

# Characterization of esophageal motility disorders in refractory gastroesophageal reflux disease patients with esophageal symptoms

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### Citation:

Castañeda A, Hani AC, Leguizamo AM, Muñoz O, Ardila AF, Costa VA. Characterization of esophageal motility disorders in refractory gastroesophageal reflux disease patients with esophageal symptoms. *Rev Colomb Gastroenterol.* 2021;36(2):212-217. <https://doi.org/10.22516/25007440.678>

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Received: 16/10/20  
Accepted: 17/02/21



## Abstract

**Introduction:** Refractory gastroesophageal reflux disease (GERD) can lead to potential complications such as persistent esophagitis, esophageal stricture, Schatzki ring, and Barrett's esophagus. This study describes motility in patients with refractory GERD, and its association with esophageal symptoms. **Materials and methods:** An analytical observational study was carried out in a retrospective cohort of patients diagnosed with refractory GERD and esophageal symptoms who underwent high-resolution esophageal manometry and impedance testing. Clinical characteristics, demographics, and the association between motility disorders and esophageal symptoms are described. **Results:** 133 patients were included (mean age  $54.1 \pm 12.5$  years). Heartburn and regurgitation (69.2%), and esophageal dysphagia (13.5%) were the most common symptoms. Normal motility (75.2%), complete bolus clearance (75.2%), and ineffective esophageal motility (IEM) (18%) were the most frequent manometric findings. Type II and IIIb gastroesophageal junction were observed in 35.3% and 33.8% of the cases, respectively. Esophageal aperistalsis (3.8%) and Jackhammer esophagus (0.8%) were rare findings. Incomplete bolus clearance was associated with esophageal dysphagia ( $p=0.038$ ) and IEM ( $p=0.008$ ). No esophageal symptoms were significantly related to motility disorders. **Conclusions:** The results of the present study suggest that motility disorders are rare in patients with refractory GERD. They also suggest that esophageal motility disorders are not associated with the presence of esophageal symptoms and, therefore, the type of symptom experienced does not allow predicting the existence of such disorders.

## Keywords

Refractory gastroesophageal reflux; High-resolution manometry; Esophageal motility.

## INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most causes of consultation worldwide. Its prevalence has increased markedly in recent decades and is higher in North America (19.8%), compared with East Asia (5.2%), the Middle East (14.4%), Europe (15.2%), and Colombia (11.8%)<sup>(1-4)</sup>. Between 10% and 40% of patients with GERD have refractory reflux, defined as the persistence of symptoms despite optimal proton pump inhibitor (PPI) therapy

at double doses, 30 to 60 minutes before meals, for at least 8 weeks<sup>(5,6)</sup>. This refractoriness can lead to potential complications such as persistent esophagitis, esophageal stenosis, Schatzki's ring, and Barrett's esophagus that could end in adenocarcinoma<sup>(1)</sup>.

Previous studies show that the involvement of 1 or more protection systems is required to produce refractory reflux and the main ones are reduced integrity of the anti-reflux barrier, either caused by hypotonic lower esophageal sphincter (LES) or axial displacement between the sphinc-

ter and the crural diaphragm (hiatal hernia); incomplete clearance of acid and bolus contents which is altered in patients with abnormal peristalsis and impaired salivation; reduced mucosal integrity, with dilated intercellular spaces; and slow gastric emptying, which can lead to increased gastric distension and the onset of reflux events through transient LES relaxations. Inherent causes of drug processing are also described, depending on the genetic polymorphism of CYP2C19 activity; the presence of an acid pocket; hypersensitivity to reflux; eosinophilic, infectious or pill-induced esophagitis; the presence of comorbidities that cause an increase in intra-abdominal pressure, such as ascites; and the use of medications that delay gastrointestinal transit<sup>(5,7-11)</sup>.

Regarding esophageal motor disorders<sup>(12)</sup>, it has been described that a decrease in the capacity of the esophagus to clean the contents of reflux ends up generating refractoriness to management<sup>(9)</sup>. Published studies on motility disorders in patients with refractory reflux are limited and do not associate these findings with esophageal symptoms. In addition, there are no studies in this area of interest carried out in the Colombian population.

Consequently, this study describes motility disorders and their relationship to esophageal symptoms (analyzed using high-resolution esophageal manometry) in a group of patients with refractory reflux treated at a referral hospital in Colombia.

## METHODS

Analytical observational study based on a retrospective cohort. All patients over 18 years of age with refractory reflux<sup>(5,6)</sup> and esophageal symptoms who underwent high-resolution esophageal manometry plus impedancometry between July 1 and December 31, 2019, were included. Pregnant patients were excluded. The project was evaluated and approved by the Ethics committee of the Hospital Universitario San Ignacio (HUSI) and the Pontificia Universidad Javeriana.

Patients were identified from the procedure database of the Department of Gastroenterology and Digestive Endoscopy of the HUSI, Bogotá, Colombia. Demographic information and esophageal symptoms were extrapolated from a format designed for this purpose, which systematically records data obtained in a survey of all patients prior to esophageal manometry. This procedure was performed with equipment from Medtronic, Given Imaging (Medtronic, Los Angeles, California, USA).

Following multiple publications, including the Montreal Consensus, the diagnosis of gastroesophageal reflux disease was based on clinical parameters<sup>(4,13-15)</sup>, that is, typical or atypical esophageal symptoms, such as dysphagia or chest

pain, in patients in whom a heart etiology was already ruled out<sup>(4)</sup>. Cases of atypical extraesophageal symptoms were not included based on a lower level of agreement, as also stated in the consensus<sup>(4)</sup>. To define the symptoms of refractoriness, the pathophysiological mechanisms of refractoriness were taken into account (increased transient LES relaxations, hiatal hernia, LES hypotension, altered esophageal contractility, increased mucosal permeability and delayed gastric emptying), which are related to symptoms of dysphagia, non-cardiogenic chest pain, heartburn, and regurgitation<sup>(5)</sup>. Motility patterns and esophageal motility disorders were defined according to the Chicago 3.0 criteria<sup>(12)</sup>. Esophageal symptoms were defined according to the American College of Gastroenterology (13) guidelines for the diagnosis and management of GERD. *Typical reflux syndrome* was defined as *the presence of heartburn and regurgitation*.

Clinical, demographic and functional characteristics were described using central tendency and dispersion measures, according to the distribution of data. A Shapiro-Wilk test was used to assess the assumption of normality. Categorical variables were reported as absolute numbers and proportions. A Chi-square test ( $\chi^2$ ) was used to evaluate the association between symptoms and motility disorders. The STATA 15 statistical package was used for statistical analysis.

## RESULTS

A total of 133 patients were included and their demographic characteristics and type of symptoms are shown in **Table 1**. The majority of patients were women (72.2 %) with a mean age of 54 years ( $\pm 12.5$ ). All patients were being treated with a PPI. The most frequent symptom was heartburn and regurgitation (69.2 %), followed by esophageal dysphagia (13.5 %), oropharyngeal dysphagia (12 %), and non-cardiogenic chest pain (8.3 %).

**Table 1.** Demographic characteristics of patients and esophageal symptoms

Variable	n = 133
Average age (SD)	54.1 (12.5)
Female, n (%)	96 (72.2)
Symptoms n (%)	
- Oropharyngeal dysphagia	16 (12.0)
- Esophageal dysphagia	18 (13.5)
- Non-cardiogenic pain	11 (8.3)
- Heartburn and regurgitation (typical reflux syndrome)	92 (69.2)

SD: standard deviation.

**Table 2** presents the findings and motility disorders. Normal motility and complete bolus clearance were the most frequent (75.2 % for each). Ineffective esophageal motility (IEM) was the most common disorder (18%). The presence of aperistalsis in 3.8 % and jackhammer esophagus in 0.8 % of the patients was striking. With regard to manometric findings, type II and IIIB gastroesophageal junction (GEJ) were the most frequent (35.3 % and 33.8 %, respectively), while hypotonia of the lower esophageal sphincter (LES) was observed in 15 %. Other motility disorders were present in less than 1.5 % of patients.

**Table 2.** Findings on high-resolution esophageal manometry plus impedance manometry.

Manometric variables	Number of patients (n = 133)
GEJ type, n (%)	
- I	25 (18.8)
- II	47 (35.3)
- IIIA	16 (12)
- IIIB	45 (33.8)
Bolus clearance, n (%)	100 (75.2)
Achalasia, n (%)	
- 1	0 (0)
- 2	2 (1.5)
- 3	0 (0)
Outflow tract obstruction, n (%)	1 (0.8)
Distal esophageal spasm, n (%)	0 (0)
Jackhammer esophagus, n (%)	1 (0.8)
Aperistalsis, n (%)	5 (3.8)
IEM, n (%)	24 (18)
Fragmented peristalsis, n (%)	0 (0)
Normal motility, n (%)	100 (75.2)
LES hypotonia, n (%)	20 (15)

LES: lower esophageal sphincter; IEM: ineffective esophageal motility; GEJ: gastroesophageal junction.

The association between manometric disorders with heartburn and regurgitation is shown in **Table 3**. When comparing patients with these symptoms, none were significantly associated with any finding or motility disorder, and most had normal manometry. For the other esophageal symptoms, it should be noted that no significant associations were found with any type of motility finding or disorder.

Patients with incomplete clearance presented with more esophageal dysphagia than those with complete clearance (24 % vs. 10 %,  $p = 0.038$ ). Likewise, IEM was associa-

ted with delayed clearance (33 % vs 13 %,  $p = 0.008$ ). All patients with type II achalasia and aperistalsis had delayed bolus clearance. Among patients with normal motility, 86 % had complete clearance compared with only 14 % with motility impairment ( $p < 0.005$ ).

**Table 3.** Association between typical reflux syndrome and manometric disorders

Esophageal manometry variables	Heartburn and regurgitation (n=92)	No heartburn and regurgitation (n=41)	p-value
GEJ type, n (%)			0.73
- I	16 (17.4)	9 (22)	
- II	35 (38)	12 (29.3)	
- IIIA	10 (10.9)	6 (14.6)	
- IIIB	31 (33.4)	14 (34.5)	
Bolus clearance, n (%)	71 (77.2)	29 (70.1)	0.42
Achalasia, n (%)			
- 1	0 (0)	0 (0)	
- 2	2 (100)	0 (0)	0.34
- 3	0 (0)	0 (0)	
Outflow tract obstruction, n (%)	1 (100)	0 (0)	0.50
Distal esophageal spasm, n (%)	0 (0)	0 (0)	
Jackhammer esophagus, n (%)	1 (100)	0 (0)	0.50
Aperistalsis, n (%)	2 (40)	3 (60)	0.15
IEM, n (%)	19 (20.6)	5 (12.2)	0.24
Fragmented peristalsis, n (%)	0 (0)	0 (0)	
Normal motility, n (%)	68 (68)	32 (32)	0.61
LES Hypotonia, n (%)	13 (14.1)	7 (17)	0.66

LES: lower esophageal sphincter; IEM: ineffective esophageal motility; GEJ: gastroesophageal junction.

## DISCUSSION

Refractory GERD has an impact on the risk of complications such as persistent esophagitis, esophageal stenosis, Schatzki's ring, and Barrett's esophagus that could end in adenocarcinoma<sup>(1)</sup>. The factors that impact refractoriness include alterations of the anti-reflux barrier, impaired esophageal clearance, reduced mucosal integrity, slow gastric emptying, causes inherent in pharmacodynamics, and esophageal motility disorders<sup>(5,9)</sup>. The present study found that most patients with refractory GERD have no associa-

ted manometric disorders and that IEM was the most frequent among those with some alteration. Moreover, it was found that the presence of esophageal motility disorders is not related to the presence of esophageal symptoms.

Most of our patients were women (72.2 %) with a mean age of 54.1 years, findings consistent with those reported by Abdallah, who found a higher prevalence of the female sex (68.8 %) and a mean age of 46.6 years<sup>(10)</sup>. On the one hand, normal esophageal manometry was the most frequent finding (75.2 %) and IEM was the most common motility disorder, which is consistent with previous publications<sup>(7,9,16)</sup>. On the other hand, we found that type II (35.3 %) and IIIB (33.8 %) GEJ were the most frequent findings in relation to the presence of hiatal hernia, results in proportion higher than those reported in other studies that document up to 18 % of hiatal hernia in the context of refractory reflux.<sup>(10)</sup> These findings could be related to the volume of patients evaluated in our study since HUSI is a referral center.

The presence of major motility disorders such as jackson esophagus and aperistalsis was noteworthy, although they were infrequent (proportion less than 3.8 %). Previous publications have already found an association between symptoms suggestive of reflux and major motility disorders, findings that could be explained by insufficiency in primary peristalsis or by a vigorous and sustained response (spastic) to abnormal exposure to reflux<sup>(6,8,9,16)</sup>. A probable evolutionary sequence has even been proposed, going from a minor disorder to a major one in the context of hypomotility<sup>(17)</sup>. Spastic motility may occur concomitantly or as a result of other conditions, such as GERD, resulting in hypercontractility. Furthermore, it has been described that they can improve with PPI therapy<sup>(18,19)</sup>. Reflux may be regarded a sign of a major underlying motility disease; nonetheless because GERD is the most common, it is critical to identify underlying causes of resistance to PPIs.

Heartburn and regurgitation (typical reflux syndrome; 69.1 %) were the symptoms most frequently associated with refractory reflux, findings consistent with data published by other authors<sup>(10)</sup>. Our findings suggest that the type of symptom does not predict whether there is a motility disorder or not, which acquires important clinical significance when evaluating these patients. Patcharatkul and

Ala *et al.* agree with our findings in that there is a poor association of typical symptoms with some type of esophageal dysmotility, suggesting that there is usually no esophageal contraction during the onset of these symptoms<sup>(16,17)</sup>.

Alterations in esophageal motility are known to be factors related to bolus clearance. In agreement with our study, Roman and Bulsiewicz<sup>(20-22)</sup> demonstrated that spatial separation or absence of peristalsis is associated with incomplete bolus transit and probably esophageal dysphagia. However, abnormal bolus clearance can be observed in patients with normal motility, findings also described by Bogte<sup>(23,24)</sup>. Regarding motility disorders associated with elevated integrated relaxation pressure (IRP), previous studies show that patients with achalasia present with altered bolus clearance compared with normal values for patients with outflow tract obstruction, findings similar to those described in our work. This secondary tool may be useful to differentiate between these two alterations<sup>(25)</sup>. In turn, failed contractions and ineffective contractility have been associated with incomplete bolus clearance and it has been shown that 30 % or more failed contractions and 70 % or more ineffective contractions have the best sensitivity and specificity to predict impaired clearance<sup>(26,27)</sup>.

The strengths of our study are the number of patients diagnosed with refractory GERD who underwent esophageal manometry and the characterization of motility disorders. However, limitations related to the retrospective nature of the study and the limited presence of some motility disorders should be acknowledged, as they limited the evaluation of the association with the symptoms evaluated. In addition, using clinical parameters to define the presence of gastroesophageal reflux in the absence of pH impedance and endoscopy in all patients assessed can be considered as a limitation; however, according to the Lyon Consensus<sup>(14)</sup>, these tests have a sensitivity and specificity of 70 % and 67 %, respectively, which makes evident the similarity of diagnostic performance when compared to clinical criteria. Finally, our results cannot be extrapolated to patients who are not receiving pharmacological treatment. Further multicenter studies are required to evaluate the association between refractory GERD and motility disorders with pH impedance findings.

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