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Original Article

# ULTRA-DISTAL REFLUX EVALUATION WITH MULTIPLE CHANNEL PHMONITORING

*Avaliação de refluxo ultra-distal com pHmetria de múltiplos canais*

Francisco Carlos Bernal da Costa **SEGURO,** Marco Aurélio **SANTO,** Sérgio **SZACHNOWICZ,** Fauze **MALUF-FILHO,**Humberto Setsuo **KISHI,** Ângela Marinho **FALCÃO,** Ary **NASI,** Rubens Antônio Aissar **SALLUM,** Ivan **CECCONELLO**

From Serviço de Cirurgia do Esôfago do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brasil.

**ABSTRACT** – ***Background*** - Esophageal adenocarcinoma and dysplasia in patients with Barrett's esophagus are seen after surgical treatment of GERD (fundoplication). Esophageal pH monitoring shows no evidence of acidity, suggesting distal reflux to the conventional catheter positioning. ***Aim*** - To develop methodology for assessing ultra-distal reflux (1 cm above the top edge of the lower esophageal sphincter). ***Method*** - Were selected 11 patients with Barrett's esophagus previously submitted to Nissen fundoplication, without reflux symptoms and with endoscopy and contrasted study of esophagus without signs of relapse. Esophageal manometry was used to evaluate the location and length of the lower sphincter of the esophagus (LES). After that, esophageal pH monitoring with four channels was done: channel A at 5 cm above the top edge of the LES; channel B at 1 cm above; channel C, intra-sphincteric; channel D, intragastric. The DeMeester score was assessed on channel A. The number of episodes of acid reflux, the number of episodes of prolonged reflux and fraction of time pH<4.0 were compared on channels A and B. The fraction of time pH<4.0 was compared on channels B and C. The fraction of time with pH<4.0 above 50% on channel D was used as parameter of no proximal migration of the catheter. ***Results*** - Significant increase in the number of reflux episodes and fraction of time pH<4.0 in channel B in relation to channel A. Reduced fraction of time pH<4.0 in channel B compared to channel C was seen. Two cases of esophageal adenocarcinoma were diagnosed in the group. ***Conclusions*** - The zone 1 cm above the top edge of the LES is more exposed to acidity than the one 5 cm above, although at reduced levels. The region 1 cm above the top edge of the LES is less exposed to acidity than the intrasphincteric zone, demonstrating efficacy of fundoplication.

**HEADINGS** – Gastroesophageal reflux/ surgery. Barrett esophagus. Esophageal pH monitoring. Fundoplication.

**Correspondência:**
Francisco Carlos Bernal da Costa Seguro,
e-mail: fc.seguro@uol.com.br

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**RESUMO - *Racional* -** Displasia e adenocarcinoma esofágico surge em pacientes com esôfago de Barrett submetidos a tratamento cirúrgico (fundoplicatura) com pHmetria esofágica sem evidência de acidez, o que sugere existir refluxo distal ao cateter de pHmetria convencional. ***Objetivo*** - Desenvolver metodologia para avaliar refluxo ultra-distal (1 cm acima da borda superior de esfíncter inferior do esôfago). ***Método*** - Foram selecionados 11 pacientes com esôfago de Barrett previamente submetidos à fundoplicatura à Nissen, sem sintomas de refluxo, com endoscopia e estudo contrastado de esôfago sem sinais de recidiva. Foi realizada manometria esofágica para avaliar a localização e a extensão do esfíncter esofágico inferior (EIE). Realizou-se então pHmetria esofágica com quatro canais: canal A a 5 cm acima da borda superior do EIE; canal B a 1 cm acima; canal C intraesfincteriano; canal D intragástrico. Avaliou-se o escore de DeMeester no canal A. Comparou-se o número de episódios de refluxo ácido, o número de episódios de refluxo prolongado e a fração de tempo com pH<4,0 nos canais A e B. Comparou-se a fração de tempo de pH<4,0 nos canais B e C. A fração de tempo com pH<4,0 acima de 50% no canal D foi usada como parâmetro para não migração proximal do cateter. ***Resultados*** - Houve aumento significativo do número de episódios de refluxo e da fração de tempo com pH<4,0 no canal B em relação ao canal A. Houve redução do tempo de pH<4,0 no canal B em comparação ao canal C. Dois casos de adenocarcinoma esofágico foram diagnosticados nos pacientes do grupo estudado. ***Conclusões*** - A região 1 cm acima da borda superior do EIE está mais exposta à acidez do que a região 5 cm acima, embora em níveis reduzidos. A região 1 cm acima da borda superior do EIE está menos exposta à acidez do que a região intraesfincteriana, demonstrando eficácia da fundoplicatura.

**DESCRITORES** - Refluxo gastroesofágico/ cirurgia. Esôfago de Barrett. Monitoramento do pH esofágico. Fundoplicatura.

## INTRODUCTION

The gastroesophageal reflux disease (GERD) is highly prevalent in the population. In the West, the occurrence of heartburn or acid regurgitation once a week ranges from 15 to 25% of the population, while in Asia is less than 5%[26]. In Brazil, about 12% of the population has heartburn at least once a week[17]. GERD is defined as a condition that develops when the reflux of gastric contents causes symptoms or complications that affect the quality of a patient's life[26].

Barrett's esophagus is an alteration of the esophageal mucosa due to gastroesophageal reflux that requires intense and prolonged development of columnar metaplasia of the intestinal type, and occurs in 1-2% of cases of GERD[26]. However, 10% to 15% of patients with chronic reflux symptoms undergoing endoscopy can be with Barrett's esophagus[17].

The importance of it lies in its potential relationship with esophageal adenocarcinoma. In the Western world, the frequency of adenocarcinoma of the esophagus showed a great increase in recent years, now characterized as the most common esophageal tumor in some countries, surpassing the incidence of squamous cell carcinoma[24,25,30].

The goal of treatment of patients with Barrett's esophagus is stop the tissue damage that causes inflammation and progression to dysplasia and cancer. To this end, one should avoid gastroesophageal acid reflux, seen as the main stimulus for damaging the esophageal mucosa. The treatment can be clinical, based on behavioral measures to reduce reflux and the use of drugs to inhibit production of stomach acid. Surgical treatment avoids the occurrence of reflux through the production of anti-reflux valve, causing increased levels of pressure of lower esophageal sphincter (LES) and normalization of distal esophageal exposure to acid and thus greater control of reflux, and so the best treatment for patients with Barrett's esophagus[2,8,11,23].

To evaluate the success of treatment can be used clinical parameter to control the symptoms related to reflux, or exams. Upper endoscopy can detect treatment failure, presence of esophagitis or progression of the metaplastic epithelium. The contrast study evaluates the occurrence of esophageal reflux during the examination. However, prolonged esophageal pH monitoring is the best test for determining the presence of gastroesophageal acid reflux, considered as the standard for this purpose[6,13,18].

Draws attention to the existence of some patients who develop dysplasia and even adenocarcinoma confirmed by additional tests - including conventional pH monitoring - during follow-up after successful treatment[1,22]. This raises the possibility of reflux in the distal segment of the esophagus, not detectable by currently used methods of investigation, because the conventional pH monitoring assesses reflux is positioned 5 cm above the superior border of the LES, with restraint to assess acidity below this level in the region ultra-distal esophagus.

Some authors studied the pattern of ultra-distal reflux with different methods. Fletcher et al.[9] performed a study of pH meter with two channels, securing the catheter to the esophagus with endoscopic clips. Pandolfini et al.[20] and Wenner et al.[31,32]. used the system of Bravo wireless pH monitoring with sensors attached to the esophageal mucosa just above the transition gastric esophageal. All authors observed a greater acid exposure at the higher levels of the distal esophagus.

As there is wide variation in techniques used, the purpose of this study was the development of appropriate methodology to standardize the study of ultra-distal acid reflux in the esophagus.

## METHOD

Eleven patients with Barrett's esophagus previously operated with Nissen fundoplication for gastroesophageal reflux treatment were selected using the following inclusion criteria: length of follow-up (period of at least one year), extension of columnar epithelium with intestinal metaplasia at or more than 1 cm in the preoperative period, complete control of symptoms of gastroesophageal reflux without the use of proton pump inhibitor for any reason, endoscopy with absence of esophagitis and hiatal hernia or paraesophageal hernia, topical and fundoplication appropriate morphology; contrast examination of the esophagus showing the presence of intra-abdominal fundoplication and integrity, and absence of gastroesophageal reflux.

After, esophageal manometry took place, aiming to evaluate the location of the LES and proximal and distal edges, its length and resting pressure to allow proper positioning of the pH meter.

Finally, the study involved the completion of pH monitoring catheter with four channels, arranged as follows (Figure 1): channel A was positioned 5 cm above the superior border of the LES, as standardization for prolonged esophageal pH monitoring; channel B was located 4 cm below the channel A, ie 1 cm above the superior border of the LES to assess acid reflux in a more distal esophagus; channel C was positioned within the scope of the LES, 3 cm below the B channel; channel D remained in the stomach, just below the bottom border of the LES, 3 cm below the channel C. The channel B was 2 cm below the top border of the LES to evaluate the effectiveness of containment reflux of intra-sphincter region 1 cm above the superior border of the LES by comparing the results obtained in the channel C with the results obtained in B. The channel C had the

function to evaluate the permanence of the catheter in its original position during exam time, because the sustained high pH suggest proximal migration of the

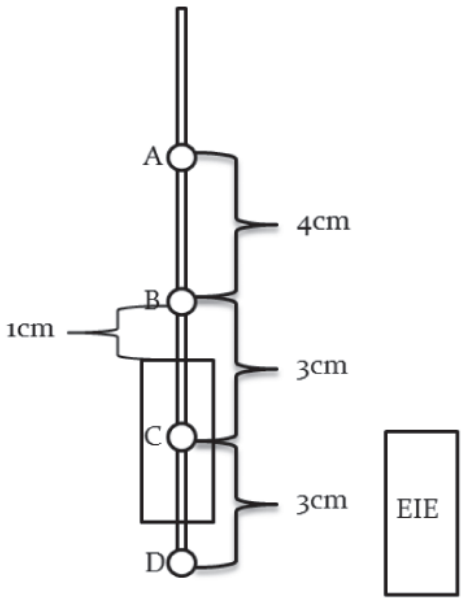


**FIGURE 1** - Catheter pH monitoring of multiple channels

catheter, invalidating the result.

The parameters measured in channel A were the number of acid reflux episodes, number of reflux episodes (longer than five minutes), fraction of time with pH below 4.0 (considered as normal up to 4.2% of fraction of total time) and DeMeester score.

On channel B, it was evaluated the number of reflux episodes, number of prolonged episodes and the fraction of time with pH below 4.0, considering normal up to 1.5% of the total fraction of the time. The DeMeester score was not used because it is well-established parameter for assessment of reflux in pH monitoring conventional catheter 5 cm above the superior border of the LES, without standardization for interpreting results at other levels of the esophagus.

In channels C and D, only the fraction of time with pH below 4.0 was used to analyze the results.

Using the Wilcoxon method, was compared the results between the channels A and B and between the channels B and C.

## RESULTS

The results of the channel A showed the number of reflux episodes ranged from 0 to 57 occurrences, with a median of 2. The number of prolonged episodes ranged from 0 to 3, with a median of 0. Regarding the fraction of time with pH below 4.0, the range was 0% to 9.8% with a median of 0.1%. The DeMeester score

**TABLE 1** - Results obtained in channel A

| Patient | Nº of episodess | Nº of prolonged | Fraction of time pH <4,0 | DeMeester score |
|---|---|---|---|---|
| 1 | 0 | 0 | 0,0% | 0,6 |
| 2 | 2 | 0 | 0,10% | 0,8 |
| 3 | 1 | 0 | 0,1% | 0,7 |
| 4 | 8 | 1 | 1,0% | 4,6 |
| 5 | 5 | 0 | 0,4% | 2,8 |
| 6 | 13 | 0 | 0,1% | 2,2 |
| 7 | 0 | 0 | 0,0% | 1,1 |
| 8 | 1 | 0 | 0% | 0,5 |
| 9 | 0 | 0 | 0,0% | 0,3 |
| 10 | 2 | 0 | 0,1% | 1,3 |
| 11 | 57 | 3 | 9,8% | 52,5 |

ranged from 0.3 to 52.5, with a median of 1.1 (Table 1).

The results showed that the B channel number of reflux episodes ranged from 2 to 274, with a median of 78. The number of prolonged episodes ranged from 0 to 20, with a median of 0. The fraction of time with pH below 4.0 ranged from 0.1% to 41.9% with a median

**TABLE 2** - Results on the B channel

| Patient | Nº of episodess | Nº of prolonged | Fraction of time pH <4,0 |
|---|---|---|---|
| 1 | 32 | 1 | 0,9% |
| 2 | 27 | 0 | 0,40% |
| 3 | 2 | 0 | 0,1% |
| 4 | 58 | 0 | 1,2% |
| 5 | 100 | 3 | 5,2% |
| 6 | 125 | 2 | 6,7% |
| 7 | 7 | 0 | 0,1% |
| 8 | 78 | 0 | 1,70% |
| 9 | 94 | 0 | 1,3% |
| 10 | 207 | 8 | 23,1% |
| 11 | 274 | 20 | 41,9% |

of 1.3% (Table 2).

When analyzing the channel C from all patients, the fraction of time with pH below 4.0 ranged from 19.7% to 95.2% with a median of 38.7% (Table 3).

When comparing the results obtained in channels A and B, there was a significant increase in the number of reflux episodes in channel B and the fraction of time with pH <4.0. There was an increased number of prolonged reflux episodes, but without statistical significance (Table 4).

The results obtained in channels B and C allow us to observe that in all cases a significant reduction of acid exposure at the level of channel B compared to channel C, demonstrating the ability of the fundoplication to contain the ultra-distal reflux (Table 5).

**TABLE 3** - Results obtained in the channel C

| Patient | % Time pH <4 |
|---|---|
| 1 | 26,4% |
| 2 | 20,4% |
| 3 | 28,1% |
| 4 | 38,7% |
| 5 | 39,4% |
| 6 | 72,4% |
| 7 | 19,7% |
| 8 | 29,1% |
| 9 | 62,0% |
| 10 | 77,3% |
| 11 | 95,2% |

**TABLE 4 -** Comparison of results between channels A and B

| Variable | Comparison | Average | Median | p |
|---|---|---|---|---|
| Nº. of episodes | A<br>B | 8,091 (16,724)<br>91,273 (84,854) | 2<br>78 | 0,0010 |
| Nº. of prolonged | A<br>B | 0,364<br>3,091 (6,107) | 0<br>0 | 0,1526 |
| % Time pH <4 | A<br>B | 1,055 (2,916)<br>7,509 (13,221) | 0,1<br>1,3 | 0,0070 |

**TABLE 5**- Comparison of results between channels B and C

| Variable | Comparison | Average | Median | p |
|---|---|---|---|---|
| % Time pH < 4 | B | 7,509 (13,221) | 1,3 | 0,0008 |
| | C | 46,225 (26,070) | 38,7 | |

What is observed is that the reduction in acid exposure between the channels B and C is more pronounced than the increase in exposure between channels A and B, which also reinforces the assertion that the fundoplication was effective in containing the reflux, because the acid exposure at the level of the sphincter is very high and yet the esophagus is not exposed to the acidity (Figure 2).

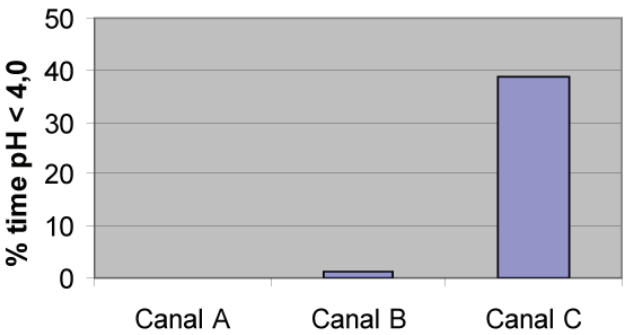


**FIGURE 2** – Comparison between acid exposure of channels A, B and C

During follow-up of these patients, two were diagnosed with esophageal adenocarcinoma.

## DISCUSSION

The interest of this study was to assess whether there is an effective method of study to determine the control of gastroesophageal acid reflux, with greater sensitivity than the tests currently used routinely. For this reason, the choice of the group of patients was based on strict criteria for control of reflux, to avoid the inclusion of questionable cases of control that could affect results.

To this end, it was chosen to include patients with treatment that is most effective in terms of control of reflux, which are those undergoing hiatoplasty and Nissen fundoplication, and without any clinical sign or laboratory tests that could suggest treatment failure.

Barrett's esophagus is a disease of clinical interest marked in particular by its association with the development of esophageal adenocarcinoma. The treatment of patients with this disease aims to interruption of gastroesophageal reflux, especially the acid component, so as to stop the progression of tissue damage and degeneration to prevent dysplasia and cancer.

There is evidence that patients with failure of medical and surgical treatment have increased risk of developing esophageal adenocarcinoma, by keeping the aggression metaplasia [19]. However, there is difficulty in explaining the occurrence of cancer in patients with apparent success of treatment as assessed by clinical and laboratory tests, even for esophageal pH monitoring.

The proposed methodology should ensure that the catheter does not influence the results. Published studies have previously shown that the presence of the catheter through the LES does not induce gastroesophageal reflux in both healthy volunteers and patients with GERD [20,21].

Another crucial point is that the channel B must always remain in contact with the esophageal mucosa. It is known that the esophagus undergoes shortening during peristalsis, which could lead to distal migration of the B channel to the stomach and hinder the correct interpretation of the detection of acidic pH during the examination. Nevertheless, the catheter was not fixed to the esophageal mucosa. Fixing it is done endoscopically, which did not allow accurate positioning of the channels in relation to the upper edge of the LES, as standardized for the realization of conventional pH monitoring. Furthermore, the endoscopic fixing clip difficult catheter removal, requiring traction detachment to the clips, with a risk of laceration of esophageal mucosa and possible bleeding.

The shortening of esophageal peristalsis is the usual component, reaching up to 2 cm [22-24]. Thus, it is estimated that the B channel of the catheter can

vary its position in approximately 2 cm distally, ie. up to 1 cm below the top border of the LES.

Csendes et al. (1993), in a study involving a large number of healthy volunteers, compared the LES location by manometry and gastric esophageal transition (TEG) located by endoscopy, and noted that the TEG does not correspond to the lower border of the LES, but near the midpoint between the top edge and bottom edge [25] of the LES. Thus, in patients with sphincter of 3 cm in length, located approximately 1.5 cm below the upper edge of the LES and in cases where the LES measures 4 cm, 2 cm below the top edge.

Based on this information, it is known that the distal migration of the pH meter, which normally occurs during esophageal contraction would cause the B channel of the catheter be positioned within 1 cm below the upper edge of the LES, still in the distal esophagus, closer to the TEG, but not migrate to the stomach, even without setting the esophageal mucosa. Channel C, in turn, changes its position, which was close to the TEG, either in the distal esophagus and proximal stomach at the moment.

The D channel remains in the stomach and is not used as a measure of proximal migration of the catheter during the examination. The stomach has a pH not less than 4.0 in 100% of the time. The explanation for this is the buffering of gastric acid by saliva and food and the occurrence of bile reflux. Gastric pH monitoring studies show that this happens between 80% and 87% of survey time [26-27,] but in these studies, the catheter was placed in the gastric body, between 10 cm and 15 cm below the lower border of the LES. Katzka et al. (1998), in healthy volunteers, evaluated the pH region 5 cm below the top border of the LES, ie, coincident with the position taken by the D channel of this study. The data show that the fraction of time pH below 4.0 ranged from 0.9% to 76.1% with an average of 32.2% [28.] In this study, it was considered that the D channel should have at least the fraction of 50% of the time with pH below 4.0 as a parameter of no proximal migration of the catheter from its original position, which occurred in all patients.

The parameters for evaluation of reflux in the position of channel A are well established, since it coincides with the default position for performance of prolonged esophageal pH monitoring. Now with regard to channel B, there is no standardization for the interpretation of results. There are studies that were conducted in non-operated patients to compare the acid exposure seen in the study of conventional pH monitoring and a distal segment of the esophagus and all noted that this region is more exposed to pH below 4.0 than the region conventionally studied (5 cm above the superior border of the LES). However, there was great variation in results. In healthy volunteers, the percentage of time with pH below 4.0 ranged from 1.5% to 11.7%. In patients with GERD, the results ranged from 6% to 9.5% [15-18.]

In this study, was adopted as a criterion for evaluation of channel B fraction of 1.5% of the time limit of acid exposure. Thus, only patients with exposure at or below the minimum observed in healthy volunteers, as described in the above studies, would be considered as no change in acid exposure.

One patient of the group, despite good control of clinical, endoscopic and radiological gastroesophageal reflux postoperatively, showed pathological reflux in the usual location of esophageal pH. This shows that only pH monitoring can determine if there is really effective control of acid reflux, as already suggested by other authors [4,14,29,30,31.]

The median acid exposure in channel B was 1.3% lower than the parameter used for analysis. The results identified five patients with fractional acid exposure time above proposed as normal. Therefore, the multi-channel pH monitoring identified some cases with prolonged acid exposure in Barrett's esophagus, who were not identified by the conventional technique of pH monitoring. This demonstrates that the multi-channel pH study may add valuable data on the follow-up.

Comparing the results obtained in the channel A with the channel B, there was significant increase in acid exposure in B, although the median of channel B is still below the parameter used as a limit. There was also a significant reduction in acid exposure, about 30 times the channel C to channel B, which shows the efficacy of fundoplication in containing the acid reflux to the level of the distal esophagus.

Two patients were diagnosed with adenocarcinoma during the study. The first was with only 22 months after surgery for fundoplication. Is estimated six years the time required for the development of adenocarcinoma in Barrett's esophagus with low grade dysplasia [32.] Thus, the development of cancer in early postoperative period, as occurred in this case, it may not signify disease progression after surgery, but because of changes prior to surgery. However, the study draws attention pH monitoring of this patient. On channel A, he did not have any change, with 0% of time pH < 4.0 and DeMeester score of 0.5. However, on the B channel, he had 78 episodes of acid reflux, with 1.7% fraction of acid exposure. The second case occurred 72 months after fundoplication. This time period is the limit to be considered that possible changes prior to fundoplication were responsible for the development of cancer. This patient had normal pH monitoring on channels A and B, with 1.3% acid exposure time on channel B. This raises the possibility that perhaps the acid is not only factor involved in the evolution of metaplasia to dysplasia and cancer.

The finding of two cases of adenocarcinoma in this series does not allow us to conclude that fundoplication exerts a protective role or not in relation to esophageal cancer, because the small

number of cases studied precludes such a conclusion. Both patients had the diagnosis made by routine examination without symptoms. Had obvious injuries, not being diagnosed by biopsies of metaplastic epithelium. Nevertheless, endoscopy has enabled early diagnosis of malignancy in both cases; treatment with curative intent had a good outcome, both early and late. Thus, one may suggest that there was a benefit of endoscopic surveillance routinely performed in this service.

## CONCLUSIONS

There is significant reduction in acid exposure in the region 1 cm above the superior border of the LES when compared to the intra-sphincteric, demonstrating efficacy of fundoplication in reflux contain this level. Moreover, the region of the esophagus 1 cm above the upper edge of the lower esophageal sphincter is more exposed to acid than 5 cm above the superior border of the LES, but stay at low levels. The surgical treatment by the Nissen fundoplication in patients with Barrett's esophagus, allows significant reduction in acid exposure level in ultra-distal esophageal pH monitoring, and multiple channels constitutes an important technical procedure for comparative assessment of acid exposure in the various levels of the distal esophagus.

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