Dysmotility and reflux disease

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Purpose of review
In the last decade, with the advent of new oesophageal testing [i.e. 24-h impedance-pH monitoring, combined impedance-manometry, high-resolution manometry (HRM)], relevant progress in understanding the mechanisms contributing to the development of gastro-oesophageal reflux disease (GORD) has been made, allowing a better management of patients with this disorder. The aim of our review is to report the state-of-the-art about oesophageal motor disorders in patients with reflux disease and to stimulate new research in this field.

Recent findings
Hypotensive lower oesophageal sphincter (LOS), transient LOS relaxations, impairment of oesophagogastric junction including hiatal hernia, oesophageal bolus transit abnormalities and presence of ineffective oesophageal motility have been strongly implicated in GORD development. In particular, the majority of recent studies carried out with HRM and impedance-pH testing reported that these motor abnormalities are increasingly prevalent with increasing severity of GORD, from nonerosive reflux disease and erosive oesophagitis to Barrett's oesophagus.

Summary
Defining and characterizing oesophageal dysmotility in patients with reflux disease is of maximum importance in order to properly diagnose these patients and to treat them with the best management of care. New studies are needed in order to better understand the physiomechanic basis of oesophageal dysmotility in GORD patients.

Keywords
gastro-oesophageal reflux disease, high-resolution manometry, hypotensive lower oesophageal sphincter, ineffective oesophageal motility

INTRODUCTION

Gastro-oesophageal reflux disease (GORD) is one of the most common gastrointestinal disorders in Western countries and its predominant symptom, that is heartburn, has been reported to occur at least once a week in up to 20% of the general population [1,2]. GORD may present with different manifestations, including Barrett's oesophagus, erosive oesophagitis and nonerosive reflux disease (NERD). The last one represents the majority of GORD patients, accounting for 60–70% of the reflux population [3▪▪]. In the last decade, relevant progress in understanding the pathogenesis of GORD has been made [4–9], although further advances are necessary to clarify these complex mechanisms.

His angle, competence of lower oesophageal sphincter (LOS), crural diaphragm, normal thorax-abdomen pressure gradient and adequate oesophageal motility are the main factors implicated in the protection against abnormal reflux from the stomach and/or duodenum into the oesophagus. Impairment of one or more of these mechanisms may favour gastro-oesophageal reflux, leading over time to typical/atypical GORD symptoms and/or oesophageal lesions [10]. In particular, hypotensive LOS, impairment of the oesophagogastric junction (OGJ), including both LOS and crural diaphragm, and ineffective oesophageal motility (IOM) have been strongly implicated in GORD development [10]. Literature in this field has evolved over the past few decades in parallel with the advent of new oesophageal testing [i.e. 24-h impedance-pH monitoring, combined impedance-manometry, high-resolution manometry (HRM)] that has

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KEY POINTS

- Recently, thanks to the advent of novel oesophageal testing, such as impedance-pH monitoring and high-resolution manometry, relevant progress in understanding the mechanisms contributing to the development of GORD has been made.
- Hypotensive LOS, TLOSRs, impairment of the oesophagogastric junction, including hiatal hernia, oesohageal bolus transit abnormalities and the presence of ineffective oesophageal motility, have been strongly implicated in GORD development.
- In particular, the majority of recent studies carried out with HRM and impedance-pH testing reported that these motor abnormalities are increasingly prevalent with the severity of GORD, from nonerosive reflux disease, erosive oesophagitis to Barrett's oesophagus.
- Defining and characterizing these oesophageal motor abnormalities is of paramount importance in order to properly diagnose these patients and identify those who could have more benefit from surgery due to the restoration of OGJ integrity or the reduction of TLOSRs.
- However, further studies are needed in order to better define the prevalence and the type of dysmotility disorders in the different types of GORD patients, thus providing the best management of care.

allowed a better understanding of these components and their role in the pathogenesis of GORD [4,11,12▪▪]. In particular, HRM-based studies underlined the relevance of OGJ impairment for the occurrence of acid and weakly acidic reflux episodes [13–16], whereas the majority of data regarding the frequency and the importance of hypotensive LOS and IOM come from studies carried out by using combined impedance-manometry [17,18,19▪▪,20].

The aim of our review is to report the state-of-the-art about oesophageal motor disorders in patients with GORD and to stimulate new research in this field.

MATERIALS AND METHODS

We performed a systematic computerized (Medline) and manual literature search for the period up to May 2013, with particular focus on the last decade. The following medical subject heading terms were used: 'GORD', 'gastro-oesophageal reflux disease', 'reflux disease', 'acid reflux', 'weakly acidic reflux', 'nonacid reflux', 'NERD', 'hypersensitive oesophagus', 'lower-oesophageal sphincter', 'oesophageal motility disorders', 'oesophageal transit abnormalities', 'bolus transit abnormalities', 'oesophageal dysmotility', 'hypotensive lower-oesophageal sphincter', 'ineffective oesophageal motility', 'impairment of the OGJ', 'pH-metry', 'impedance-pH testing', 'manometry testing', 'high-resolution manometry'. These terms were used alone or in combination with the following ones: 'definition', 'epidemiology', 'pathogenesis', 'pathophysiology', 'management', 'treatment', 'endoscopic therapy', 'surgical therapy', 'fundoplication'.

We critically reviewed all full-text articles and relevant abstracts published in English. The reference lists from the articles identified were searched to identify any additional studies that may have been missed during the process.

EPIDEMIOLOGY

Little is known about the epidemiology of oesophageal motility abnormalities in patients with GORD. Moreover, it is difficult to compare data from different studies because various definitions of oesophageal motility abnormalities, as well as GORD, in particular NERD, have been used [3▪▪]. The majority of studies referred to Spechler and Castell criteria to define oesophageal dysmotility and have been applied in investigations using conventional manometry testing [21]. The definition of hypotensive LOS and IOM, according to these criteria, is reported in Table 1 [21,22]. Moreover, in this context, it is fundamental to define two other oesophageal defects that participate in the occurrence of reflux events and oesophageal mucosal injuries, the transient LOS relaxations (TLOSRs) and bolus transit abnormalities (Table 1). The first one is considered to be the main mechanism of gastro-oesophageal reflux in both GORD patients and normal individuals [23–25]. Oesophageal bolus transit abnormalities are dysfunctions of the oesophagus [11,20,26], which may determine bolus stasis/retention within the organ and may occur despite a normal motility pattern, as we have recently demonstrated in patients with severe GORD and associated mucosal injuries [19▪▪].

In 1986, Kahrilas *et al.* [27] reported that peristaltic dysfunction (defined as failed or hypotensive primary peristalsis) was increasingly prevalent with the degree of peptic oesophagitis, occurring in 25 and 48% of patients with mild and severe oesophagitis, respectively. Moreover, they showed that even the number of patients with hypotensive LOS increased with the severity of reflux disease, but no correlation was found between the two motility abnormalities in the study population [27]. These results were later confirmed by Diener and colleagues, showing that severe IOM (presented in 21% of the patients) was associated with more severe GORD presentation [28], and by Quigley [29] and

Table 1. Manometric criteria for oesophageal motility and bolus transit abnormalities associated with gastro-oesophageal reflux disease

Conventional manometry	Hypotensive LOS: LOS basal pressure <10 mmHg
	Ineffective oesophageal motility: ≥30% wet swallows with contraction amplitude <30 mmHg in the distal oesophagus 3 and 8 cm above the LOS
	TLOSRs: periods (lasting 10–60 s) of spontaneous (not preceded by a swallow) LOS relaxation
High-resolution manometry with oesophageal pressure topography	Hypotensive LOS: LOS basal pressure <10 mmHg
	Weak peristalsis with large (i) and small peristaltic defects (ii):
	(i) Mean integrated relaxation pressure <15 mmHg and >20% swallows with large breaks in the 20 mmHg isobaric contour (>5 cm in length)
	(ii) Mean integrated relaxation pressure <15 mmHg and >30% swallows with small breaks in the 20 mmHg isobaric contour (2–5 cm in length)
	TLOSRs: periods (lasting more than 10–60 s) of spontaneous LOS relaxation characterized by
	(i) absence of swallowing for 4 s before to 2 s after the onset of LOS relaxation,
	(ii) relaxation rate of ≥1 mmHg/s,
	(iii) time from onset to complete relaxation of ≤10 s,
	(iv) nadir pressure of ≤2 mmHg.
	LOS relaxations associated with a swallow and fulfilling the above mentioned criteria (ii), (iii) and (iv) that lasted more than 10 s are considered as TLOSR
	Oesophagogastric junction:
	Type 1: no separation between the LOS and the crural diaphragm
	Type 2: minimal separation (>1 and <2 cm) making for a double-peaked pressure profile that is not yet indicative of hiatal hernia
	Type 3: more than 2 cm separation between the LOS and the crural diaphragm at inspiration so that two high-pressure zones can be clearly identified
	3a: respiratory inversion point distal to the LOS
	3b: respiratory inversion point proximal to the LOS
Bolus transit abnormalities	Incomplete bolus transit: if bolus entry occurs at the most proximal site (20 cm above LOS) and bolus exit is not identified at any one of the three distal impedance measuring sites (15, 10 and 5 cm above the LOS)
	Oesophageal transit abnormalities: if 30% or more of liquid swallows have incomplete bolus transit or if 40% or more of viscous swallows have incomplete bolus transit

LOS, lower oesophageal sphincter; TLOSRs, transient lower oesophageal sphincter relaxations.

Ho and Kang [30], who demonstrated that the mean resting LOS pressure was significantly lower in patients with erosive oesophagitis than in those with NERD.

Our group, comparing the main oesophageal pathophysiological characteristics among patients with Barrett's oesophagus, erosive oesophagitis and controls, reported that LOS basal pressure was significantly higher ($P < 0.01$) in controls than in patients with erosive oesophagitis and Barrett's oesophagus. Moreover, mean peristaltic wave amplitude was found significantly lower ($P < 0.01$) in Barrett's oesophagus and in patients with erosive oesophagitis than in controls [31]. When considering the different entities of NERD population, Frazzoni *et al.* [32] revealed that the mean LOS tone was significantly lower in NERD and erosive oesophagitis patients, than in controls and functional heartburn patients (NERD 18.5 mmHg vs. erosive oesophagitis 17 mmHg vs. controls 26.9 mmHg vs. functional heartburn 28.4 mmHg; $P < 0.05$) and that the mean distal oesophageal wave amplitude was lower in patients with erosive oesophagitis, than in patients with NERD, functional heartburn and controls (erosive oesophagitis 69.7 mmHg vs. NERD 87.2 mmHg vs. functional heartburn 101.5 mmHg vs. controls 99.3 mmHg; $P < 0.05$). They also found that the prevalence of hiatal hernia was significantly higher in NERD and erosive oesophagitis, than in functional heartburn and controls (NERD 49% vs. erosive oesophagitis 68% vs. functional heartburn 31% vs. controls 25%; $P < 0.01$) [32]. Comparing erosive oesophagitis with NERD, Wu *et al.* [33] observed that the former had lower LOS pressure (28.8 vs. 10.8%; $P = 0.002$) and more severe IOM (26.1 vs. 13.3%; $P = 0.03$). They also showed that

patients with erosive oesophagitis had more frequently hiatal hernia than NERD (35.1 vs. 17.7%, $P = 0.009$) [33]. More recently, we found that patients with reflux disease have a greater prevalence of oesophageal manometric abnormalities, in terms of abnormally low LOS pressure, IOM and hiatal hernia, compared with patients with functional heartburn and controls ($P < 0.01$). In particular, we observed that IOM gradually increased from controls and functional heartburn to NERD and from erosive oesophagitis to Barrett's oesophagus patients (controls 4% vs. functional heartburn 8% vs. NERD 19% vs. erosive oesophagitis 38% vs. Barrett's oesophagus 42%; $P < 0.01$) [19▪▪].

On the contrary, there are other studies in medical literature in contrast with the above data [34–36], in which no statistically significant differences were found in terms of hypotensive LOS and IOM frequency between erosive oesophagitis and NERD. However, in the majority of these studies, the authors defined NERD patients on the sole basis of a negative upper endoscopy and thus they erroneously included, among their NERD population, also patients with functional heartburn, who are characterized by motor and reflux features similar to controls [19▪▪,37–39]. This may have led to underestimating the frequency of motility abnormalities in NERD patients.

It is important to note that all the aforementioned studies were conducted with conventional manometry and not with HRM, which is nowadays the gold standard technique to assess oesophageal dysmotility. With this novel technique, the physiomechanic basis of oesophageal motility abnormalities is better defined. Using HRM, Daum *et al.* [40] showed that the frequency of oesophageal dysmotility in GORD patients was higher than that reported in previous studies done with conventional manometry [27]. In fact, they reported a peristaltic dysfunction in 56% of NERD and 76% of ERD patients, with no significant difference between the two groups. One possible explanation for these results is that more stringent criteria are adopted with HRM than with conventional manometry in order to define normal motility. Anyway, further studies with HRM are needed in order to better define the prevalence of oesophageal motor abnormalities in GORD and to clarify their implication in its pathogenesis.

CAUSE

Primary determinants of GORD occurrence are dysfunctional antireflux barrier and impaired oesophageal clearance. Antireflux barrier prevents reflux of gastric contents into the oesophagus, whereas peristalsis helps to clear the refluxate and reduce exposure to noxious components of gastric juice. In this context, there are three dominant mechanisms of reflux: TLOSRs, LOS hypotension or anatomic distortion of the OGJ inclusive of (but not limited to) hiatus hernia. Moreover, defects in the integrity of the peristaltic wave lead to impaired bolus transit and prolonged oesophageal acid and bolus exposure, thus determining the more severe forms of GORD.

TLOSRs differ from swallow-associated LOS relaxations in various aspects [41]. TLOSRs are not triggered by a swallow but by gastric distention-activated stretch receptors in the gastric wall, and the duration of TLOSRs is longer than that of swallow-associated LOS relaxations (Table 1). These may occur spontaneously with a relatively stable LOS pressure or immediately after the completion of a normal swallow-induced LOS relaxation. In patients with reflux, up to 75% of reflux events occur during TLOSRs, but the proportion of reflux episodes that can be attributed to TLOSRs reduces on the basis of the severity of GORD, probably due to the increasing prevalence of defective basal LOS pressure in patients with severe GORD. Moreover, TLOSRs appear to play a less important role for reflux episodes in patients with hiatal hernia than in patients without hiatal hernia [15]. It is important to highlight that recent studies showed that apart from acidic gastric contents, air and nonacid liquids can also escape from the stomach during a TLOSR [14,16].

Presence of hypotensive LOS (Table 1) [42] represents another major determinant for OGJ incompetence and then for the occurrence of reflux. It can be associated with hiatal hernia or not, but by itself alone has been strongly associated with the development of GORD. Indeed, several studies documented that patients with GORD have a reduced LOS basal pressure compared with healthy controls and that the mean value of this pressure is inversely correlated with the severity of GORD [19▪▪,27,29–33,43]. In particular, patients with Barrett's oesophagus and erosive oesophagitis usually present the highest frequency of abnormally low LOS pressure [19▪▪,31]. Disruption of OGJ can be related to an abnormal gastro-oesophageal flap valve [44], radial disruption of the crural canal [45] and hiatus hernia (Table 1). These defects are not mutually exclusive and can be cumulative in terms of their effect on disrupting the antireflux barrier. Moreover, using prolonged measurements, Bredenoord *et al.* [15] demonstrated that an intermittent separation of the LOS and the crural diaphragm occurred in GORD patients and was associated with increased acidic and weakly acidic reflux.

Finally, impaired oesophageal clearance prolongs the period during which aggressive gastric refluxate may damage oesophageal mucosa. Impaired clearance can be caused by motility abnormalities such as ineffective peristalsis or failed peristalsis [17,18]. Different studies documented an increased oesophageal acid exposure in patients with IOM and this association was found to be more evident when patients with severe GORD were evaluated [19▪▪]. Data supporting and confirming the relevance of oesophageal clearance for the development of GORD were derived from studies carried out in patients with scleroderma who are characterized by failed or absent peristalsis and low basal LOS pressure. These patients are frequently affected by GORD and are at a higher risk of developing Barrett's oesophagus or complications related to abnormal gastroesophageal reflux [46–48].

ASSESSMENT AND TREATMENT

The gold standard testing to diagnose oesophageal motility abnormalities is oesophageal manometry, a technique that measures intraluminal pressure changes of the oesophagus during swallowing. Nowadays, this evaluation can be done by using conventional (impedance-) manometry or high-resolution (impedance-) manometry with oesophageal pressure topography.

Coventional manometry includes the 'pull-through' technique, introduced by Fyke and colleagues in 1956, and 'sleeve' manometry, introduced by Dent in 1976, in which the maximum LOS pressure is measured continuously [49]. Current guidelines recommend pressure monitoring with four to eight sensors, including a sleeve sensor as the current gold standard for oesophageal studies [50]. With this technique, the criteria used to classify oesophageal motility abnormalities are those proposed by Spechler and Castell [21].

HRM, with up to 36 pressure sensors closely spaced (<2 cm), reveals the dynamic action of the upper oesophageal sphincter, the segmental character of oesophageal peristalsis and the functional anatomy of OGJ [51]. Moreover 'spatio-temporal' plots, constructed from HRM data, provide objective measurements of the forces that drive food and fluid from the pharynx to the stomach, establishing an objective link between pressure values and bolus movement/reflux events [51]. With HRM, on the basis of a systematic analysis of motility patterns [52], new criteria (Chicago classification) have been proposed to classify oesophageal motility abnormalities [53▪]. On the basis of this classification, IOM definition has changed by leveraging the spatial resolution of HRM to measure the actual defect lengths in the contractile wave fronts. Roman *et al.* [54] have defined that defects of 2–5 cm (weak peristalsis with small breaks) or greater than 5 cm (weak peristalsis with large breaks) are uniformly associated with impaired bolus transit. A distinct form of weak peristalsis associated with a defect in the transition zone or the proximal trough can be associated with dysphagia and poor proximal bolus clearance [55–57]. As to OGJ assessment, HRM permits to accurately assess the intrinsic LOS and the crural component contribution to the OGJ high-pressure zone (Table 1 and Fig. 1). The crural component can be assessed by measuring the inspiratory augmentation during baseline recordings and recent data suggest that this measurement may be a predictor of GORD [13]. In addition, the separation between the intrinsic LOS and crural diaphragm can be measured simultaneously during HRM studies to document the presence of hiatal hernia, as shown in Fig. 1 [58]. Finally, HRM represents an accurate method to detect TLOSRs associated with reflux events and can be used to predict the risk of having GORD [59].

Furthermore, the application of impedance technology to both these techniques offers the possibility to identify abnormal bolus transit during swallows and to correlate pressure data to real functional abnormalities of the oesophagus, as shown in Fig. 2 [11]. This additional information may help to predict the occurrence of dysphagia after reflux surgery, to detect TLOSRs associated with reflux episodes and to better identify patients who will benefit from endoscopic or surgical procedures [60].

In daily practice, following the AGA medical position statement on the management of GORD, oesophageal manometry is not indicated for diagnosis of GORD because motor dysfunction associated with abnormal reflux is nonspecific. Indeed, the main indications for manometry in these patients are to accurately locate the pH electrode 5 cm above the upper border of LOS and to exclude severe oesophageal motility disorders such as achalasia and absent peristalsis before antireflux surgery [61,62]. Moreover, recent studies highlighted the importance of manometry testing with concurrent pH and impedance monitoring in order to distinguish rumination syndrome from GORD in patients with predominant regurgitation [63▪].

Theoretically, treatment with prokinetic drugs such as metoclopramide, bethanecol and domperidone, given as mono or add-on therapy usually before meals, accelerates gastric emptying, increases LOS pressure or hastens clearance of refluxate from the oesophagus. However, the currently available prokinetics are poorly effective in treating this disease [64,65]. Moreover, the frequent central nervous

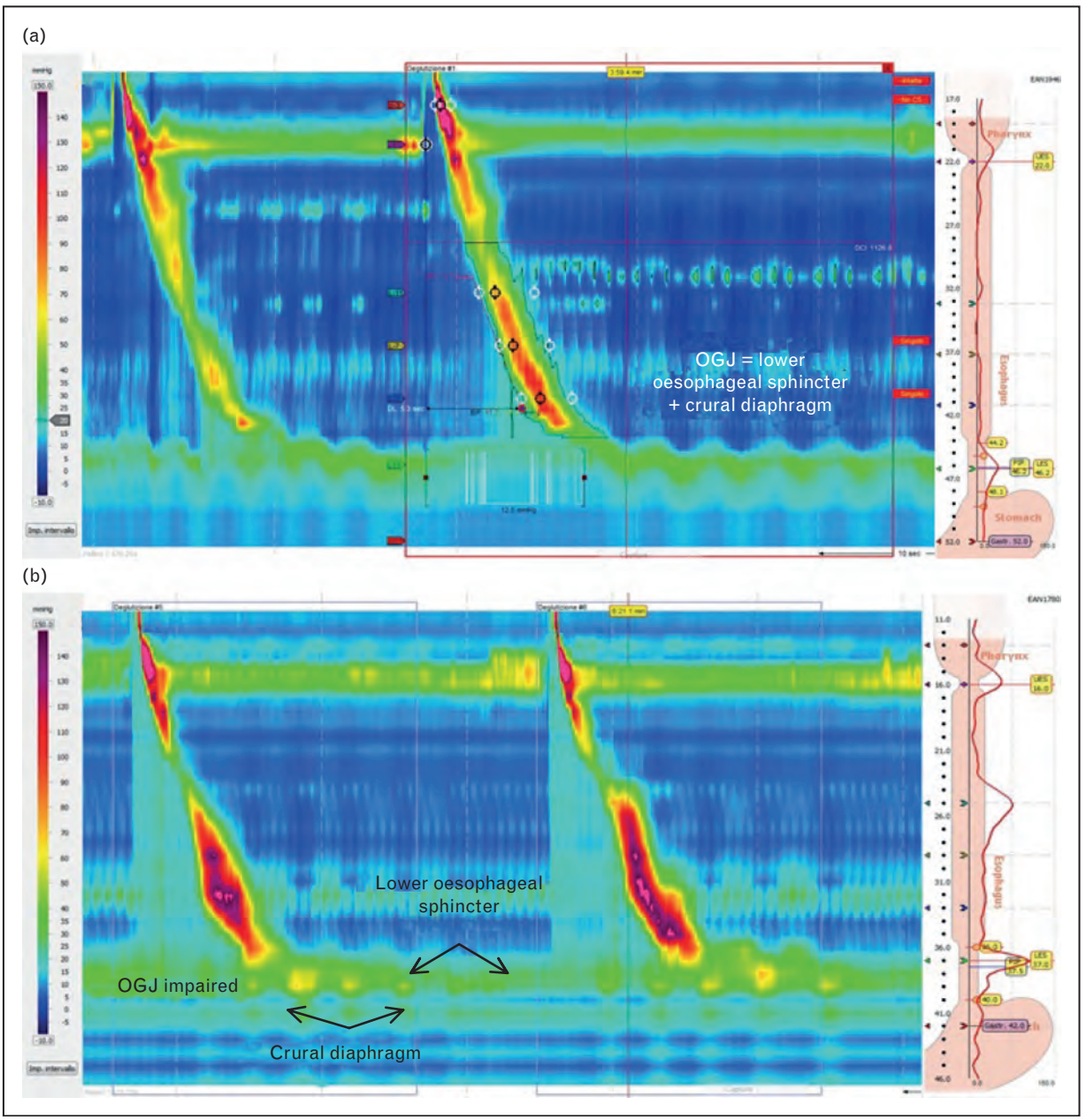

FIGURE 1. Portion of high-resolution manometry tracings showing an example of normal oesophagogastric junction (type 1) with no separation between the lower oesophageal sphincter (LOS) and crural diaphragm (a) and an example of impaired oesophagogastric junction (type 3) with more than 2 cm separation between LOS and crural diaphragm at inspiration so that two high-pressure zones can be clearly identified (b).

system side effects (drowsiness, irritability and so on) caused by the former two medications and hyperprolactinemia caused by domperidone in 10–15% of treated patients largely limit a widespread use of these drugs [66,67]. New prokinetics are desperately needed.

As most reflux episodes happen during TLOSRs, drugs able to inhibit this phenomenon could be useful to treat GORD. The γ-aminobutyric acid (GABA)B-receptor agonist baclofen reduces the incidence of TLOSRs and reflux episodes, but this drug is not suitable for treatment of GORD because of its central side effects [68]. Results of trials with new TLOSR inhibitors have been disappointing because of side effects and limited efficacy, but also the selection of the patients has been questioned [69].

To date, the only effective treatment of GORD-associated motility abnormalities is represented by surgical fundoplication that has been shown to be

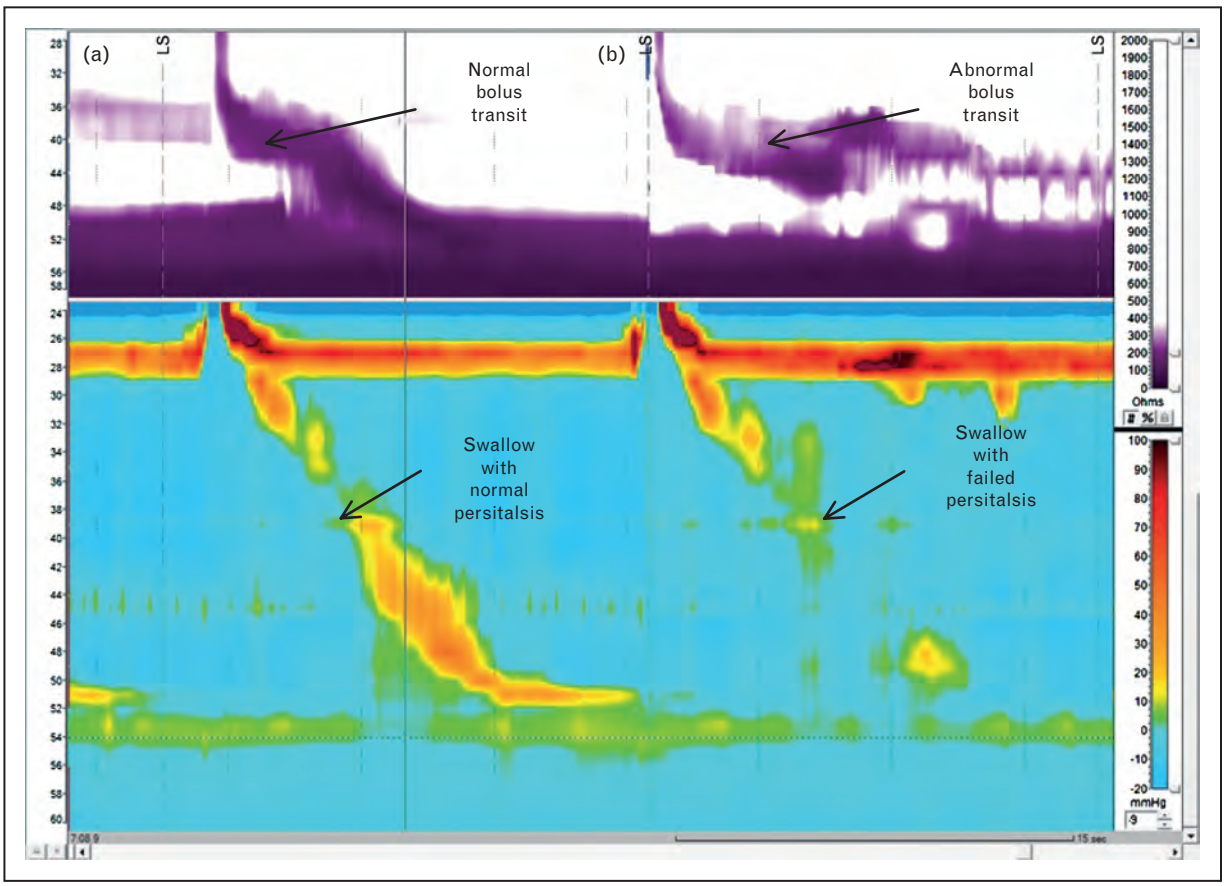

FIGURE 2. Portion of high-resolution impedance manometry tracing showing an example of complete bolus transit during a peristaltic swallow (a) and an example of incomplete bolus transit with bolus retention during a failed swallow (b).

able to reduce the volume of proximal stomach and to affect the rate of TLOSRs [70,71]. Moreover, fundoplication decreases the proportion of TLOSRs leading to reflux, due to the observed increase in nadir pressure during TLOSRs. Finally, the surgical approach permits to restore the abnormalities at the OGJ (including the correction of diaphragmatic crural defects, reestablishment of an intraabdominal oesophageal segment and enhancement of pressure and length of gastro-oesophageal high-pressure zone) and to modify the spatial separation of LOS and diaphragm (small and large hiatal hernia) that predisposes to acid and weakly acidic reflux [72]. All these effects on OGJ and TLOSRs lead to an effective reduction in reflux episodes and symptoms, as clearly demonstrated in several past and recent trials [73,74,75▪].

CONCLUSION

To date, the advent of new techniques, such as impedance-pH monitoring, combined impedance-manometry and HRM, has highlighted the cardinal importance of oesophageal motility abnormalities, in particular hypotensive LOS, TLOSRs, impairment of OGJ and presence of IOM, in the pathogenesis of GORD. To date, the majority of studies in this field report that these oesophageal motility abnormalities are increasingly prevalent with increasing severity of GORD, from NERD, to patients with erosive oesophagitis and Barrett's oesophagus. Thus, a more comprehensive diagnosis and characterization of reflux patients with oesophageal dysmotility is nowadays possible and this additional information may be of help in identifying patients who could potentially have more benefit from surgery due to restoration of OGJ integrity or reduction of TLOSRs. However, further studies are needed in order to better define the prevalence and the type of dysmotility disorders in the different types of GORD patients in order to enable the best management of care.

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Conflicts of interest

We declare no conflict of interest and no sources of funding.

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