The role of the transdiaphragmatic pressure gradient in the pathophysiology of gastroesophageal reflux disease

Leonardo M DEL GRANDE1, Fernando A M HERBELLA1, Rafael C KATAYAMA1, Francisco SCHLOTTMANN2 and Marco G PATTI2

ABSTRACT – Gastroesophageal reflux disease (GERD) is the most common disease of the upper gastrointestinal tract in the Western world. GERD pathophysiology is multifactorial. Different mechanisms may contribute to GERD including an increase in the transdiaphragmatic pressure gradient (TPG). The pathophysiology of GERD linked to TPG is not entirely understood. This review shows that TPG is an important contributor to GERD even when an intact esophagogastric barrier is present in the setting of obesity and pulmonary diseases.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common disease in the Western world with a raising prevalence in the last decades. It is currently the most common chronic disorder of the upper digestive tract (1) and it is estimated that GERD affects 10%-20% of the population (2). In the US, GERD symptoms are felt at least weekly by 10%-25% of the population (3-6).

GERD pathophysiology is multifactorial with different factors contributing to its genesis. A defective esophagogastric barrier is commonly found in patients with GERD, since 75% of the individuals have a hypotonic lower esophageal sphincter (LES) (7). A quarter of the individuals; however, have normal LES pressure and length. Some studies showed that transient LES relaxation (TLESR) may be the cause for GERD in these patients (7,8). Others believe on the role of esophageal body dysmotility that leads to a faulty esophageal clearance exacerbating mucosal damage and allowing reflux to reach higher levels (9) or on the defective action of the diaphragm as an extrinsic sphincter in the absence of hiatal hernia (HH) (10). Other possible factors are still the composition of the refluxate, mucosal integrity, visceral sensitivity, esophagogastric diminished compliance, and delayed gastric emptying (11,12).

Transdiaphragmatic pressure gradient (TPG) is part of GERD pathophysiology as well. The difference in pressure between positive gastric/abdominal pressure (AP) and the negative esophagogastric pressure (TP) may exceed the pressure of the esophagogastric barrier represented by the LES and the diaphragm. This gradient may account for GERD (13). Some groups of patients – such as those with lung diseases (9) or obesity (10) – have a higher risk of developing an elevated TPG and, not surprisingly, are at higher risk to have GERD. The mechanism is a raise in AP in the case of obesity (11) and a decrease in TP in chronic pulmonary disorders (12).

This review focuses on the role of TPG on GERD pathophysiology.

Transdiaphragmatic pressure gradient quantification by esophageal manometry

AP and TP are parameters not routinely measured during esophageal manometry. At the time of conventional manometry, only few studies (13,15) tried to measure TPG in GERD patients comparing inspiratory, mean respiratory or both pressures with variable methodology and without establishing reference values for normal individuals (16-20). This is related to several limitations faced by conventional manometry, such as: (a) catheter movement artifacts that may include LES pressure with gastric or thoracic pressures if measurements are taken close to the sphincter; (b) inability to identify altered respiratory movements such as thoracic pressurization during moments of stress; (c) different parameters for zeroing baseline if different channels are used to measure thoracic or abdominal pressure; and (d) inability to identify gastric contractions that may be included during abdominal pressure recording (16).

High resolution manometry eliminates some of these limitations and recently some studies are focused on TPG at the light of this technology (16-20). There is not, however, a standardization of methodology yet. Our preference is to calculate TPG subtracting the thoracic pressure measured at 2 cm above the upper border of the LES considering its respiratory excursion and the abdominal pressure at 2 cm below the lower border of the LES also considering its respiratory excursion. Both pressures are calculated based on the average pressure in a 30 s period encompassing all phases of the respiration (mid-respiratory measurement) (17) (FIGURE 1). We also measure LES retention pressure as defined by LES mid-respiratory basal pressure minus TPG.
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Transdiaphragmatic pressure gradient in health

There is no reference values originated from healthy volunteers available. We use the parameters obtained from 32 healthy volunteers studied in our laboratory (n=32, mean age 33.1±8.7, 70% females). The results are expressed in TABLE 1.

transdiaphragmatic pressure gradient and gastroesophageal reflux disease

The role of TPG on GERD pathophysiology is not well understood. Apart from altered AP and TP, TPG may be also influenced by compliance of the distal esophagus, changes in diaphragmatic morphology(13,23-25). The important role of TPG must be; however, associated to TLESR, obesity, hiatal hernia and pulmonary diseases.

• Transient lower esophageal sphincter relaxation and the transdiaphragmatic pressure gradient

TLESR is a physiologic phenomenon secondary to gastric distension, defined by LES relaxation occurring in absence of swallowing, lasting more than 10 seconds, and associated with crural inhibition(26). GERD patients have two times more episodes of reflux during TLESR as compared to normal individuals(27). A possible explanation for an increase in the episodes of reflux is an increase in the TPG in these patients(8,18,22-23,25,27-30) that occurs shortly before TLESR(31). This may explain GERD in the setting of a normotonic LES(5,32).

• Obesity and transdiaphragmatic pressure gradient

Obesity increases the risk for GERD(11,33). Different studies showed that increase in weight is linked to a higher prevalence of GERD(10,11,34-36). Moreover, obese individuals have more symptoms(35,36), increased esophageal acid exposure(39), higher incidence of Barrett’s esophagus(39), and HIH(11,30) as compared to lean individuals. Although TPG is intuitively considered part of GERD pathophysiology in obese individuals, this condition has been poorly studied objectively. Increased AP (and consequent increased TPG) found in the obese favors GERD(14,39). Increased waist circumference and body mass index are associated to a raise in TPG(14,17,40). For each 1-point increase in body mass index, AP is expected to increase 10%(41). Few studies however, were able to demonstrate a direct link between AP and esophageal acid exposure in the obese(14,42).

Obesity may affect not only AP(11). Diaphragm elevation due to intraabdominal visceral obesity can lead to respiratory restriction, and consequent higher effort in the respiratory drive with a consequent decrease in the TP(43). Moreover, sleep apnea is highly prevalent in the obese population(44) and affects TP as well(45).

TABLE 1. Transdiaphragmatic pressure gradient in healthy individuals.

<table>
<thead>
<tr>
<th>Manometric parameter</th>
<th>Method</th>
<th>Average ± Standard deviation</th>
<th>Median (interquartile 25-75)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pressure (mmHg)</td>
<td>2 cm bellow lower border LES</td>
<td>11.6±4.5</td>
<td>11.4 (7.8-15.1)</td>
<td>2.6–19.6</td>
</tr>
<tr>
<td>Thoracic pressure (mmHg)</td>
<td>2 cm above upper border LES</td>
<td>7.4±5.4</td>
<td>7.4 (4.2-8.8)</td>
<td>-3.7–18.4</td>
</tr>
<tr>
<td>Transdiaphragmatic pressure gradient</td>
<td>Abdominal pressure</td>
<td>4.5±2.9</td>
<td>4.4 (2.0-7.1)</td>
<td>-0.2–10.6</td>
</tr>
<tr>
<td>LES retention pressure (mmHg)</td>
<td>LES basal pressure</td>
<td>16.5±12.1</td>
<td>13.3 (6.6-28.9)</td>
<td>-1–39.7</td>
</tr>
</tbody>
</table>

LES: lower esophageal sphincter.
Hiatal hernia and transdiaphragmatic pressure gradient

HH is an independent risk factor for GERD. HH leads to a morphologic alteration at the esophagogastric junction leading to the loss of some natural antireflux mechanisms and decreasing LES pressure. TPG may also be increased due to pressurization of the herniated supra-diaphragmatic gastric pouch and a decrease of the esophageal compliance.

On the other side, an increased TPG may increase the chance of a HH. Pandolfino et al. demonstrated that spatial separation of the LES and the diaphragm at the high resolution manometry is higher in overweight and obese individuals with increased TPG (due to an increased AP). Also, there is a high incidence of HH in patients with pulmonary interstitial fibrosis probably due to a decreased TP.

TPG may challenge the hiatal repair performed during an antireflux operation and affect HH recurrence. HH recurrence seems to be higher in the obese. In the chronic pulmonary diseases population, although antireflux operations are currently performed even in end-stage transplant-list patients, late results and the real HH recurrence rate are elusive in the literature.

Pulmonary diseases and transdiaphragmatic pressure gradient

The association of GERD and pulmonary disease is a frequent one and certainly a causality association not a spurious relation. Several recent studies showed an increased prevalence of GERD in patients with asthma, pulmonary fibrosis, chronic cough and chronic obstructive pulmonary disease (COPD). GERD may damage the lung due to aspiration of gastric contents but pulmonary diseases may cause GERD due to changes in the TPG. The increased respiratory effort common in certain lung disorders may alter TP. This was clearly demonstrated in patients with COPD and GERD. This group of patients has a lower TP compared to patients with COPD but without GERD, even though LES pressure is similar for both. Interestingly, TP is significantly increased after bronchodilators are inhaled. In other lung disorders, such as interstitial fibrosis; however, an intrinsic failure of the LES is the most common finding.

Transdiaphragmatic pressure gradient – therapeutic applications

GERD has a complex pathophysiology with many factors contributing to the ascent of gastric contents to the esophagus. However, in summary, GERD occurs as a result of failure of the esophagogastric barrier, either due to an intrinsic defect of the valve apparatus or its retention capacity subdue by an altered TPG. GERD control, in patients in whom TPG may play an important role, may be thus aimed towards the esophagogastric barrier or normalization of TPG.

Non-obese, non-pulmonary patients

Laparoscopic fundoplication is very effective in controlling GERD. This technique not only restores the competence of the esophagogastric barrier by improving LES pressure but also decreases the number of TLESR. Scheffer et al. showed that TPG is higher when an episode of reflux is associated to a TLESR and that a fundoplication decreases TPG during TLESR. Moreover, a fundoplication improves esophageal body contractility. This action may influence distal esophageal compliance raising TP.

Obese patients

Weight loss leads to a reduction in AP. This is translated in a decrease in GERD symptoms and pH monitoring parameters.

Fundoplication in the obese is a controversial topic. While it does not act in the major component of GERD pathophysiology, i.e., TPG, it is a simple and efficient procedure with good outcomes even in the obese. However, there are data showing a higher rate of complications, technical difficulty and worse results. A recent tendency is to offer a bariatric operation to these patients.

Some bariatric procedures – such as gastric band and sleeve gastrectomy – lead to a decrease in visceral adiposity and consequent lower AP but may have controversial results in regards to intra-gastric pressure. While some believe there is a raise in intra-gastric pressure due to flow restriction, others support that gastric emptying is accelerated. Studies focused on the development or amelioration of GERD after these restrictive procedures are still very controversial.

Roux-en-Y gastric bypass on the other hand is considered an excellent treatment for GERD in the obese. Several series show improvement in symptoms, acid exposure and extra-esophageal manifestations. Weight loss summed to maintenance of esophageal and rapid gastric emptying favorably act on favor of decreasing TPG and GERD control that is added to a decrease in the population of acid-producing parietal cells and bile diversion.

Pulmonary patients

GERD plays an important role in the pathogenesis of pulmonary diseases, and efforts must be made to accurately diagnose it and properly treat it. A laparoscopic fundoplication does not act directly in the pulmonary mechanics to improve TPG but it controls GERD. Asthma exacerbations and medication usage are decrease after GERD treatment. Idiopathic fibrosis is also improved by GERD control. Better respiratory parameters are achieved in COPD patients after antireflux surgery that may affect TP towards normalization.

CONCLUSION

GERD has a multifactorial and complex pathophysiology. TPG may be an important contributor to GERD even with an intact esophagogastric barrier during TLESR and in the setting of obesity and pulmonary diseases. The current literature on the topic is still faulty. Clear conclusions on the influence of TPG in GERD pathophysiology are currently not possible but plausible theories may be drawn based on data extrapolation.

Authors’ contribution

Del Grande LM: acquisition of data, drafting the article, analysis and interpretation of data, final approval of the version to be published. Herbella FAM: conception and design, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be published. Katayama RC: acquisition of data, final approval of the version to be published. Schlottmann F: review for intellectual content, final approval of the version to be published. Patti MG: conception and design, analysis and interpretation of data, review for intellectual content, final approval of the version to be published.
RESUMO – O papel do gradiente pressórico transdiafragmático (GPT) na fisiopatologia da doença do reflexo gastroesofágico. Arq Gastroenterol.


