

Abstract

The letter to the editor analyzes the articles on high-resolution manometry (HRM) for the study of the esophagus and esophageal-gastric junction (EGJ) in normal and symptomatic dysphagia. The volunteers were selected как здоровые to determine the normal values with methodological violations. On all radiographs, presented as an example of the norm, there is clear evidence of gastroesophageal reflux disease (GERD). As a result of the erroneous interpretation of X-ray studies, the authors of the articles came to the erroneous conclusions: about the partial identity of the lower esophageal sphincter and the phrenic ampulla; about the different nature of the contraction (peristalsis) of the proximal esophagus and ampoule; about the proximal displacement of the EGJ during swallowing, etc. Of all the parameters that have been studied using HRM, the authors recommend using only the upright integrated relaxation pressure (IRP) to determine clinically significant cases of esophagogastric junction outflow obstruction. However, this index has no physiological meaning. An upright integrated relaxation pressure > 12 mmHg identified patients with radiographic evidence of EGJOO with 97.9% sensitivity and 15.7% specificity. But since it was considered that the selection of the norm and the evaluation of radiographs were erroneous, the diagnostic value of this parameter is much lower. Analysis of the articles shows that high resolution manometry for the diagnosis of EGJ pathology is a little informative study. The X-ray studies presented in the articles as diagnostic method, with the correct interpretation and understanding of physiological processes, exceed IRP many times. A wide discussion on this issue is needed.

Dear Editor,

In recent years, many articles on the use of high-resolution manometry (HRM) have been published from the Feinberg School of Medicine, Northwestern University, Chicago (including in your journal). This topic has become fashionable and messages from other institutions have appeared. However, these studies were carried out with serious methodological disorders, with erroneous interpretation of radiological data with an obvious disregard for the known data on physiology of the esophagus. There is no possibility and need to analyze each article. I will focus on two articles on the definition of standards [1,2] and the state of the problem today [3].

Selection of volunteers as healthy individuals is erroneous:

First, the absence of symptoms does not exclude gastroesophageal reflux disease (GERD), because this disease for a long time can proceed without clinical manifestations. So, for example, with a screening gastroscopy examination of 6,683 healthy Koreans, 14.66% had GERD diagnosed [4]. In another study of 57 healthy subjects, 13 (23%) had an esophageal pathology in endoscopy, and 10 (17%) had an esophageal hernia [5].

Secondly, as histological studies of recent years have shown, GERD begins with reflux only into the abdominal segment of lower esophageal sphincter (LES), when the acidic gastric contents do not yet enter the esophagus, and, consequently, the disease cannot be detected using pH-metry. There are no symptoms of GERD at this stage [6].

Since no histological studies have been carried out, the selected volunteers cannot be considered healthy and therefore the obtained results cannot be considered normative.

All radiographs presented as a study of healthy volunteers have strong evidence of GERD. An analysis of radiographs from the article by Kwiatek et al [1] is below (**Figure 1**).

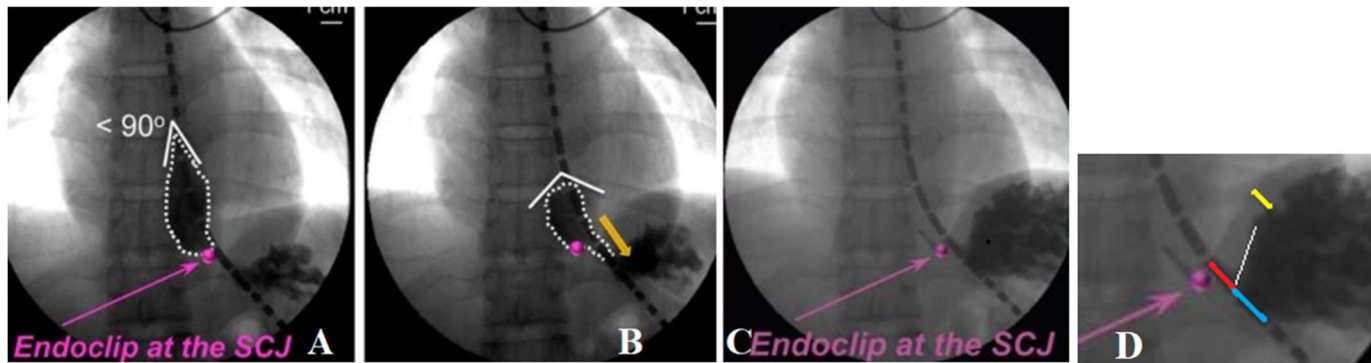


Figure 1. Radiographs from the article [1], which is discussed, and the scheme (D) to the figure (C). In all the pictures endoclip is on the same place - to the left of the lower contour of the D-10. On Figure C, performed after numerous swallows, the pressure in the stomach increased, as evidenced by the large amount of barium in the stomach and the sharp decrease in the distance between the contour of the diaphragm and the stomach (the yellow line in the diagram). This led to the opening of the abdominal part of the LES (blue line), with the shortening of the distance between the endoclip and the stomach (the red line is the contracted part of the LES). Knowing that the true height of the D-10 is equal to 2.3 cm, we can calculate the true length of the functioning LES (red). It is equal to 7-8 mm, with the norm of 3.60 ± 0.08 cm (range 3.2-4.2 cm) [4]. Such a strong shortening of the LES is characteristic of a severe form of GERD. However, the degree of shortening of the LES can also be explained by other factors: the influence of the probe itself, the continuation of the action of midazolam and fentanyl, and the trauma of the LES when fixing the endoclip.

According to the authors, an endoclip was placed at the SCJ (Figure 1). If this point corresponded to the caudal border of LES displaced cranially, this would mean that the phrenic ampulla coincides with the LES. There is no doubt that the clip was attached to the proximal point of the LES. This error is due to two false

dogmas that result in two widely believed fundamental errors. First, these are the belief that cardiac epithelium normally lines the proximal stomach and, secondly, that the GEJ is defined by the proximal limit of rugal folds [6]. In GERD, the inflammatory process leads to the expansion and damage of the mucous not only in the esophagus, but also at the level of the LES. Therefore, during the contraction of the LES, thin longitudinal folds are visible, which is impossible to confuse with gastric rugal folds. In severe GERD, folds appear in the esophagus. Their shape depends on the width of the lumen and the tone of the segment (**Figure 2**).

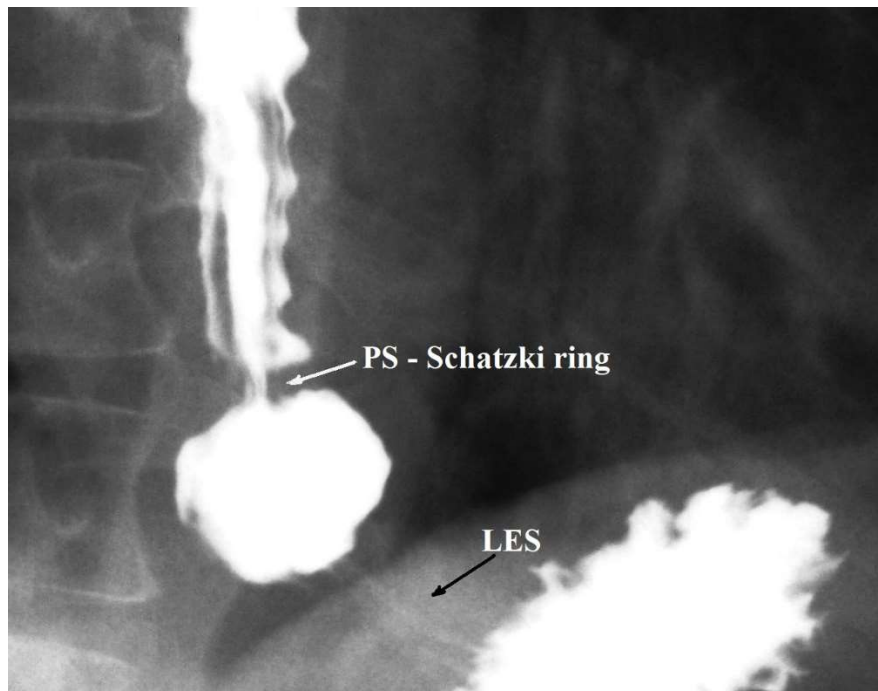


Figure 2. The elderly person with severe GERD and esophagitis. Folds, as a sign of inflammation, are defined in the esophagus and in the LES. There is not the slightest reason to assert that the GEJ has shifted cranially.

Analysis of radiographs confirms the erroneous selection of patients as the norm. 1) The phrenic ampulla appears during GERD as a result of the expansion of the esophagus above the LES; 2) The endoclip was attached to the proximal and not the distal border of the LES, where the longitudinal folds that occurred in response to inflammation ended; 3) During swallowing, the endoclip did not

move and there was no shortening of the esophagus, as claimed by the authors of the article; 4) The shortening of the LES with respect to the norm due to the opening of its abdominal part is a reliable diagnostic symptom of GERD [8].

The high-pressure zone near the EGJ was measured in different phases of bolus advancement. There is no division between the phrenic ampulla and the LES. Ranges are very large {zone length measure 1.8–5.6) cm for the length of the median of 4.0 (1.3–4.3) cm and baseline length of 1.9 (0.6–3.7) cm} and not tied to functional structures, which prevents their use in the diagnostic process.

An analysis of the study from the article by Pandolfino et al [2] with a parallel recording of HRM and esophagography is shown in **Figure 3**.

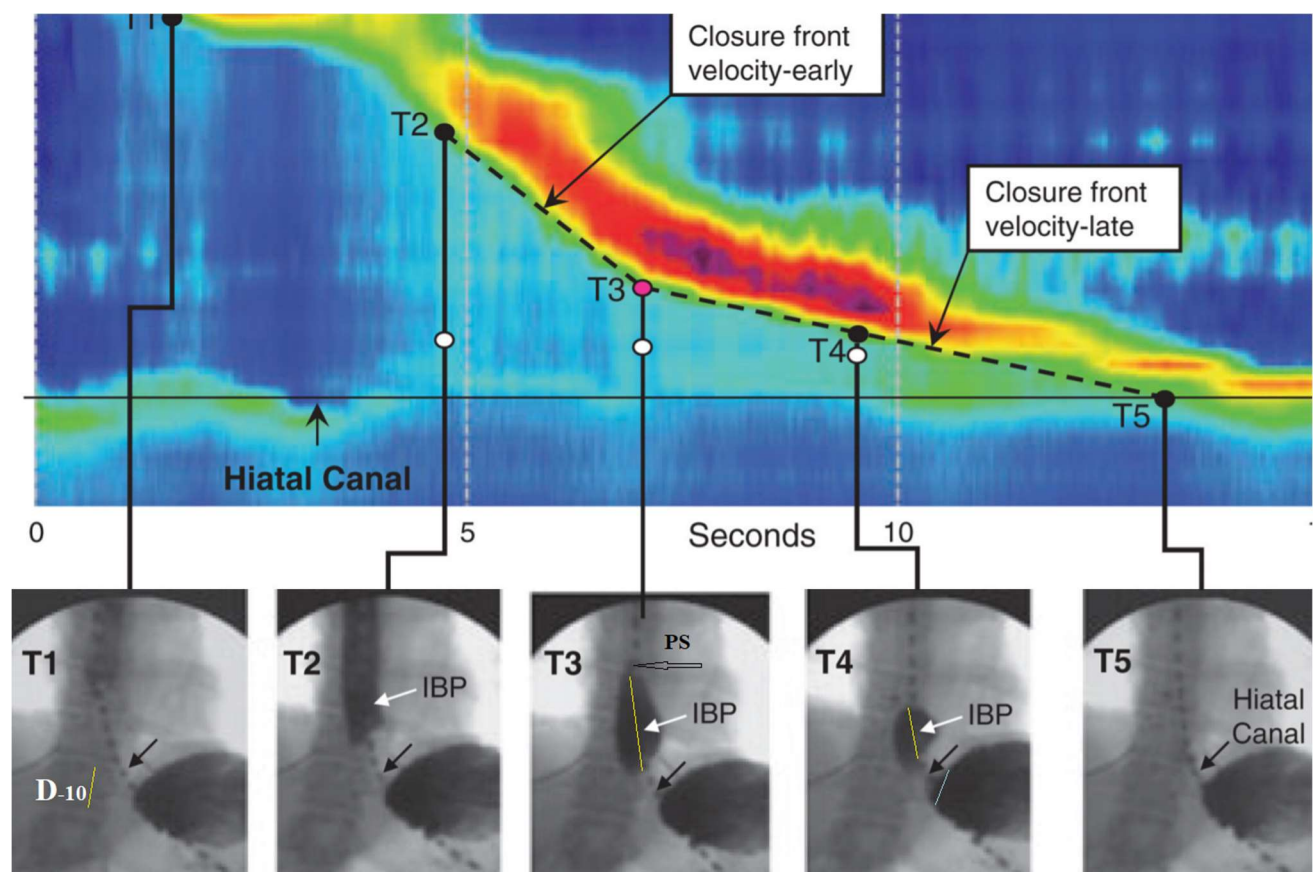


Figure 3. From the article Pandolfino et al [2]. Knowing that the true height of D-10 in adults is 2.3 cm, we can calculate the length of the LES on the T2 radiograph, as the distance without a contrast agent between barium in the

esophagus and the stomach. It is equal to 3.2 cm, which is the lower limit of the norm for adults (**Table**).

Table. Normal length of LES in different age groups [7].

	Length of the lower esophageal sphincter (cm)					
Age	Up to 1 year	1-3 years	4-7 years	8-10 years	11-15 years	21 – 65 years
Range	0.7 – 1.0	1.2 – 1.5	1.5– 1.8	1.9 – 2.3	2.3 – 2.9	3.2 – 4.2
M \pm m	0.86 \pm 0.03	1.40 \pm 0.02	1.72 \pm 0.07	2.10 \pm 0.05	2.45 \pm 0.11	3.60 \pm 0.08

The delay of barium over the contracted LES indicates a weak peristaltic wave. On the radiograph of T3, a phrenic ampulla appeared, as a closed cavity between the closed proximal wave (proximal functional sphincter - PS) and the LES. The wave propagation in cranio-caudal direction causes a sharp rise in pressure (red point). When the pressure reached the threshold pressure, the LES opened and the ampulla injected of barium bolus into the stomach. This is accompanied by a drop-in pressure in the ampulla. At the same time, there is a sharp shortening of the LES due to the opening of its abdominal part (the angle bounded by the blue line). Diagnosis of GERD is beyond doubt.

In summary the authors, against the background of several proposals, clearly identified only one conclusion: about "... the transition from peristaltic clearance to formation and emptying of the phrenic ampulla. However, analysis of the article suggests that the function of the ampoule is a continuation peristaltic wave in the dilated part of the esophagus., because the functional characteristics of the ampulla comply with the Bayliss-Starling law. This law stating that a stimulus within the intestine (that is, the presence of food) initiates a band of constriction

on the proximal side and relaxation on the distal side and results in a peristaltic wave [Wikipedia].

Despite the erroneous selection of volunteers to determine standards, incorrect interpretation of radiological studies, and neglect of the known facts of the physiology of the esophagus and EGJ, owners of modern equipment for high resolution manometry actively published their research. They created Chicago Classification, the state (not diagnosis) of esophagogastric junction outflow obstruction was highlighted, various gauge characteristics were studied, but this did not bring us closer to understanding the physiology of the EGJ and did not improve the diagnosis of diseases.

Currently, of all the parameters that the authors studied using high resolution manometry, they began to use only one, to determine whether adding upright swallows to the standard Chicago Classification protocol could help define clinically significant esophagogastric junction outflow obstruction [9]. "The upright integrated relaxation pressure (IRP) was derived as the median value from the five upright swallows; an "abnormal upright IRP" was considered at median upright IRP > 12 mmHg, while a "normal upright IRP" was considered at a median upright IRP \leq 12 mmHg" [9]. From our point of view, this indicator has no physiological sense. An upright integrated relaxation pressure > 12 mmHg identified patients with radiographic evidence of EGJOO with 97.9% sensitivity and 15.7% specificity. But since it was considered that the selection of the norm and the evaluation of radiographs were erroneous, the diagnostic value of this parameter is much lower.

It summarizes the resting pressure of the LES and the pressure during its relaxation, as well as the basal pressure in the ampulla, which is lower than the pressure in the stomach, and during its contraction, which creates pressure higher than the gastric one. Secondly, the summation of the pressure of five sips occurs. In healthy people, every swallow-bolus with a fast-peristaltic wave without delay

transfer to the stomach. In patients with GERD, the bolus is delayed in the ampoule. Not every peristaltic wave closes the ampoule proximally, so that a high threshold pressure was created in it to open the LES. Since the number of peristaltic waves for the same time period in normal and patients with GERD are different, there is no reason to assume that $IRP \leq 12$ mmHg indicates obstruction. For example, in GERD, the tone of the LES is reduced and its functional length is shortened, and the tone of the extended esophagus is reduced. Therefore, barium is retained over the LES, not as a result of obstruction, but because of weak peristalsis in the extended esophagus (phrenic ampulla).

Analysis of the articles shows that the high resolution manometry for the diagnosis of EGJ pathology is a little informative study. The X-ray studies presented in the articles as diagnostic method, with the correct interpretation and understanding of physiological processes, exceed the manometric index (IRP) many times. From my point of view, the study of the pathological physiology of the EGJ by this method led to a dead end. A wide discussion on this issue is needed.

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