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Ratio Between Proximal/Distal Gastroesophageal Reflux Does Not Discriminate Abnormal Proximal Reflux

Sebastião Carlos Pannocchia Neto · Fernando A. M. Herbella · Luciana C. Silva · Marco G. Patti

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Abstract

Introduction The threshold for pathologic proximal acid reflux is a controversial topic. Most values previously published are based on absolute numbers. We hypothesized that a relative value representing the quantitative relation between the amount of acid reflux that reaches proximal levels and the amount of distal reflux would be a more adequate parameter for defining pathologic proximal reflux.

Methods We studied 20 healthy volunteers (median age 30 years, 70 % women) without gastroesophageal reflux disease (GERD); 50 patients (median age 51 years, 60 % women) with esophageal symptoms of GERD (heartburn, regurgitation); and 50 patients (median age 49 years, 60 % women) with extra-esophageal symptoms of GERD. All individuals underwent manometry and dual-probe pH monitoring. GERD was defined as a DeMeester score >14.7. The proximal/distal reflux ratio was calculated for all six parameters that constitute the DeMeester score.

Results Absolute numbers for proximal reflux were not different for the three groups except for the number of episodes of reflux, which was higher for patients with GERD and esophageal symptoms than for patients with GERD and extra-esophageal symptoms ($p = 0.007$). The number of episodes of distal reflux reaching proximal levels was significantly higher in volunteers than in all patients with GERD and significantly higher in patients with GERD and esophageal symptoms than in those with extra-esophageal symptoms.

Conclusions Our results suggest that the proximal/distal reflux ratio is not a good normative value for defining proximal reflux.

Introduction

Gastroesophageal reflux disease (GERD) has myriad clinical presentations encompassing esophageal and extra-esophageal symptoms, making the diagnosis of the disease difficult in some cases [1, 2]. Patients with extra-esophageal symptoms are commonly referred for evaluation of GERD as a potential cause. However, pathologic distal reflux is not a guarantee that GERD is the cause of the problem.

Accurate diagnosis of pathologic proximal reflux has been challenging. pH monitoring is the gold standard test for diagnosing GERD [3]. Although the threshold for distal reflux is well defined and widely accepted [4], the normative value for proximal acid reflux is a controversial topic in the management of GERD. Even though several previous studies have tried to study the normal limit for proximal reflux in healthy volunteers [5], no single value is universally accepted. Most reports defined normative values based on absolute numbers [5]. It is not uncommon for patients to have a significant number of distal episodes of reflux without a single episode reaching high levels, whereas other individuals have a small number of distal

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S. C. P. Neto · F. A. M. Herbella (✉) · L. C. Silva
Department of Surgery, Escola Paulista de Medicina, Federal University of Sao Paulo, Rua Diogo de Faria 1087 cj 301, São Paulo, SP 04037-003, Brazil
e-mail: herbella.dcir@epm.br

M. G. Patti
Department of Surgery, Pritzker School of Medicine, University of Chicago, Chicago, IL, USA

episodes of reflux with a high percentage of them reaching the pharynx.

We hypothesized that a relative value representing the quantitative relation between the acid exposure that reaches proximal levels and the exposure of the distal reflux would be a more adequate parameter to define pathologic proximal reflux. This study aimed to compare the proximal/distal reflux ratios in volunteers and GERD patients.

Methods

Population

We studied healthy volunteers and GERD patients and divided them into three groups.

- Group 1 comprised 20 healthy volunteers [median age 30 years (27–40 years), 70 % women] without GERD symptoms or antacid therapy during the last year—prospectively recruited
- Group 2 comprised 50 patients [median age 51 years (37–68 years), 60 % women] with esophageal symptoms of GERD (heartburn, regurgitation) as the main symptoms; median symptom index at pH monitoring 67 % (17–90 %)—retrospectively studied
- Group 3 comprised 50 patients [median age 49 years (40–56 years), 62 % women] with extra-esophageal symptoms of GERD (cough, hoarseness, laryngitis) as the main symptoms; median symptom index at pH monitoring 33 % (0–80 %)—retrospectively studied

Patients with previous foregut surgery or primary esophageal motility disorders were excluded from the study. All GERD patients were on proton pump inhibitors before pH monitoring. All GERD patients underwent pathologic pH monitoring for distal reflux.

Esophageal function tests

All individuals underwent esophageal manometry to allow correct placement of the pH catheter and to exclude motility disorders. Esophageal pH monitoring was performed on all patients. Acid-suppressing medications were discontinued before the study. During the study, the patients consumed an unrestricted diet, and meals periods were not included in the analysis. Subjects maintained a diary to identify the beginning and end of each meal, supine position, and eventual symptoms. Ambulatory pH monitoring was performed by placing a pH probe with dual sensors that had an external reference (Alacer Biomédica, São Paulo, Brazil). The distal probe was placed 5 cm above the upper border of the manometric device determined by the lower esophageal sphincter, and the proximal probe was 20 cm above the lower esophageal sphincter. Data were stored in a data logger (AL3; Alacer Biomédica, São Paulo, Brazil) and were analyzed with the help of dedicated software (AL3 software; Alacer Biomédica). Tracings were manually reviewed for artifacts.

GERD was defined as a DeMeester score >14.7. The criteria for defining an episode of proximal reflux were as follows: (1) pH decreased to <4; (2) the fall in pH occurred during or immediately after acid exposure in the distal esophagus; and (3) the pH decrease in proximal sensor was rapid and acute, and the episode of reflux was not related to the feeding period [6]. The data were incorporated into a composite score (DeMeester score) [7]. When the score was >14.7 the patient was labeled as having GERD. The proximal/distal reflux ratio was calculated for all six parameters that constitute the DeMeester score

Statistics

Variables are expressed as the median (25–75 % quartile). Mann–Whitney and Fisher tests were used when appropriate. A value of p was considered significant at the 0.05 level.

Ethics

The Research Ethics Committee of the Sao Paulo Federal University approved this study. All volunteers signed an informed consent. There were no conflicts of interest. The authors are responsible for the manuscript. No ghost or professional writer was hired.

Results

Demographics

There was no differences regarding the distribution of the sexes among the three groups. In regard to age, volunteers were younger than patients with esophageal symptoms (group 1 vs. group 2: $p = 0.0002$) and patients with esophageal symptoms were older than those with extra-esophageal symptoms (group 2 vs. group 3: $p = 0.0236$). Groups 1 and 3 had similar age distributions ($p = 0.1112$).

pH monitoring

The distal sensor results are shown in Table 1. The values for all six parameters were much lower for group 1 than for the GERD patients (groups 2 and 3). Also, group 2 showed higher scores than group 3.

The proximal sensor location is shown in Fig. 1. There are no differences in anatomic location according to groups ($p = 0.5$). The pH parameters are depicted in Table 2. The

Table 1 DeMeester score parameters values for the distal sensor

Parameter	Group 1 (healthy volunteers) ($n = 20$)	Group 2 (GERD + esophageal symptoms) ($n = 50$)	Group 3 (GERD + extra-esophageal symptoms) ($n = 50$)	p
Reflux episodes (no.)	11.5 (4.7–15.0)	48.5 (35.2–65.0)	39.5 (29.0–57.0)	1 × 2 = 0.0001 1 × 3 = 0.0003 2 × 3 = 0.0443
Episodes >5 min (no.)	0	9.0 (3.0–27.0)	18.5 (7.0–31.0)	1 × 2 = 0.0001 1 × 3 = 0.0001 2 × 3 = 0.0001
Longest episode (min)	2.5 (1.0–3.0)	8.0 (4.2–13.0)	6.0 (3.0–11.2)	1 × 2 = 0.0001 1 × 3 = 0.0009 2 × 3 = 0.0003
pH < 4				
% Total time[a]	1.1 (0.3–2.0)	8.3 (7.0–11.0)	7.4 (4.0–11.2)	1 × 2 = 0.0001 1 × 3 = 0.0004 2 × 3 = 0.0342
% Supine[b]	0.1 (0–0.6)	7.5 (3.0–16.2)	7.4 (3.6–13.1)	1 × 2 = 0.0001 1 × 3 = 0.0001 2 × 3 = 0.0001
% Upright[c]	1.3 (0.6–2.6)	8.3 (5.4–12.3)	7.1 (2.8–11.2)	1 × 2 = 0.0001 1 × 3 = 0.0001 2 × 3 = 0.0001

[a] Percentage of total time pH < 4

[b] Percentage of time pH was <4 in supine position

[c] Percentage of time pH was <4 in upright position

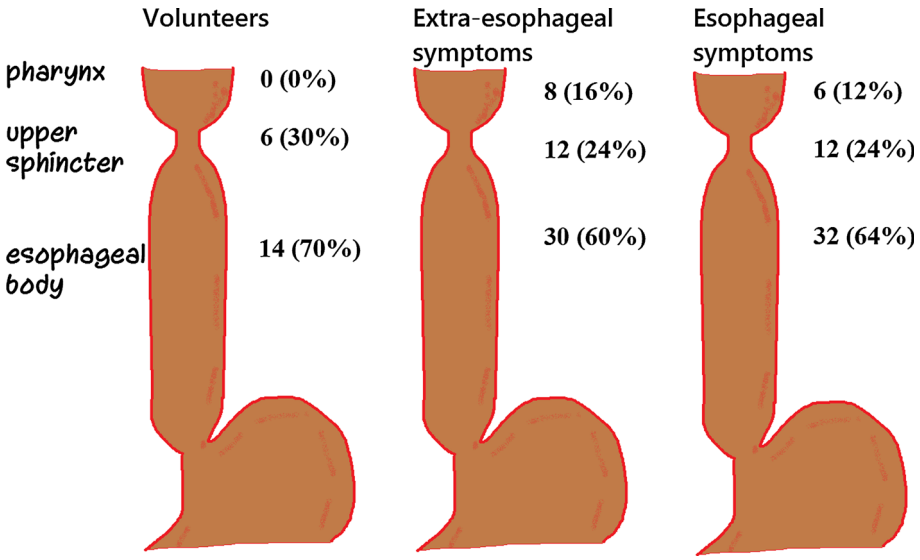

Fig. 1 Anatomic location of the proximal sensor in the three groups

groups showed similar proximal acid exposure with the exception of the number of episodes of reflux, which was higher in group 2 than in group 3.

The results regarding the proximal/distal ratio are shown in Table 3. Group 1 experienced a more distal episodes of reflux that reached the proximal level than did those in group 2. Also, group 2 had a higher number than the subjects in group 3.

A subanalysis including only individuals with the proximal sensor located in the proximal esophagus is depicted in Table 4. More distal episodes of reflux reached the proximal level in group 2 than in group 3.

Discussion

Our results show that: (1) acid exposure that reaches proximal levels is not different among volunteers, patients with GERD, and patients with esophageal or extra-esophageal symptoms; and (2) a significantly higher number of

Table 2 DeMeester score parameters values for the proximal sensor

Parameter	Group 1 (healthy volunteers) ($n = 20$)	Group 2 (GERD + esophageal symptoms) ($n = 50$)	Group 3 (GERD + extra-esophageal symptoms) ($n = 50$)	p
Reflux episodes (no.)	2 (0.75–8.0)	3.5 (1–15)	1 (0–4)	1 × 2 = 0.1
				1 × 3 = 0.1
				2 × 3 = **0.007**
Episodes >5 min	0	0	0 (0–1)	1 × 2 = 0.3
				1 × 3 = 0.09
				2 × 3 = 0.1
Longest episode	0 (0–1)	0	0	1 × 2 = 0.09
				1 × 3 = 0.1
				2 × 3 = 0.5
pH < 4				
% Total time[a]	0 (0–0.25)	0.1 (0–0.3)	0.05 (0–0.3)	1 × 2 = 0.1
				1 × 3 = 0.3
				2 × 3 = 0.2
% Supine[b]	0	0	0	1 × 2 = 0.1
				1 × 3 = 0.1
				2 × 3 = 0.4
% Upright[c]	0.1 (0–0.45)	0.1 (0–0.5)	0.05 (0–0.2)	1 × 2 = 0.3
				1 × 3 = 0.3
				2 × 3 = 0.07

[a] Percentage of total time pH < 4

[b] Percentage of time pH was <4 in supine position

[c] Percentage of time pH was <4 in upright position

*Boldface type indicates significance

Table 3 DeMeester score parameters values for the proximal/distal ratio

Parameter	Group 1 (healthy volunteers) ($n = 20$)	Group 2 (GERD and esophageal symptoms) ($n = 50$)	Group 3 (GERD and extra-esophageal symptoms) ($n = 50$)	p
Reflux episodes (no.)	0.2 (0–1.0)	0.08 (0.02–0.2)	0 (0–0.1)	1 × 2 = **0.05**
				1 × 3 = **0.003**
				2 × 3 = **0.02**
Episodes >5 min	0	0	0	1 × 2 = 0.09
				1 × 3 = **0.01**
				2 × 3 = 0.1
Longest episode	0 (0–0.5)	0	0	1 × 2 = 0.06
				1 × 3 = 0.09
				2 × 3 = 0.4
pH < 4				
% Total[a]	0 (0–0.2)	0	0	1 × 2 = 0.3
				1 × 3 = 0.5
				2 × 3 = 0.3
% Supine[b]	0	0	0	1 × 2 = 0.2
				1 × 3 = 0.1
				2 × 3 = 0.3
% Upright[c]	0.1 (0–0.3)	0 (0–0.1)	0 (0–0.1)	1 × 2 = 0.2
				1 × 3 = **0.04**
				2 × 3 = 0.1

[a] Percentage of total time pH < 4

[b] Percentage of time pH was <4 in supine position

[c] Percentage of time pH was <4 in upright position

*Boldface type indicates significance

episodes of distal reflux reach proximal levels in volunteers than in all patients with GERD and with GERD plus esophageal symptoms than in patients with extra-esophageal symptoms.

Various series have tried to established normative values for proximal GERD [5]. Even though a consensual methodology was never achieved (e.g., placing the probe on a fixed position from the lower esophageal sphincter—which

Table 4 DeMeester score parameters values for the proximal/distal ratio in patients with the proximal probe at the proximal esophagus only

Parameter	Group 1 (healthy volunteers) ($n = 20$)	Group 2 (GERD and esophageal symptoms) ($n = 50$)	Group 3 (GERD and extra-esophageal symptoms) ($n = 50$)	p
Reflux episodes (no.)	0.2 (0.0–1.0)	0.1 (0.1–0.3)	0.1 (0–0.2)	1 × 2 = 0.3
				1 × 3 = 0.1
				2 × 3 = 0.02
Episodes >5 min	0	0 (0–0.1)	0 (0–0.1)	1 × 2 = 0.4
				1 × 3 = 0.06
				2 × 3 = 0.06
Longest episode (min)	0 (0–0.5)	0	0	1 × 2 = 0.7
				1 × 3 = 0.1
				2 × 3 = 0.08
pH < 4				
% Total[a]	0 (0–0.2)	0	0 (0–0.1)	1 × 2 = 0.8
				1 × 3 = 0.09
				2 × 3 = 0.06
% Supine[b]	0	0	0 (0–0.1)	1 × 2 = 0.07
				1 × 3 = 0.2
				2 × 3 = 0.7
% Upright[c]	0.1 (0–0.2)	0 (0–0.2)	0 (0–0.1)	1 × 2 = 1.0
				1 × 3 = 0.7
				2 × 3 = 0.7

[a] Percentage of total time pH < 4

[b] Percentage of time pH was <4 in supine position

[c] Percentage of time pH was <4 in upright position

*Boldface type indicates significance

is also inconstant [8] or variable according to anatomy landmarks [9], this was probably not the limiting factor for a widely accepted normal value for proximal reflux.

First, the values found are very different even when the same methodology is applied [5]. Whereas some argued that a single episode of reflux is pathologic at the level of the pharynx [10, 11], others showed a significant number of proximal reflux episodes in volunteers, with up to 24 episodes at the level of the upper esophageal sphincter [12] or 18 episodes at the level of the pharynx [9].

Second, various authors failed to show different proximal acid exposure in asymptomatic volunteers compared to patients with extra-esophageal GERD symptoms [13], volunteers and patients with otolaryngologic diseases other than posterior pharyngitis [14], patients with esophageal and extra-esophageal symptoms of GERD [15, 16], or patients with and without an abnormal pharyngoscopic evaluation [13, 17].

As most previously obtained values were based on absolute numbers, we hypothesized that a relative value representing the quantitative relation between the acid exposure that reaches proximal levels and the exposure of distal reflux would be a more adequate parameter to define pathologic proximal reflux. We surprisingly found that patients with GERD and extra-esophageal reflux symptoms had the same proximal acid exposure as volunteers and patients with esophageal symptoms. Also, fewer episodes of reflux ascended to proximal levels in these patients.

In view of the fact that healthy individuals and patients with proximal reflux share the same acid exposure, the supposition that visceral sensitivity is responsible for extra-esophageal symptoms of GERD comes to mind. A temporal symptom–reflux correlation during pH monitoring is probably the best method to measure this sensitivity indirectly. About two decades ago, Patti et al. [18] demonstrated that a positive symptomatic correlation with proximal reflux discriminates a subgroup of patients who suffer from a pan-esophageal motor dysfunction that affects all three barriers to aspiration: the lower esophageal sphincter, esophageal peristalsis, and the upper esophageal sphincter. Furthermore, a positive correlation predicts the response to treatment [19].

Other possibilities to explain the genesis of extra-esophageal symptoms disconnected from proximal acid exposure are neural reflexes and non-acid reflux. It is well known that acidic stimulation of the distal esophagus may lead to bronchial and even coronary spasm [20]. In regard to non-acid reflux, series of impedance pH measurements in patients on antacids showed that non-acid proximal reflux may cause extra-esophageal symptoms [21, 22]. However, clinical use of impedance pH may be contraindicated because of studies with controversial results [23], the rarity of isolated non-acid reflux because it seems that it parallels acid reflux [23, 24], and a lack of clinical implication regarding prognosis, therapeutic decisions, or postoperative evaluation [23].

This study may be criticized in some points. First, a small number of volunteers were studied because of the difficulty recruiting asymptomatic volunteers and the difficulty of recruiting volunteers for pH monitoring that did not allow selection for age-matching. Second, we adopted placement of the proximal probe on a fixed position. This methodology followed previous experience and avoided the need to maintain multiple customized catheters or to use two catheters. Other previous studies used the same methodology [8, 25–27]. However, this practice led to variation in the placement of the proximal sensor according to anatomic structures and a higher chance of artifacts in patients with the proximal sensor at the level of the pharynx, even though all tracings were manually reviewed. A subanalysis of the patients with the proximal sensor located in the esophagus, however, did not change the results significantly, although the number of patients studied decreased. Finally, there is no gold standard test to compare our results because a technique for determining pathologic proximal acid exposure is still elusive.

Conclusions

Our results suggest that the proximal/distal reflux ratio is not a good normative value for proximal reflux. Also, even though proximal acid evaluation does not discriminate pathologic proximal acid reflux disease, patients should still be tested by pH monitoring. The temporal symptom–reflux correlation should be evaluated as well. Nevertheless, the diagnosis of pathologic proximal reflux must be based on a sum of clinical parameters.

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