEM has been investigated in GERD-patients (3–7). The prevalence of IEM in these patients is reported between 10–50% (3,4,6,53–57). In a previous study from our group we found 14% of GERD patients to have IEM (4). However, an isolated pathophysiologic defect is was found in 2% (4). In the present study, we documented IEM in 8.8% of the GERD study population, indicating that the majority of GERD-patients do not develop a severe, detectable IEM.

Other factors involved in the development of GERD are less common, such as DGE causing stasis of gastric contents, ultimately leading to reflux. In the literature, DGE is present in GERD in 5–33%, while in this study we detected it in 6.8% of patients (6,16,21,58).

Obesity, defined as a body mass index greater than or equal to 30 is associated with an increased prevalence of GERD as compared to the non-obese patient population (59-62). A variety of explanations for increased frequency of GERD with increasing weight have been proposed (4,59-62). Obesity can cause increased esophageal acid exposure with increased chance of reflux (61). Studies showed a statistically significant inverse relationship between BMI and LES pressure (61). Our subjects had a mean BMI of 27, with only 15.8% of patients falling in the category of BMI >30; this may explain the apparent lesser contribution of obesity to GERD in our patients.

In conclusion, in our evaluation of GERD patients referred for surgical intervention, the most important pathophysiologic component in severe GERD, appears to be mechanical incompetence and anatomical alterations of the anti-reflux barrier. These results emphasize the necessity of mechanical augmentation of the LES in successful long-term therapy for severe GERD.

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### Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tgh.2020.02.12>). SH reports other from stock option from Torax medical, outside the submitted work. The other authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the hospital institutional review board. All 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.

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