Manometric parameters in patients with suspected gastroesophageal reflux disease and normal pH monitoring

Parâmetros manométricos em pacientes com suspeita de doença do refluxo gastroesofágico e pHmetria normal

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Abstract

Background: pH monitoring is the gold standard test for the evaluation of Gastroesophageal reflux disease (GERD) but esophageal manometry is classically not indicated for making or confirming a suspected diagnosis of GERD. This study aims to evaluate the manometric findings in patients with suspected GERD and normal pH monitoring. **Methods:** 100 adult patients with suspected GERD were retrospectively studied. Patients were divided in Group A: normal reflux score (n=60, 72% women, mean age 51 years) and Group B: abnormal reflux score (n=40, 70% women, mean age 54 years). All patients underwent an upper endoscopy, esophageal manometry and pH monitoring**. Results**: Heartburn was more frequent in group B and epigastric pain was more frequent in the group A, while the prevalence of other symptoms was similar between groups. Abnormal endoscopy, hiatal hernia and esophagitis were more frequent in group B with significant risk for GERD. Lower esophageal sphincter (LES) length and pressure were lower in patients from group B. Esophageal motility was similar between groups. **Conclusions:** Our results show that: (1) symptoms are unreliable to diagnose GERD, (2) abnormal endoscopy is more frequent in patients with GERD, (3) LES length and pressure are decreased in patients with GERD, and (4) patients with clinical predictors for GERD are not more likely to have manometric parameters to suggest GERD.

Keywords: Gastroesophageal Reflux Disease, Manometry, pHmonitoring, Symptoms.

Resumo

Introdução: A pHmetria é o padrão ouro na avaliação da doença do refluxo gastroesofágico (DRGE), porém, a manometria não é, classicamente, indicada para diagnosticar ou confirmar suspeita de DRGE. Este estudo visa avaliar os achados manométricos em pacientes com DRGE e pHmetria normal. **Método:** Foram estudados retrospectivamente 100 pacientes adultos com suspeita de DRGE. Foram divididos em grupo A: índice de refluxo normal (n=60, 72% mulheres, idade média 51 anos) e grupo B: índice de refluxo anormal (n=40, 70% mulheres, idade média 54 anos). Todos os pacientes fizeram endoscopia, manometria e pHmetria esofágicas. **Resultados:** Pirose foi mais frequente no grupo B e epigastralgia no grupo A, enquanto que a prevalência dos demais sintomas foi similar entre os grupos. Endoscopia anormal, hérnia de hiato e esofagite foram mais frequentes no grupo B, com risco significante para DRGE. O comprimento e a pressão do esfíncter esofagiano inferior foram menores

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nos pacientes do grupo B. A motilidade esofágica foi similar entre os grupos. **Conclusão:** Nossos resultados mostram que: 1 - os sintomas não são discriminatórios no diagnóstico de DRGE; 2 - endoscopia anormal é mais frequente em pacientes com DRGE; 3 - comprimento e pressão do esfíncter esofagiano inferior foram menores em pacientes com DRGE, e 4 - pacientes com preditores clínicos para DRGE não têm necessariamente achados manométricos que possam sugerir a DRGE.

Unitermos: Doença do Refluxo Gastroesofágico, Manometria, pHmetria, Sintomas.

Introduction

Gastroesophageal reflux disease (GERD) is a very common disease; however, it has a complex physiopathology[1] and a myriad of clinical presentations encompassing esophageal and extra-esophageal symptoms[2]. Thus, the diagnosis of GERD may be difficult in some cases. pH monitoring is the gold standard test for the evaluation of GERD even though a significant percentage of false negative results may be linked to this test[3].

Manometry may evaluate changes in the esophageal motility that may be associated to GERD physiopathology, such as the lower esophageal sphincter (LES) competence and esophageal body peristalsis; however, according to the American Gastroenterological Association[4] and the American College of Gastroenterology[5], manometry is not indicated for making or confirming a suspected diagnosis of GERD.

This study aims to evaluate the manometric findings in patients with suspected GERD and normal pH monitoring.

Methods

Population

One-hundred non-selected adult patients that underwent esophageal manometry and ambulatory pH monitoring for suspected GERD were retrospectively studied. Patients were grouped on the basis of the results of ambulatory pH monitoring test, group A: normal reflux score (n=60, 72% women, mean age 51 years) and group B: abnormal reflux score (n=40, 70% women, mean age 54 years).

Patients with previous foregut surgery or primary esophageal motility disorders were excluded from the study. Patients were questioned regarding the presence of symptoms that were divided into the following subgroups: esophageal symptoms (heartburn, regurgitation); extra-esophageal symptoms (thoracic pain, respiratory symtpoms, such as cough and asthma or ear nose and throat symptoms) and gastric symptoms (epigastric pain, gastric bloating or fullness and vomiting)

Work up

All patients were submitted to an upper endoscopy to evaluated the presence of hiatal hernia (HH), esophagitis and Barrett`s esophagus.

In 48.3% of group A (29 patients) and 45% of group B (18 patients) a barium esophagram was also performed and the presence of HH and gastroesophageal reflux were assessed.

Manometry

Esophageal manometry was performed in all patients. Medications that interfere with esophageal and gastric motility were discontinued 3 days before the study.

Esophageal manometry was performed with an eight-lumen manometry catheter, continu-ously perfused by pneumohydraulic capillary infusion system connected to a polygraph at least af-ter 8h of fasting. Position, pressure (at the mean respiratory point) and length of the lower eso-phageal sphincter (LES) were measure using the station pull-through technique. Esophageal body function was assessed by giving 10 swallows of 5 ml of water at 30-s intervals. Amplitude and propagation of the peristaltic waves were assessed. The data were analyzed by computer, using a dedicated software program.

LES length was considered normal when $>$ 2cm and abdominal length when $>$ 1 cm. LES pressure was considered normal between 14-36 mmHg. A defective LES was defined as the pres-ence of abnormal LES total length or abnormal abdominal length or hypotonicity. Distal esophag-eal amplitude (DEA) was considered normal when the mean pressure in distal esophagus (sensor located 3cmm above the upper border of the LES) was between 60 and 140 mmHg. DEA was con-sidered hypotensive if $<$ 60 mmHg.

pH monitoring

Esophageal pH monitoring was performed on all patients. Acid suppressing medications were dis-continued 14 days before the study. During the study, the patients consumed an unrestricted diet. Ambulatory pH monitoring was performed by placing a pH probe 5cm above the upper border of the manometricly determined LES. The data were incorporated into a composite score (DeMeester score), and a score greater than 14.7 was set as abnormal.

Statistics

The student`s t test, Bayesian calculations for diagnostic tests, relative risk, Receiver Operating Characteristic (ROC) and Fisher`s test were used when appropriated. A value of *p* was considered significant at the 0.05 level. Variables are expressed as mean ± standard deviation.

Ethics

This study was approved by the Research Ethics Committee of the Sao Paulo Federal University.

Results

Population

Group A and B were comparable according to age and gender (table 1).

Symptomatic Evaluation

Heartburn was more frequent in group B and epigastric pain was more frequent in the group A, while the prevalence of other symptoms was similar between groups. However, only heartburn showed a significant risk for GERD (table 1).

Work up

Abnormal endoscopy, hiatal hernia and esophagitis were more frequent in group B with significant risk for GERD (table 2). Four patients had Barrett´s esophagus (all of them from group B).

There was no difference in the presence of abnormal esophagram, hiatal hernia or reflux be-tween groups at the esophagram (table 2).

Manometry

LES length and pressure were lower in patients from group B. Esophageal motility was similar be-tween groups. A defective LES was more frequently found in group B and it was the only manometric parameter to increase the risk for GERD (table 3).

The sensitivity and specificity to diagnostic GERD based on abnormal LES length was 22 and 85%, respectively. The sensitivity and specificity to diagnostic GERD based on a hypotonic LES was 70 and 50%, respectively. The sensitivity and specificity to diagnostic GERD based on a defective LES was 87 and 22%, respectively.

A ROC analysis of the LES pressure as a predictor for GERD showed an area under the curve of 0.6 (95% confidence interval 0.5 to 0.7 p=0.02). The sensitivity and specificity for differ-ent cutoff values are depicted on figure 1.

Table 1. Demographics and symptoms for groups with and without gastroesophageal reflux disease.

	Group A (GERD -) (n=60)	Group B (GERD +) (n=40)	*p*	Relative risk (95% confidence interval)
Age (years)	51.5 ± 12.9	53.6 ± 13.73	0.43	NA
Gender (% females)	72	70	0.17	0.9 (0.6-1.6)
Heartburn	33 (55%)	32 (80%)	< 0.01	2.1 (1.1 – 4.1)
Regurgitation	33 (55%)	25 (62.5%)	0.12	1.2 (0.7-2.0)
Epigastric pain	32 (53%)	14 (35%)	0.03	0.6 (0.4-1.1)
Dysphagia	7 (11.6%)	5 (12.5%)	0.24	1.0 (0.5-2.1)
Cough	9 (15%)	8 (20%)	0.17	1.2 (0.7-2.2)
Asthma	2 (3,3%)	2 (5%)	0.17	1.3 (0.5-3.5)
Vomiting	9 (15%)	8 (20%)	0.17	1.2 (0.7-2.2)
Retrosternal pain	10 (16.6%)	7 (17.5%)	0.21	1.0 (0.5-1.9)
Esophageal symptoms	45 (75%)	34 (85%)	0.3	1.5 (0.7-3.1)
Extra-esophageal symptoms	26 (43%)	16 (40%)	0.8	0.9 (0.5-1.5)
Gastric symptoms	54 (90%)	36 (90%)	1	1 (0.4-2.2)

NA: not applicable

Subgroups analysis

The analysis of manometric parameters of subgroups with normal pHmonitoring and predictors for gastroesophageal reflux disease showed that the LES pressure is lower inpatients with heartburn and an abnormal endoscopy compared to other patients from group A (table 4).

Table 2. Preoperative work up for groups with and without gastroesophageal reflux disease.

	Group A (GERD -) (n=60)	Group B (GERD +) (n=40)	*p*	Relative risk (95% confidence interval)
Abnormal endoscopy	31 (51.6%)	35 (87.5%)	0.02	3.6 (1.5-8.3)
- Hiatal hernia	20 (33.3%)	28 (70%)	< 0.01	2.5 (1.5-4.4)
- Esophagitis	20 (33.3%)	25 (62.5%)	< 0.01	2.0 (1.2-3.4)
Abnormal esophagram	21 (72.4%)	13 (72.2%)	0.24	0.9 (0.6-1.6)
- Hiatal hernia	21 (72.4%)	11 (61.1%)	0.18	0.8 (0.5-1.4)
- Reflux	8 (27.5%)	7 (38.8%)	0.18	1.2 (0.6-2.2)

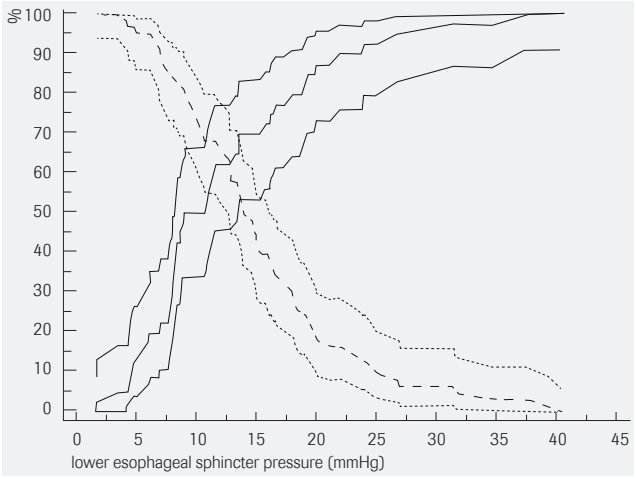
NA: not applicable

Table 3. Esophageal manometry for groups with and without gastroesophageal reflux disease.

	Group A (GERD -) (n=60)	Group B (GERD +) (n=40)	*p*	Relative risk (95% confidence interval)
LES length (cm) % abnormal	2.2 ± 0.516 9 (15%)	2.2 ± 1.055 9 (22.5%)	< 0.01 0.4	1.3 (0.8-2.3)
LES abdominal length (cm) % abnormal	0.7 ± 0.7 33 (55%)	0.5 ± 0.6 28 (70%)	0.16 0.10	1.5 (0.9-2.6)
LES pressure (mmHg) % hypotonic	15.6 ± 6.6 30 (50%)	12.4 ± 4.9 28 (70%)	0.05 0.06	1.7 (1.0-2.9)
Defective LES	39 (65%)	35 (87.5%)	0.02	2.4 (1.1-5.6)
Relaxation pres-sure of LES (mmHg)	-1.1 ± 1.5	-1.3 ± 1.2	0.35	
Mean wave amplitude (mmHg)	124.0 ± 55.9	102.5 ± 58.4	0.06	1.6 (1-2.6)
hipocontractility	8 (13%)	11 (27.5%)	0.11	
Peristalsis (%)	94.9 ± 12.6	95.7 ± 12.5	0.74	

LES: lower esophageal sphincter

Figure 1. Sensitivity and specificity for different cutoff values in a Receiver Operating Characteristic (ROC) curve of the lower esophageal sphincter pressure as a predictor for positive pHmonitoring.



Discussion

Our results show that: (1) symptoms are unreliable to diagnose GERD, (2) abnormal endoscopy is more frequently find in patients with GERD, (3) LES length and pressure are decreased in patients with GERD, and (4) patients with clinical predictors for GERD are not more likely to have ma-nometric parameters to suggest GERD.

Table 4. Analysis of manometric parameters of subgroups with normal pHmonitoring and predictors for Gastroesophageal reflux disease.

	Heartburn + GERD – (n=33)	Abnormal endoscopy GERD – (n=30)	Hiatal hernia (n=20)	Esophagitis (n=20)	Abnormal EDA and Heartburn + (n=17)	Group A (GERD -) (n=60)	Group B (GERD +) (n=40)
Abdominal LES length	6 (18%) p = 0.77 *vs* GERD – p = 1 *vs* GERD +	8 (27%) p = 0.25 *vs* GERD – p = 0.78 *vs* GERD +	6 (30%) p = 0.18 *vs* GERD – p = 0.54 *vs* GERD +	6 (30%) p = 0.18 *vs* GERD – p = 0.54 *vs* GERD +	5 (29%) p = 0.28 *vs* GERD – p = 0.73 *vs* GERD +	9 (15%)	9 (22%)
Abdominal length	22 (67%) p = 0.37 *vs* GERD – p = 0.8 *vs* GERD +	19 (63%) p = 0.5 *vs* GERD – p = 0.61 *vs* GERD +	13 (65%) p = 0.6 *vs* GERD – p = 0.77 *vs* GERD +	14 (70%) p = 0.3 *vs* GERD – p = 1 *vs* GERD +	13 (76%) p = 0.16 *vs* GERD – p = 0.75 *vs* GERD +	33 (55%)	28 (70%)
LES pressure	22 (67%) p = 0.13 *vs* GERD – p = 0.8 *vs* GERD +	18 (60%) p = 0.5 *vs* GERD – p = 0.44 *vs* GERD +	13 (65%) p = 0.3 *vs* GERD – p = 0.77 *vs* GERD +	13 (65%) p = 0.3 *vs* GERD – p = 0.77 *vs* GERD +	14 (82%) p = 0.02 *vs* GERD – p = 0.51 *vs* GERD +	30 (50%)	28 (70%)
Defective LES	26 (79%) p = 0.23 *vs* GERD – p = 0.35 *vs* GERD +	21 (70%) p = 0.81 *vs* GERD – p = 0.12 *vs* GERD +	14 (70%) p = 0.78 *vs* GERD – p = 0.15 *vs* GERD +	15 (75%) p = 0.58 *vs* GERD – p = 0.27 *vs* GERD +	14 (82%) p = 0.23 *vs* GERD – p = 0.68 *vs* GERD +	39 (65%)	35 (87%)
Hypocontractility	2 (6%) p = 0.48 *vs* GERD – p = 0.02 *vs* GERD +	3 (10%) p = 0.74 *vs* GERD – p = 0.07 *vs* GERD +	1 (5%) p = 0.43 *vs* GERD – p = 0.04 *vs* GERD +	2 (10%) p = 1 vs GERD – p = 0.18 *vs* GERD +	1 (6%) p = 0.67 *vs* GERD – p = 0.08 *vs* GERD +	8 (13%)	11 (27%)

LES=lower esophageal sphincter/GERD = Gastroesophageal reflux disease

GERD diagnosis

Different previous publications showed that symptoms are unreliable for the diagnosis of GERD[6, 7] , although the labeling of patients as refluxers based on symptoms questionnaires is still a common practice, even in important scientific publications[8, 9], in spite of that most of these questionnaires were not validated in comparison to esophageal ambulatory pHmonitoring[10]. In our series, heart-burn was the only symptom with a mathematical association to GERD; however, more than half of the patients without GERD complaint of heartburn. A thoughtfully investigation of patients with suspect GERD especially with pHmonitoring may avoid much improper and costly medical ther-apy [11]. Upper digestive endoscopy is quoted as highly specific but with a low sensitivity for the di-agnosis of GERD[12]. It is well-known that the absence of esophagitis does not preclude the diagno-sis of GERD; however, the presence of esophagitis is considered an appanage of refluxers by most authors[13]. In our series, esophagitis was found in one third of the GERD – patients by pHmonitor-ing, a rate ranging from 20 to 47% in other previous studies[6,14].

We cannot hypothesize the basis for esophagitis in patients without GERD. It may probably reflect a false negative pHmonitoring or a decreased mucosal resistance even to physiologic reflux. Whether these patients (with esophagitis and a negative pHmonitoring) should be considered GERD + will depend on a case by case clinical judgment. Similarly, HH was more frequently found in GERD + patients although a significant number of GERD – also presented with this finding. Despite the fact that one third of GERD – pa-tients may have clinical significant findings at the endoscopy, this test showed a high diagnostic yield for GERD and it should be routinely performed in patients with suspected GERD. Barium swallow (esophagram) did not show a good diagnostic test to discriminate GERD.

Ambulatory prolonged pHmonitoring is still the gold standard test for the diagnosis of GERD[13,15] although some argue that impedance-pH should take this position at the podium[16]. A false negative ranging from 4 to 7% may be associated to the test in non-selected populations, such as non-erosive GERD or chest pain[17-18] that may be explained by hypersalivation linked to the presence of the transnasal catheter, changes in life style during the period of the test, and daily var-iability[19]. Also, visceral hypersensitivity may lead to GERD in patients with normal esophageal acid exposure[20]. We intended to demonstrate in the current study whether patients with clinical predictors for GERD would present with esophageal manometry parameters that could identify a false negative pHmonitoring.

Manometry and GERD

GERD has a complex physiopathology[1] and the observation of only esophageal manometry parameters may not diagnosis the disease. A defective LES is not a guarantee of GERD since other natural antireflux mechanisms may be acting efficiently[1,21]. On the other side, a manometric nor-mal LES may be found in refluxers since abnormal transient relaxation of the LES may be impli-cate in the genesis of GERD and it is not easily detected by routine manometry[21]. In our results, although mean LES length and pressure are decreased in patients with GERD and a defective LES leads to a 2.5 increased chance to GERD still a normal LES was found in 13% of the GERD + patients and a defective LES was found in 65% of the GERD – patients.

The prevalence of a defective LES do not suggest pathologic reflux even when a subgroup of GERD - patients with a high likelihood to be real refluxers (abnormal endoscopy and heartburn) are evaluated. Very interestingly too, a ROC curve analysis of the cutoff value for LES pressure showed that the best specificity and sensitivity for GERD diagnosis was found exactly at the current adopted lower limit for LES normal pressure (14 mmHg). The analysis of a different series failed to show differences of the LES between GERD + and GERD – patients[6]. Esophageal peristalsis is also an important component of the antireflux mechanism because it is the main determinant of esophageal clearance of the refluxate [(1)]. We did not find differences in esophageal amplitude or peristalsis in patients GERD – or GERD +, as observed by others as well[6].

Although esophageal manometry parameters do not diagnosis GERD they may grade the disease. A direct correlation between acid exposure and progressive deteriorate degrees of LES and esophageal peristalsis function was demonstrated[22]. Also, weakened peristalsis and defectives LES has been long associated to more severe GERD and Barrett´s esophagus[23-25]. Esophageal manome-try parameters have also been tested as predictors for GERD therapy outcomes, but different studies failed to link motility and outcomes for surgical treatment of GERD[25-28].

Conclusions

The current study has some limitations. First, it is a retrospective study with the bias associated to this study design. Second, we only measured acid reflux although we believe that non-acid reflux parallels acid reflux and our results would be unchanged[29]. Lastly, we did not follow the patients up or evaluate response to antacids since some of them were not treated in the same institution where the esophageal function

tests were performed. Despite these limitations, we showed that esophageal manometry must not be used as a unique tool to diagnosis GERD; however, the finding of a defective LES must be summed to other clinical parameters to allow a correct judgment of GERD diagnosis in difficult cases. Furthermore, esophageal manometry is also a useful tool to cor-rect placement of pHmonitoring catheters and allows the diagnosis of unsuspected primary motility disorders. As such, esophageal manometry should be liberally done in patients under evaluation for suspected GERD.

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