

On the pathogenesis of gastroesophageal reflux disease. (Part 2).

Evidence-based medicine versus the Delphi method.

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Introduction There are two points of view on the pathogenesis of GERD in the literature: (1) based on scientific evidence and (2) the Delphi method. Participants in the vote claim that the Delphi method is used in cases where there is currently no scientifically substantiated evidence. However, in addition to compiling previously published assumptions about the pathogenesis of GERD, they use diagnostic equipment based on pH monitoring as evidence. This method was developed based on the unjustified assumption that reflux of gastric juice into the esophagus with a pH <4 does not damage the esophagus [1]. This contradicted common sense, and subsequently the possibility of physiological reflux was excluded by studies by Chandrasoma and DeMeester [2]. In addition, the determination of the normal pH range in the esophagus was carried out with serious methodological violations. Fifteen individuals who did not have typical complaints were selected as a control. However, it is known that many patients with GERD do not experience any symptoms. So, for example, with a screening gastroscopy of 6,683 healthy Koreans, 14.66% had GERD diagnosed [3].

There is no point in listing all the articles that show that about a third of patients with endoscopically proven reflux or esophagitis consider themselves healthy (3, 4, 5). Meanwhile, the Montreal “global evidence-based” consensus was approved by a vote of experts: “GERD was defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications [6]. It is stated that they approved this definition based on an analysis of the literature. This means that a third of patients with reflux who have minor and rarely occurring symptoms will not receive timely treatment and will seek help only when severe symptoms appear, when a cure is no longer possible and control of symptoms is not always possible. Firstly, the decision made by the Delphi method is not evidence-based. Secondly, for this very reason it is devoid of scientific meaning. Thirdly, so far the simple, inexpensive and reliable histological examination proposed by Chandrasoma and DeMeester can diagnose GERD at an early stage, when it is possible to prevent its development, was not noticed by experts [2].

Literature reviews and all consensus statements ignore clinical studies showing the low reliability of pH monitoring. Based on a systematic review, van der Pol et al. concluded that the diagnostic accuracy of pH monitoring in children with suspected GERD remains unclear,

and the implications for practice are unclear [7]. This is due to the relatively high rate of false-negative results [8]. For example, Tovar et al. reported on 14 patients who underwent surgery for GERD despite normal pH monitoring results. The mean age was 54 months (range, 18–90). Clinical manifestations included vomiting, dysphagia, respiratory problems, anemia, and torticollis. All had radiographic evidence of GERD, and 10 had endoscopic and histologic esophagitis [9]. Not only practicing physicians, but also three researchers believe that 24-hour intraesophageal pH monitoring can produce false-negative results, which limits the overall sensitivity of the test [10]. For example, researchers using high-resolution manometry did not use pH monitoring to exclude GERD in the control group [11].

Both theoretically and in practice, pH monitoring is characterized by a significant number of false negatives. However, in articles by proponents of the Delphi method, it is becoming the "gold standard." For example, before the introduction of pH monitoring, the presence of a hernia was considered evidence of GERD. The use of pH monitoring revealed that in some cases, the DeMeester score was less than 4%. Since then, HH has been considered a cause of GERD, not a symptom. While heartburn after administration of acid into the esophagus (the Bernstein test) was previously considered evidence of GERD, heartburn with an AET < 4% is now considered functional heartburn. The new understanding of pathogenesis is erroneous, which leads to non-pathogenetic treatment.

Phrenic ampulla versus hiatal hernia

Normal physiology of the esophagogastric junction

Normally, when ingesting a liquid barium suspension in an upright position, a column of barium forms above the lower esophageal sphincter (LES). It never rises above D4. The hydrostatic pressure of this column causes relaxation of the LES, which remains open until all the barium has entered the stomach. Obviously, during gastric emptying, hydrostatic pressure decreases. This indicates that high hydrostatic pressure initiates dilation of the LES and a reflex, resulting in all barium descending into the stomach, where the pressure is lower than in the esophagus.

In the horizontal position, the pressure in the esophagus is lower than in the stomach. During barium ingestion, the final peristaltic wave creates a chamber above the LES. The advance of the wave creates high pressure in the chamber, causing the LES to open. The wave injects a bolus into the stomach, after which the LES closes, preventing chyme from entering the esophagus. This situation is consistent with the Bayliss–Starling law of the intestine [12] **(Figure 1)**.

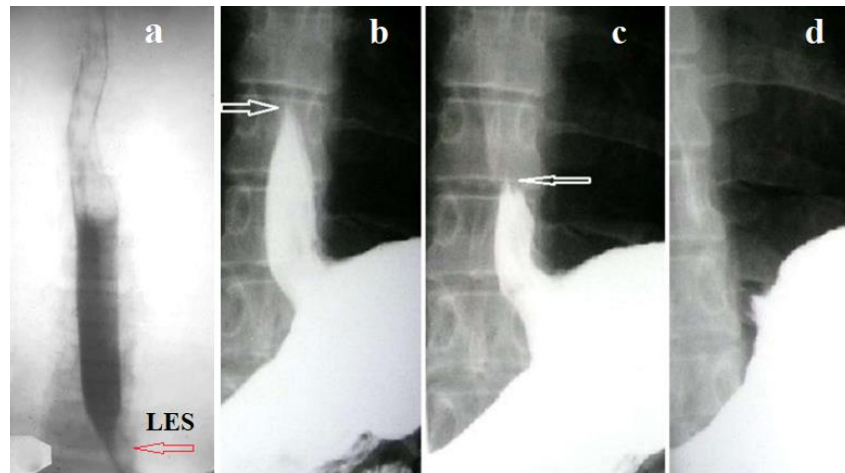


Figure 1. (a). In the upright position, liquid barium creates hydrostatic pressure, which opens the LES. **(b, c, d).** In the horizontal position, the barium moves through a peristaltic wave, which creates high pressure to open the LES. This pressure exceeds the pressure in the stomach, preventing reflux.

At rest, the esophagus is closed due to tonic contraction of the circular (inner) and longitudinal (outer) smooth muscle layers of its wall. This means that in healthy individuals, there is no content at rest. In reality, the muscles of both layers have a spiral course. After swallowing, the bolus moves forward due to the peristaltic wave, in accordance with the law of the intestine [12]: the circular muscles contract above the bolus and relax below it. It has been shown that in the peristaltic zone, longitudinal fibers contract simultaneously, facilitating bolus movement and leading to a shortening of this segment by several millimeters. This shortening zone moves caudally with the movement of the bolus. The distal smooth muscle fibers of the esophagus are attached to the gastric wall by so-called clamps along a much larger circumference than the diameter of the esophagus [13]. Therefore, when the peristaltic wave reaches the LES, the LES opens (dilates) and shortens by the same number of millimeters. All sphincters function this way, as nature has chosen the most efficient method. This has been well demonstrated in the example of the pyloric sphincter [14, 15] (Figure 2).

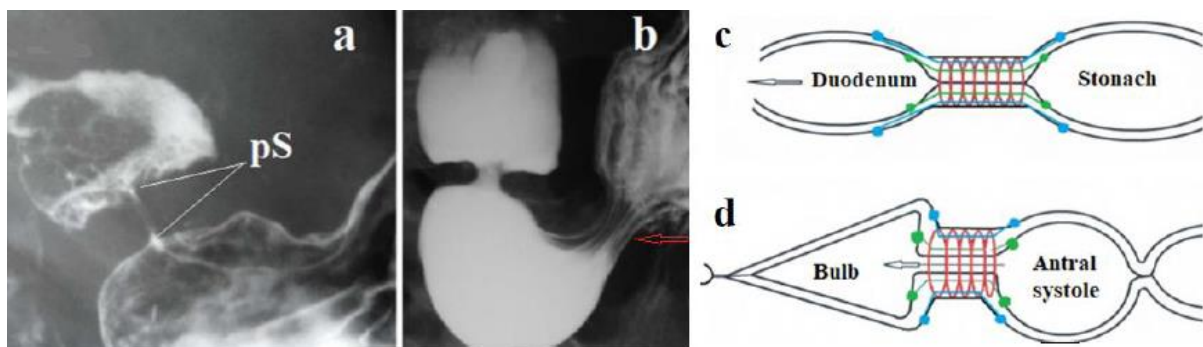


Figure 2. Radiographs of the gastroduodenal junction. **(a)** The pyloric sphincter (pS) is in a closed state. The width of the bulbus base is almost equal to that of the opposite side of the stomach. **(b)** At the moment of contraction of the antral cavity of the stomach (antral systole), when the pressure in it increases to a threshold level, a reflex opening of the pS occurs and its length decreases. **(c)** Schematic of the corresponding to the radiograph (a). **(d)** Schematic corresponding to the radiograph (b).

As shown above, based on manometric data, histological, and radiographic studies, GERD is characterized by shortening of the LES due to opening of its abdominal portion (2.1 cm) and dilation of the esophagus above the diaphragm. Normally, the esophagus width in adults is approximately 1.5 cm, and the LES length is approximately 4 cm. The ratio of the LES to the esophageal width is always greater than one. In GERD, this ratio is always less than one, except in severe esophagitis.

1. According to modern concepts, a dilation of the esophagus above the LES of up to 2 cm is considered a phrenic ampulla, while a dilation greater than 2 cm is considered a hiatal hernia (HH). This definition is illogical, because the ampulla, which is part of the esophagus, cannot become a hernia, that is, become part of the stomach, based solely on the extent of its dilation.

2. Neither an ampulla nor a hernia is detectable in the vertical position, when the opening of the LES is provoked by the hydrostatic pressure of a liquid barium suspension. This is supposedly explained by the fact that the horizontal position promotes displacement of the stomach into the chest. Therefore, HH was also called a sliding hernia.

3. All measurements confirming displacement of the stomach into the chest contradict existing scientific evidence.

(a). Radiographic studies with clips attached to esophageal mucosa show that the clips do not move relative to the bony structures. Shortening of the LES due to opening of its abdominal part results in shortening of the esophagus + LES complex, not the esophagus itself. During radiographic examination with increased gastric pressure over 30 seconds, when the CD contraction ceased due to fatigue of the striated muscles, the esophageal dilation, regardless of width, is located above the contracted LES. The LES is most often longer than the CD contraction zone (1 cm) and, regardless of size and stage of examination, is located near the D-10.

(b). Radiographic studies have shown that the rugal folds above the diaphragm are caused by inflammation and dilation of the LES wall. The longitudinal folds of the esophagus are narrower than at the level of the LES because the pressure within the LES is significantly higher

than in the esophagus. Histological studies by Chandrasoma and DeMeester have exposed the generally accepted fundamental errors: (1) that the cardiac epithelium normally lines the proximal stomach and (2) that the EGJ is defined by the proximal limit of rugal folds. Cardiac epithelium arises from metaplasia of the squamous epithelium due to exposure to gastric juice, resulting in cephalad movement of the squamocolumnar junction [2]. Thus, rugal folds are folds of the esophagus, not the stomach, and cardiac epithelium is not the epithelium of the cardiac portion of the stomach, but the result of metaplasia of the esophageal epithelium under the influence of hydrochloric acid. These studies exposed the false statements of displacement of the stomach into the chest, which served as evidence of hiatal hernia, were exposed.

Analysis. Esophageal dilation and inflammation caused by gastric reflux weaken the force of the last peristaltic wave, which is unable to create high pressure to the LES opens and maintain it at a level sufficient to prevent gastric contents from entering the esophagus during LES opening. To create high pressure above the LES, a closed chamber (ampulla) develops in the dilated esophagus. This chamber is formed by the development of a functional sphincter that closes the esophageal lumen above the ampulla. I have called this sphincter the proximal sphincter (PS) because it is located proximally to the LES. The peristaltic wave passing from the PS increases the pressure in the chamber, causing the LES to open, and the ampulla injects a bolus into the stomach. The ampulla functions in GERD in the upright position during ingestion of solid foods, as there is no hydrostatic pressure. This is sometimes felt as sudden pain as pressure behind the sternum, as contraction of the ampulla is unable to expel the thick bolus into the stomach. The attack resolves after drinking water. Contraction of the PS during reflux can prevent the refluxant from entering the upper esophagus. During gastroscopy, the PS appears as a ring. In an allergic reaction accompanied by eosinophilic infiltration, a narrowing of the PS ring, described as a Schatzki ring, sometimes occurs [16, 17] (Figure 3).

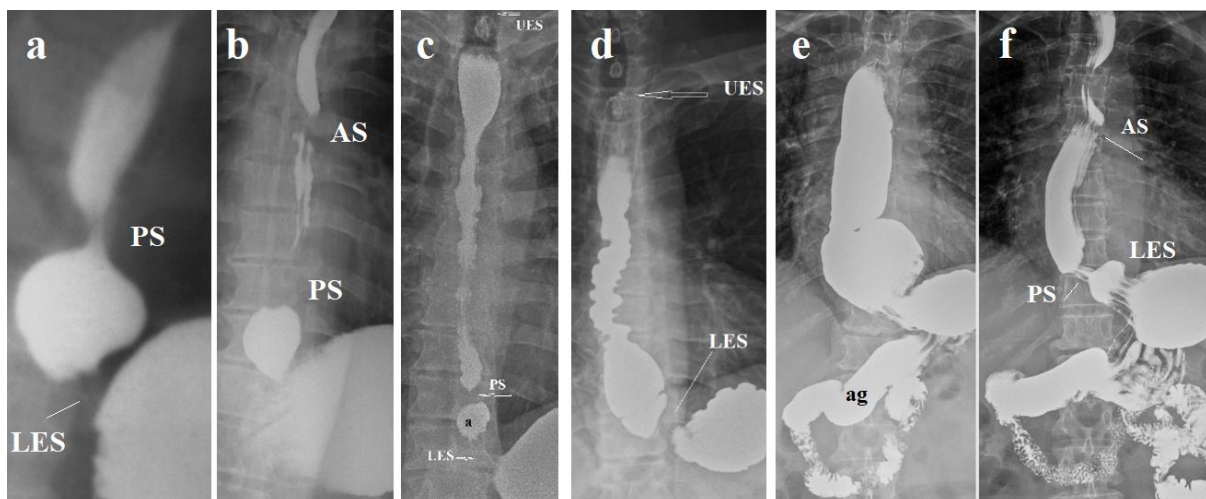


Figure 3. Radiographs of the esophagus and esophagogastric junction in the horizontal position under high gastric pressure, which causes reflex contraction of the LES. The ampulla can vary in size, but the LES always remains at the same level. In **Figure 3c**, in a patient with severe esophagitis, the length of the LES exceeds the width of the ampulla. In other observations, the opposite pattern is observed: the width of the ampulla significantly exceeds the length of the LES. Figure 3ef shows an examination of one patient (e) during high gastric pressure, (f) after 5 minutes, at rest. The AS is a physiological sphincter that occurs because of acid retention at the level of anatomical narrowing of the esophagus caused by the aortic arch. Contraction of the AS leads to non-esophageal symptoms of GERD [18]. The appearance of an ampulla in chronic inflammation is observed above other sphincters in the peristaltic systems (Figure 4).

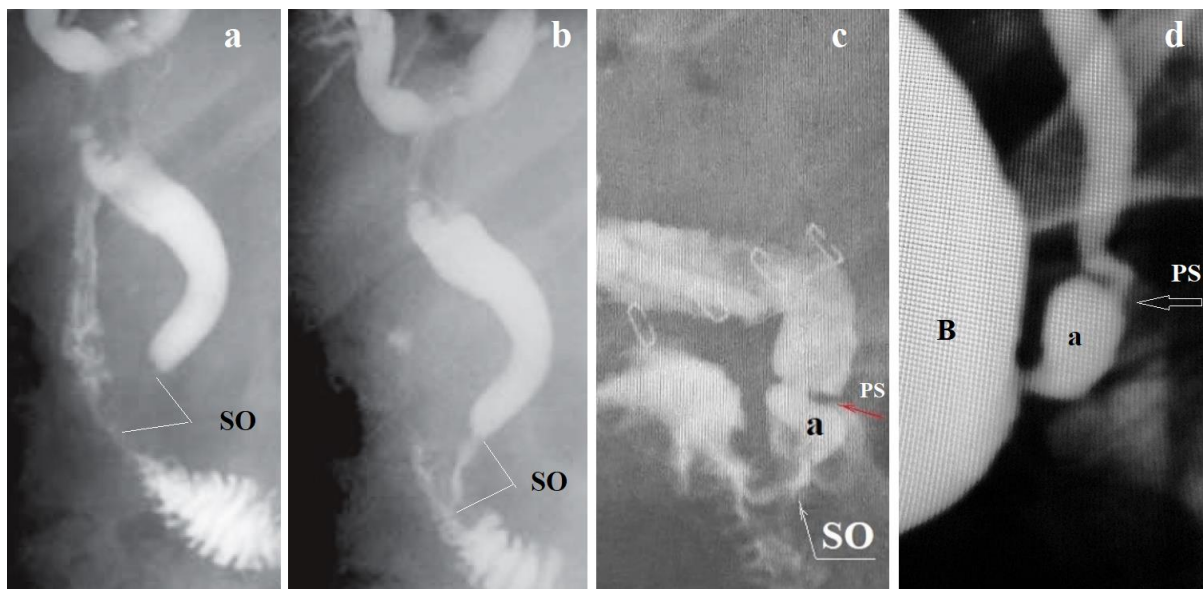


Figure 4. Formation of the ampulla and proximal sphincter (PS) during inflammatory processes above the sphincters in the peristaltic systems. **(a, b).** Contraction of the sphincter of Oddi (SO) during mild dilation of the common bile duct. The radiographic appearance of duodenitis explains the obstruction of bile outflow into the duodenum, where is high pressure. **(c).** During sharp dilation of the common bile duct, to create high pressure for opening the SO, an ampulla is formed, and above it the PS compresses the lumen (red arrow). **(d).** The ampulla and PS play the same role in vesicoureteral reflux.

Conclusion. Literature review and our own research demonstrate that ampullar esophageal dilation, regardless of size, including cases previously diagnosed as hiatal hernia, is compelling evidence of GERD. This conclusion confirms the scientific fact, known prior to the introduction of pH monitoring, that GERD is a compelling symptom of GERD. The current

notion that GERD is a predisposing factor for GERD, i.e., a cause rather than a consequence of GERD, is based on the misconception that pH monitoring is highly accurate, although with GERD can have a DeMeester score $< 4\%$. Firstly, as shown by histological studies, reflux begins with acid penetration only into the abdominal portion of the LES [2]. During this period, acid has not yet penetrated the esophagus, so the idea of recurring physiological reflux is erroneous. Secondly, if acid does not initially penetrate the esophagus, it naturally cannot be recorded by pH monitoring. Third, the determination of the normal range (DeMeester score) was carried out with serious methodological violations. Control subjects were selected solely based on their stated absence of symptoms. However, it is known that many patients with GERD are asymptomatic. For example, among 6,683 Korean health examinees who underwent gastroscopy, 14.66% had GERD, hiatal hernia was found in 2.0%, nonspecific esophagitis in 0.16%, and heterotopic gastric mucosa in 0.16% [19]. Thus, reflux disease was diagnosed in 17% of individuals who considered themselves healthy. Obviously, the actual number of patients was significantly higher, since endoscopic examination does not detect GERD in a significant number of patients. Fourth, “ambulatory 24-hour esophageal pH measurement is the standard for detecting abnormal esophageal acid exposure (AET), but it has a false negative rate of 15% to 30%” [20]. In the Japanese reflux (percentage of time below pH 4.4%) was seen in only about 20% of the patients with GERD, and this percentage of patients with reflux was lower compared to the data reported from the United States and Europe. The authors suggested that this is a feature of GERD in the Japanese [21]. In many patients with a clinical picture of GERD, often associated with other acid-related diseases, GERD was excluded based on pH monitoring. Functional dyspepsia, irritable bowel syndrome, esophageal hypersensitivity, and functional heartburn are not only frequently associated with GERD, but these are the same patients with GERD who do not receive timely pathogenetic treatment due to an AET $< 4\%$. Therefore, the rate of GERD diagnosis using various equipment in Europe and the United States may be the same as in Japan $\approx 20\%$.

Angle of His - Cause or Result of GERD?

In modern literature, the obtuse angle of the His is considered one of the causes of GERD. However, analysis of radiological, manometric, and histological studies indicates that the angle of the His becomes obtuse due to insufficiency of the LES. This occurs when the intra-abdominal portion of the LES, weakened by the inflammatory process, expands (opens) and its walls become the walls of the stomach (**Figure 5A-B**). This process is also reflected in the GERD development diagram based on histological studies [2] (**Figure. 5 CDE**).

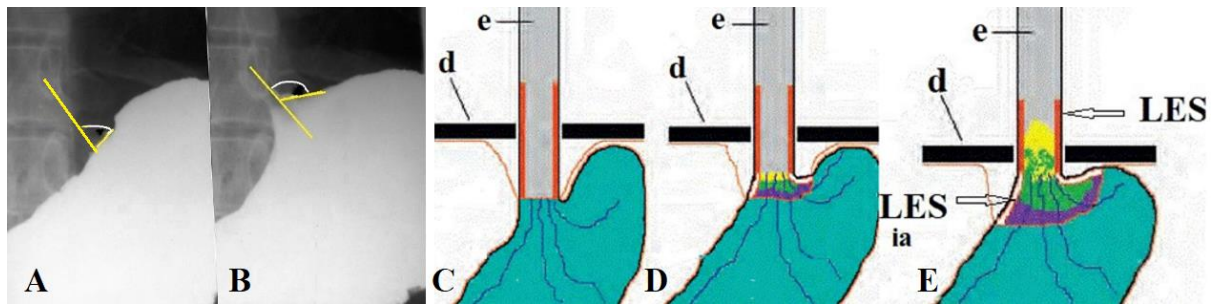


Figure 5. (A-B). Water-siphon test. A - before drinking - the angle of His is acute, B - during drinking – The angle of His is obtuse due to the opening of the intra-abdominal portion of the LES. In the diagram of GERD pathogenesis according to histological data [2]: **(C).** Normally, the lower esophageal sphincter (brown) consists of 3 parts: intra-abdominal (ia), at the level of the diaphragm (d) and in the esophagus (e). The angle of His is acute. **(D).** In the initial stage, acid (yellow) penetrates only into the abdominal part of the LES with a slight shortening of this part. **(E).** Progression of the process leads to weakening and opening of the entire abdominal part of the LES, which becomes part of the stomach (white line). The angle of His is straightened. A weakened LES cannot prevent the chyme from entering the esophagus.

Thus, the angle of the His becomes obtuse because of weakened LES function during GERD, due to the opening of its abdominal portion. This appearance is a symptom of GERD, not its cause.

Two views on belching

The generally accepted hypothesis. The literature review on belching by Sawada et al. [22] fully reflects the “conventional” opinion. It concentrates on the ideas that are referred to in all publications on this topic. Based on studies of patients using pH monitoring, twenty-four-hour impedance-pH monitoring, high-resolution manometry (HRM), and high-resolution impedance manometry (HRIM), it is argued that gastric belching is a reflux of gas from the stomach into the esophagus. This physiological mechanism allows swallowed air collected in the fundus of the stomach to escape during transient lower esophageal sphincter (LES) relaxation (TLESR). However, if belching is bothersome when excessive, then according to the consensus decisions (Rome IV), adopted by the Delphi method, such belching is a painful condition. In their previous study, off-PPI impedance-pH monitoring (MII-pH) found the prevalence of pathological supragastric belching (>13 episodes/24 h) [22].

This hypothesis is based on the false notion that belching is a physiological necessity, since swallowed air is released only through belching. Instead of interviewing healthy individuals, the percentage of whom is higher in children and adolescents, the authors rely on the results of diagnostic equipment. My research has shown that healthy people do not belch at all. They are

unaware that such a phenomenon occurs. X-rays show that gas penetrates the intestines and is utilized there [22]. Anyone reading these lines can verify my correctness by interviewing their young relatives. If even one of them claims that they do not belch or that they belch no more than once a month, you will understand the value of diagnostic equipment and the scientific value of Delphi voting. Belching is a sign of weakness of the LES, which relaxes periodically. Normally, the LES contracts when gastric pressure increases. In GERD, the weak LES, periodically relaxes, unable to withstand the rise in gastric pressure. Therefore, both belching and transient lower esophageal sphincter (LES) relaxation are observed only in GERD. The assertion that they can occur in healthy individuals is due to the high rate of false-negative results with pH monitoring. Figure 6 shows the mechanism of belching.

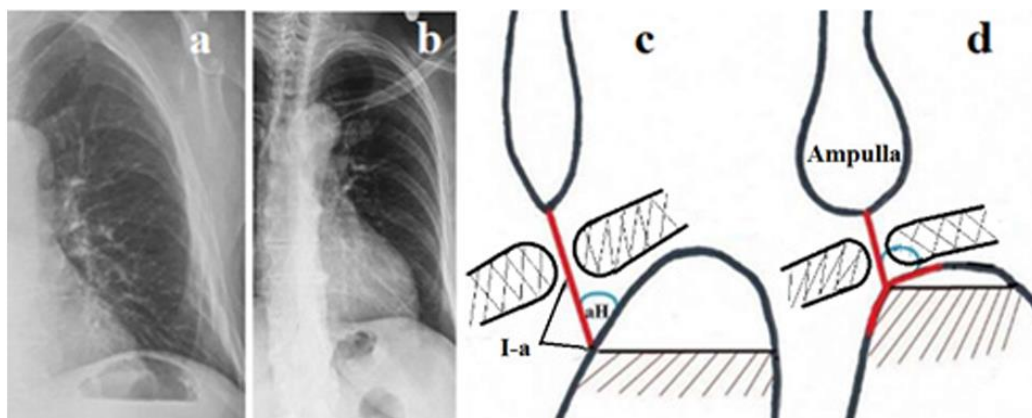


Figure 6. (a). Radiograph of the left dome of the diaphragm of a healthy person. **(b).** A patient with GERD. **(c).** Scheme of the EGJ with normal LES function (red line is LES length). The angle of His (aH) is acute. Large gas bubble in the stomach. **(d).** In GERD, the LES is shortened because the intra-abdominal part of the LES (I-a) is not functioning. This leads to an increase in the angle of His and a decrease in the gas bubble of the stomach due to belching during transient relaxation of the weakened part of the LES.

Literature review and our own research [23] prove that belching and transient lower esophageal sphincter (LES) relaxation (TLESR) are evidences of LES weakness.

Is acid pocket a result of GERD or a predisposing factor?

The acid pocket is considered to be a factor in the multifactorial pathogenesis of GERD. "The acid pocket was first described in 2001 when it was detected as an area of low pH immediately distal to the cardia using dual pH electrode pull-through studies 15 minutes after a meal» [24]. Nian et al, state that «a postprandial proximal gastric acid pocket (PPGAP), defined by the presence of acidity ($\text{pH} < 4$) in a segment of the proximal stomach between distal (food) and proximal (lower esophageal sphincter or distal esophagus) nonacid segments, occurs in healthy individuals and patients with GERD» [25]. Virtually all studies are conducted using diagnostic

equipment. Authors use non-precise anatomical names. Secondly, if the pH in the stomach is <4 , this is normal and unrelated to the phenomenon described. Thirdly, how can the authors determine the location of the LES using pH monitoring, HRM et al? X-ray imaging allows us to determine the mechanism of formation of the acidic packet, which seriously worsens the course of the disease. (Figure 7).

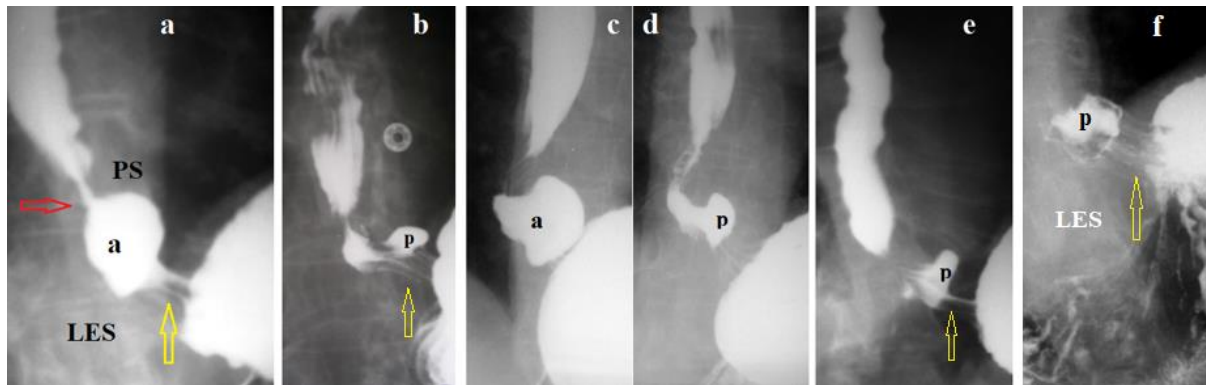


Figure 7. Patients with GERD, in whom the poorly contracting ampulla the acid bolus after reflux retained. (a). An example of the formation of an ampulla between the LES and PS. (b-e). Near the left base of the ampulla there is a weak area (p), which is unable to displace its contents during contraction of the ampulla (c, d). Radiograms of one patient, where during contraction of the ampulla an asymmetrical area like a diverticulum was discovered. (f). A centrally located acid pocket.

All radiographs show symptoms of severe reflux disease with shortening of the LES (yellow arrow) and an ampulla between the LES and PS.

Conclusion

Pathogenesis describes the progression of the disease from its onset, i.e., after exposure to the etiologic factor, to the final phase of the disease. As previously defined, the etiologic factor of GERD is hypersecretion of hydrochloric acid. What are referred to in modern literature as predisposing factors for GERD are symptoms of severe reflux disease. This is irrelevant to pathophysiology because many stages of development are omitted, from the penetration of chyme only into the abdominal segment of the LES, which is accompanied by shortening of the LES. Then, when chyme appears in the esophagus, its distal portion, called the ampulla, dilates, and so on.

Presumptive factors described in the literature are intended to demonstrate that the symptoms listed allow to differentiate GERD from functional reflux, i.e., GER. The authors proceed from the false idea that pH monitoring, like other methods based on the assumption of the possibility of functional reflux, are the gold standard for the diagnosis of reflux disease. However, these

methods do not diagnose the disease at an early stage, when chyme does not penetrate the esophagus. Secondly, all functional diseases where there is a clinical picture of acid-dependent diseases, including reflux disease, are unreasonably excluded from GERD based on pH <4%. Third, esophageal achalasia is misdiagnosed in patients with GERD based on MRI data. As a result, a completely dissected already weakened LES [25]. The inflammatory wall of the esophagus is dissected in the so-called Jackhammer Esophagus [26]. Любые forms of esophageal dyskinesia, are inevitable with its expansion and inflammatory process. It is likely that when using equipment, GERD is diagnosed in only 20% of patients, as shown in the article by Japanese authors [20].

Highlights

- GERD is an acid-dependent disease, therefore it is always accompanied, to varying degrees, by damage to the stomach (gastritis, ulcer), duodenum (duodenitis, ulcer), and bile ducts (dyskinesia, cholelithiasis, cholecystitis). Since the wall of the esophagus, unlike other sections, is not protected from chyme, the clinical manifestations of GERD are more pronounced and overshadow the clinical symptoms of other sections.
- pH monitoring and other diagnostic tests are based on the false assumption that physiological reflux is possible. Therefore, their diagnostic accuracy is very low and leads to long delays in diagnosis and untimely pathogenetic treatment. GER = GERD.
- The first and most reliable sign of GERD is weakening of the LES function: shortening of its length, decreased tone, and relaxation during increased pressure in the stomach. The second most reliable factor is dilation of the esophagus, the appearance of an ampulla and functional sphincters.
- The inflammatory process in all acid-dependent organs increases their tone. In the esophagus, pressure is also affected by the expansion of its lumen. The pathogenesis of severe forms of GERD with pressure disturbances in various sections will be the subject of analysis in Part 3 of the "Pathogenesis of GERD".
- It has been shown that all decisions based on Delphi voting have no scientific basis. They create chaos, a solution to which can supposedly only be achieved with the help of diagnostic equipment. But this is nothing more than advertising.

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