Non-achalasic motor disorders of the oesophagus

Daniel Sifrim* MD, PhD
Professor in Medicine

Fernando Fornari MD, PhD
Research Fellow
Centre for Gastroenterological Research, Catholic University of Leuven, Belgium

Motor abnormalities of the oesophagus are characterised by a chronic impairment of the neuromuscular structures that co-ordinate oesophageal function. The best-defined entity is achalasia, which is discussed in a separate chapter. Other motor disorders with clinical relevance include diffuse oesophageal spasm, oesophageal dysmotility associated with scleroderma, and ineffective oesophageal motility. These non-achalasic motor disorders have variable prevalence but they could be associated with invalidating symptoms such as dysphagia, chest pain and gastro-oesophageal reflux disease. New oesophageal diagnostic techniques, including high-resolution manometry, high-frequency intraluminal ultrasound and intraluminal impedance, allow (1) better definition of peristalsis and sphincter function, (2) assessment of changes in oesophageal wall thickness, and (3) evaluation of pressure gradients within the oesophagus and across the sphincters that can produce normal or abnormal patterns of bolus transport. This chapter discusses recent advances in physiology, pathophysiology, diagnosis and treatment of non-achalasic oesophageal motor disorders.

Key words: dysphagia; chest pain; heartburn; oesophageal motility disorders; diffuse oesophageal spasm; connective tissue diseases.

* Corresponding author. Address: Faculty of Medicine, K.U. Leuven, Lab G-I Physiopathology, Gasthuisberg, O&N 1, 7th Floor, Herestraat 49, 3000, Leuven, Belgium. Tel.: +32 16 345752; Fax: +32 16 345939.
E-mail address: daniel.sifrim@med.kuleuven.ac.be (D. Sifrim).
of the two sphincters. Normal functioning of the two sphincters and oesophageal peri-
stalsis requires fine neuromuscular co-ordination. Motor disorders of the oesophagus
are characterised by failure of such co-ordination, with abnormal oesophageal peristalsis
and/or sphincter relaxation inducing stasis or excessive entry of material into the
oesophagus. Such abnormalities may be clinically manifested as dysphagia, chest pain
and symptoms due to excessive gastro-oesophageal reflux.

The best-defined primary oesophageal motor disorder is achalasia, which usually
culminates with severe symptoms and has a negative impact on quality of life. Achalasia
is discussed in Chapter 3. Other motor disorders of the oesophagus that are poten-
tially associated with severe symptoms include diffuse oesophageal spasm (DOS),
oesophageal dysmotility associated with scleroderma, and severe ineffective oesopha-
geal motility. This chapter discusses recent advances in physiology, pathophysiology,
diagnosis and treatment of these non-achalasic oesophageal motor disorders.

CLASSIFICATION

Several classifications of oesophageal motor disorders are available, either based on
standard manometric findings (Table 1)\textsuperscript{1} or a combination of manometric findings and
pathophysiological interpretation (Table 2).\textsuperscript{2} Recent advances in oesophageal diagnostic
techniques allow (1) better definition of peristalsis and sphincter function, (2) assess-
ment of changes in oesophageal wall thickness, and (3) evaluation of pressure gradients
within the oesophagus and across the sphincters that can produce normal or abnormal
patterns of bolus transport. These advances will certainly provide a new anatomical and
functional classification of oesophageal motor disorders.

NEW TECHNIQUES TO ASSESS OESOPHAGEAL
MOTOR FUNCTION

Classical techniques such as barium swallow radiography and standard oesophageal
manometry are used routinely in clinical practice to evaluate patients with suspected oe-
sophageal dysmotility. Although many patients can be diagnosed accurately with these
techniques, non-obstructive dysphagia or chest pain cannot be attributed to clear radi-
ological or manometric abnormalities in many other patients. High-resolution manometry
(HRM) is a stationary method that uses an increased number of pressure sensors (up to
36) and provides a very detailed map of oesophageal and LOS pressure changes. It allows

<table>
<thead>
<tr>
<th>Inadequate LOS relaxation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic achalasia</td>
</tr>
<tr>
<td>Atypical disorders of LOS relaxation</td>
</tr>
<tr>
<td>Unco-ordinated contraction</td>
</tr>
<tr>
<td>Diffuse oesophageal spasm</td>
</tr>
<tr>
<td>Hypercontraction</td>
</tr>
<tr>
<td>Nutcracker oesophagus</td>
</tr>
<tr>
<td>Isolated hypertensive LOS</td>
</tr>
<tr>
<td>Hypocontraction</td>
</tr>
<tr>
<td>Ineffective oesophageal motility</td>
</tr>
<tr>
<td>LOS, lower oesophageal sphincter.</td>
</tr>
</tbody>
</table>

\textsuperscript{1} Table 1. Classification of oesophageal motility abnormalities.
detection of segmental disturbances of peristalsis, decrease in pressure gradient across the LOS, and detailed analysis of axial movement of the LOS during peristalsis or gastro-oesophageal reflux.\textsuperscript{3,4} High-frequency intraluminal ultrasound (HFIUS) is a stationary method that allows continuous imaging of the oesophageal lumen and wall layers. The cross-sectional area of the oesophageal lumen and thickness of the muscle layers (circular and longitudinal) can be measured during rest and peristalsis. This technique allows measurement of oesophageal distension during swallowing or reflux, and evaluation of oesophageal shortening due to contraction (thickening) of the longitudinal muscle layer.\textsuperscript{5} The relationship between oesophageal pressure changes and bolus transport can now be assessed by combined intraluminal impedance and manometry.\textsuperscript{6–8} Intraluminal impedance allows a non-radiological assessment of oesophageal antegrade or retrograde flow based on changes in luminal electrical conductivity during the passage of a bolus. It can be used in both stationary and ambulatory conditions. Combined with manometry, it can assess the efficiency of different pressure patterns in terms of antegrade oesophageal clearance or prevention of retrograde movement during gastro-oesophageal reflux.

Although these new techniques offer a number of complementary advantages in the diagnosis of oesophageal motor disorders, they still require further validation and standardisation before they can be used in routine clinical practice.

**DIFFUSE OESOPHAGEAL SPASM**

The concept of oesophageal spasm was introduced by Osgood\textsuperscript{9} based on six patients with episodic chest pain and dysphagia. DOS\textsuperscript{10} is defined by episodes of chest pain and/or dysphagia, and simultaneous contractions in standard oesophageal manometry
(≥20% of wet swallows) interposed with normal peristalsis in the distal oesophagus \(^{11}\) and normal LOS relaxation. Recently, it has been proposed that this entity should be renamed ‘distal oesophageal spasm’ because most of the simultaneous contractions are concentrated in the distal oesophagus. \(^{12}\)

**Epidemiology**

The prevalence of DOS is less than 10% in patients with chest pain and/or dysphagia, and is 3–4% in series of unselected patients undergoing oesophageal manometry. \(^{13,14}\) Recently, DOS was diagnosed in 9% of 350 unselected patients and 10% of 40 patients with non-obstructive dysphagia evaluated with combined intraluminal impedance and manometry. \(^{7,15}\)

**Pathogenesis**

DOS may be associated with diffuse muscular hypertrophy or hyperplasia, mainly in the smooth muscle of the oesophagus. Muscular thickening of up to 20 mm has been reported in patients with clinical and manometric diagnosis of DOS. \(^{16}\) However, there are documented cases of oesophageal spasm without muscular thickening, \(^{17}\) and patients with muscular thickening that is not clearly associated with DOS. \(^{18}\) Recent studies using HFIUS consistently found increased muscle thickness in the distal oesophagus of patients with DOS. \(^{19–21}\) In a small series of patients with DOS treated with surgical oesophagomyotomy, no histological abnormalities were demonstrated in the myenteric plexus. \(^{22}\) However, functional studies have suggested that the main pathophysiological abnormality in DOS is at the intrinsic inhibitory innervation that regulates latencies to contraction and ordered peristalsis. Simultaneous contractions in DOS are probably due to reduced swallow-induced inhibition, as demonstrated by incomplete relaxation of an artificial high-pressure zone created in the mid oesophageal body. \(^{23}\) Further experiments have attributed oesophageal spasm to altered endogenous nitric oxide (NO) synthesis and/or degradation. Administration of the NO scavenger human recombinant haemoglobin in healthy volunteers produced simultaneous contractions and chest pain. \(^{24}\) Additionally, the administration of NO synthase blocker NG-monomethyl-L-arginine in humans provoked a significant reduction in the latency period between swallows and the onset of contractions, resulting in increased propagation velocity of the peristaltic waves in the distal oesophagus. \(^{25}\) Recent studies with HFIUS showed distal muscle thickening, and the authors suggested that muscle hypertrophy could be secondary to reduced NO, known to control smooth muscle proliferation. \(^{20}\)

The mechanism producing pain in patients with DOS is not completely understood. Most studies have focused on patients with unexplained chest pain without confirmed diagnosis of DOS. Different mechanisms have been suggested, including transient ischaemia of the oesophageal wall, luminal distension and altered visceral sensitivity. \(^{26,27}\) High-amplitude contractions would decrease oesophageal blood flow and provoke oesophageal wall ischaemia. MacKenzie et al used microthermistors to measure the rewarming time of the chilled oesophagus, and found significant differences in patients with nutcracker oesophagus. \(^{28}\) To date, similar results have not been reproduced in DOS patients. In a study combining 24-h oesophageal pressure, pH and HFIUS, the majority of episodes of chest pain were preceded by a transient increase in oesophageal muscle thickness. These events were called ‘sustained oesophageal contraction’ (SEC). \(^{29}\) SEC reflects contraction of the longitudinal oesophageal muscle.
layer and is not accompanied by increases in intraluminal pressure (due to circular muscle contraction). SEC was associated with chest pain in all patients with a positive edrophonium test. The authors suggested that SEC results in ischaemia of the oesophageal wall and/or activation of oesophageal mechanoreceptors, which in turn are responsible for chest pain.5,29

Rao et al30 used impedance planimetry to perform oesophageal balloon distensions in patients with unexplained chest pain. Using isobaric distensions, hypersensitivity to oesophageal distension was found with lower thresholds for both first perception and pain. The greater reactivity to luminal distension may be partly attributable to the biomechanical properties of the oesophageal wall, i.e. patients with non-cardiac chest pain had a stiffer, less-compliant oesophageal wall compared with controls. In subsequent studies, the same investigators suggested that hypersensitivity, rather than hyperactivity, was the predominant mechanism underlying functional chest pain of oesophageal origin. This was based on the finding that elimination of contractions by atropine was associated with lowering of sensory thresholds during oesophageal balloon distensions.31

Diagnosis

Dysphagia for both liquids and solids is reported by 30–60% of patients with DOS.14,32 Dysphagia is intermittent, sometimes related to swallowing specific foods or liquids or food at extreme temperatures, and infrequently associated with food impaction. Dysphagia does not have a direct relationship with chest pain, but may be more severe during periods of pain. Unlike achalasia, dysphagia in DOS is not progressive and weight loss is rare. Chest pain is usually described as crushing or squeezing, often radiating to the neck or midline of the back and lasting for minutes to hours. DOS has also been diagnosed in gastro-oesophageal reflux disease (GORD) patients with chest pain.33 Other gastrointestinal symptoms typical of functional bowel disorders are reported with relatively high prevalence in patients with DOS. Symptoms of psychological dysfunction, especially those of anxiety and depression, are common.34 It must be emphasised that patients presenting with chest pain should have careful cardiological evaluation before a diagnosis of DOS is considered.

Radiology

An oesophagogram may show indentations of the barium columns in the smooth muscle portion of the oesophagus and delay in oesophageal transit, intermixed with swallows of normal appearance. Barium indentations are produced by dysfunctional circular muscle contractions that, in extreme situations, trap barium between powerfully contracted segments. This distorted radiographic appearance has been described as a ‘corkscrew oesophagus’, a ‘rosary bead oesophagus’ or as oesophageal ‘curling’.35 Additionally, sliding hiatus hernias appear to be more frequent in patients with the spastic disorders, possibly because of oesophageal shortening during intense muscle contraction.36 It must be emphasised that these radiological findings are not specific for DOS and may be observed in asymptomatic individuals.37

Standard and ambulatory manometry

At present, manometric evaluation of the oesophagus is considered to be the gold standard in patients with suspected DOS. The most accepted criteria for characterisation of DOS is the presence of simultaneous contractions following at least 20% of wet
swallows, intermixed with normal peristaltic sequences.\textsuperscript{11,13} The latter requirement helps to differentiate between DOS and achalasia. However, simultaneous contractions can also be found in a variety of disorders, including diabetes mellitus, alcoholism, amyloidosis and scleroderma, as well as in patients who have GORD without other diseases.\textsuperscript{38}

Besides simultaneous contractions, other manometric abnormalities have been described as associated findings, such as repetitive (more than two peaks), prolonged (>6 s), high-amplitude (>180 mmHg) and spontaneous contractions, as well as increased LOS pressure (>40 mmHg).\textsuperscript{2} As DOS has a low prevalence and intermittent characteristics, radiology and manometry have limited diagnostic sensitivity. Ambulatory 24-h manometry has been proposed to improve the diagnosis of DOS. In a study using both ambulatory and stationary recordings, Barham et al showed that stationary manometry failed to detect the majority of patients with DOS, and many patients were incorrectly diagnosed with DOS on the basis of asymptomatic manometric findings.\textsuperscript{39} Although prolonged ambulatory manometry showed higher sensitivity and specificity for DOS diagnosis, it remains a research tool and has not been generally accepted in the clinical setting.

**High-frequency intraluminal ultrasound**

Using HFIUS, Pehlivanov et al\textsuperscript{21} reported increased distal oesophageal muscle thickness in patients with DOS. The same group assessed muscle cross-sectional area (MCSA) at the LOS and distal oesophageal body in normal subjects and patients with primary motor disorders. Muscle thickness and MCSA were greatest in achalasia, followed by DOS and nutcracker oesophagus.\textsuperscript{20} There appears to be a relationship between increased MCSA and the perception of dysphagia. The authors suggested that, in patients with dysphagia, a thicker distal oesophageal wall may be a marker of outflow obstruction due to incomplete sphincter opening, even if conventional manometry shows normal LOS relaxation.\textsuperscript{19}

**High-resolution manometry**

Diagnosis of DOS with HRM has not been standardised. Simultaneous contractions in a restricted oesophageal segment can be identified with HRM. Boluses trapped within the non-propagating region can, at times, be identified as short, isobaric stripes.\textsuperscript{40} Although reported in a single patient, normal LOS relaxation during standard manometry may be a misdiagnosis in these patients, instead being a pseudorelaxation of the LOS (short or incomplete) better identified by HRM.\textsuperscript{3} A recent study with HRM described distal oesophageal peristaltic abnormalities in 281 non-achalasic patients. DOS, as defined conventionally by standard oesophageal manometry, was very rare in this series. Moreover, spasm associated with severe dysphagia and chest pain occurred three times more often in the setting of a normally conducted contraction, named spastic nutcracker, challenging the conventional diagnostic criteria of DOS.\textsuperscript{4}

**Combined impedance and manometry**

Recent studies using combined impedance and manometry reported that only half of the patients with DOS had abnormal transit for liquid boluses. These studies recognised two patterns of oesophageal dysfunction according with the main symptom; patients with chest pain had higher-amplitude contractions associated with normal bolus transit, whereas those with dysphagia had abnormal bolus transit and contractions of
Conchillo et al used combined impedance and manometry to evaluate DOS patients with dysphagia, and found impaired oesophageal transit for liquid and/or viscous boluses in two-thirds of cases.  

**Treatment**

Patients with chest pain resulting from DOS are often concerned that they have heart disease, and reassurance that their pain is oesophageal and not cardiac in origin can be helpful in managing the syndrome. Many patients may improve with confident reassurance alone, although to avoid ongoing concern, it is important not only to prove the absence of a cardiac disease or malignancy but also to establish a definite cause for the symptoms. It is unclear whether acid suppression may improve symptoms in patients with co-existing motor disorders and pathologic acid reflux. Adamek et al performed prolonged manometric and pH recording in 95 patients with non-cardiac chest pain. They observed a high rate of co-existence of hypermotility disorders and pathologic acid reflux. When patients with both disorders received omeprazole treatment, improvement in symptoms and reduction of pathologic acid reflux was observed. However, the hypermotility disorder persisted and patients did not become completely symptom-free, suggesting that the motor disorder did not depend on pathologic reflux. Few studies have dealt specifically with the contribution of GORD to chest pain in DOS, but data suggest that some patients improve using proton pump inhibitors. Accordingly, an empirical trial of such therapy is warranted in most cases.

DOS patients with dysphagia related to simultaneous high-amplitude contractions are treated with muscle relaxants. Treatments aimed at relaxing oesophageal smooth muscle may be helpful, specifically nitrates, calcium channel blockers and antimuscarinic agents. Anticholinergics have been suggested for the treatment of chest pain attributed to underlying motility abnormalities, but there are no controlled studies to justify this therapy at present. Nitroglycerin and long-acting nitrates have been shown to be beneficial in patients with symptomatic DOS. Several studies have examined the effect of the calcium channel blocker diltiazem on non-cardiac chest pain, but the results are conflicting with regard to symptom relief as well as the effect on oesophageal contraction amplitude. Nifedipine was shown to decrease the amplitude of oesophageal contractions in patients with nutcracker oesophagus, but it was no better than placebo for symptom relief after 6 weeks of treatment. Sildenafil, a phosphodiesterase inhibitor used for the treatment of sexual disorders, has a significant relaxant effect on oesophageal smooth muscle. Sildenafil has been used in experimental protocols in patients with achalasia and a small group of patients with non-achalasic primary motor disorders. Sildenafil decreases LOS pressure and the amplitude of contractions in the oesophageal body, and its effect in patients with DOS has only been described in case reports with controversial results.

Antidepressant medications are effective in some patients by modifying visceral pain perception. A beneficial effect on symptom relief was obtained with a low dose of trazodone in symptomatic patients with oesophageal contraction abnormalities. The selective serotonin re-uptake inhibitor (SSRI) citalopram is able to decrease oesophageal sensitivity in healthy controls, and a randomised placebo-controlled study found that the SSRI sertraline provided significant relief in patients with chest pain and normal coronary angiograms.

Injection of botulinum toxin in the distal oesophagus was reported to be beneficial in two open-label studies in patients with chest pain and spastic oesophageal motor
disorders. Injection of botulinum toxin into the LOS has resulted in pain relief in a substantial number of patients, but with the inconvenience of repetitive applications. Pneumatic dilation has been used with success in small series of patients with severe symptoms related to DOS and LOS dysfunction, unresponsive to medical therapy.

Finally, good results have been reported for some patients who were surgically treated with extended oesophageal myotomy and short total fundoplication. More recently, it was reported that a thoracoscopic oesophageal long myotomy provided substantial or complete pain relief in a subset of patients with non-cardiac chest pain with DOS or symptomatic hypertensive peristalsis. However, the present authors feel that surgical management of oesophageal chest pain is extremely rarely indicated, and this invasive procedure should be used with caution, reserved only for those patients who fail to respond to alternative treatments.

**OESOPHAGEAL INVOLVEMENT IN SCLERODERMA**

Most connective tissue diseases may impair oesophageal motility, predominantly affecting either the smooth muscle (scleroderma) or the striated muscle (dermatopolymyositis) in the oesophagus. Severe oesophageal dysmotility is most frequently observed in scleroderma. The gastrointestinal tract is involved in up to 90% of patients with scleroderma, and the oesophagus is the most frequently affected organ. Serious complications related to oesophageal involvement can occur in 50% of patients with scleroderma.

**Pathogenesis**

Three stages have been described in the development of oesophageal involvement of scleroderma: neuropathy, myopathy and fibrosis. The hallmark of the first stage is neural dysfunction due to arteriolar changes in the vasa nervorum. At this point, the smooth muscle may contract with methacholine, which acts directly on the muscle, but not with edrophonium, which enhances the effect of available acetylcholine by inhibiting its breakdown. The consequent muscle ischaemia characterises the second stage, leading to atrophy of the muscle layers. Finally, the muscle tissue is replaced by fibrosis, which then eliminates the response to methacholine.

In patients with systemic sclerosis, oesophageal wall thickness has been reported to be no more than 3 mm. Ultrasound images show hyperechoic areas within the normal hypo-echoic muscularis propria corresponding to fibrosis found on histological sections of the autopsy specimens. The smooth muscle in the oesophagus is most commonly affected, provoking feeble contractions in the mid and distal oesophageal body and low LOS pressure. The striated muscle in the oesophagus is less frequently affected.

Severe hypomotility in the oesophageal body and low LOS pressure promote increased gastro-oesophageal reflux and impaired oesophageal clearance, particularly in the supine position. Oesophagitis, with or without complications (ulcer or stenosis), is frequently observed in scleroderma.

**Diagnosis**

Oesophageal symptoms in scleroderma include dysphagia, odynophagia, heartburn and regurgitation. However, the absence of symptoms does not exclude oesophageal involvement. Basilisco et al found that patients with scleroderma may have impaired
oesophageal sensitivity to acid, suggesting that reflux symptoms are not a reliable guide to acid injury of oesophageal scleroderma.\textsuperscript{74}

Signs of oesophageal involvement include organ dilatation and damage related to gastro-oesophageal reflux, such as erosive oesophagitis, ulcers or strictures.

Patients with scleroderma are at particular risk for GORD due to several factors: (1) low or absent peristalsis; (2) reduced LOS pressure; (3) associated hiatus hernia (from shortening of the oesophagus); (4) gastroparesis; (5) autonomic nerve dysfunction; and (6) associated sicca syndrome (due to loss of salivary bicarbonate).

Oesophageal involvement in scleroderma can be evaluated with manometry, endoscopy, scintigraphy, barium oesophagogram and oesophageal pH-metry. Manometry has been considered as the gold standard, able to detect oesophageal dysmotility in early stages. The main manometric findings are feeble or abolished peristalsis in the smooth muscle of the oesophagus and hypotensive LOS.\textsuperscript{75} It is important to acknowledge that these manometric abnormalities are not specific for scleroderma. They can be observed in other connective tissue diseases and also in diabetes, severe alcoholism, amyloidosis, myxedema, multiple sclerosis and chronic idiopathic intestinal pseudo-obstruction. More importantly, similar hypomotility can be observed in severe end-stage GORD without scleroderma.

No data exist regarding any specific pattern for scleroderma on HRM. This technique may show early abnormalities at the transitional zone between striated and smooth muscle of the oesophagus, provided that scleroderma predominantly affects the latter.

A barium oesophagogram can be used to recognise oesophageal strictures, a potential serious complication related to systemic sclerosis. Additional information can be obtained regarding oesophageal transit ability, oesophageal dilation and associated hiatus hernia.

Endoscopic evaluation is useful to recognise and graduate mucosal damage, monitor Barrett’s metaplasia and treat eventual strictures. Endoscopic oesophagitis is found in 33–63\% of patients. It correlates with manometry, i.e. those with normal motility rarely have oesophagitis and those with severe motility disturbances usually have oesophagitis.

Although patients with systemic sclerosis frequently develop GORD, the prevalence of Barrett’s oesophagus (0–37\% with wide variation among the studies) is not significantly higher than that observed in GORD patients without scleroderma.\textsuperscript{76,77} Candida oesophagitis is more common in scleroderma-related GORD.

Twenty-four-hour pH-metry should be performed to evaluate the degree of gastro-oesophageal reflux. Patients with severe hypomotility may present high distal and proximal oesophageal acid exposure. Compared with patients without scleroderma with similar degrees of oesophagitis, patients with scleroderma had fewer reflux events but they were of significantly longer duration, and one study found that aperistalsis correlated better with proximal than distal reflux or LOS pressure. These findings indicate that the severity of reflux is determined to a greater extent by delayed clearance than low LOS pressure.\textsuperscript{78}

Monitoring of duodeno-gastro-oesophageal reflux with Bilitec has been suggested in order to assess the role of bile reflux in the pathophysiology of oesophagitis in these patients.\textsuperscript{79}

Oesophageal hypomotility and reflux may contribute to pulmonary disease by micro-aspiration of acid and by vagal stimulation from oesophageal acid causing bronchoconstriction. Oesophageal manometric abnormalities were more prevalent in patients with worse lung function and the most interstitial lung disease. Patients with oesophageal disease had faster deterioration of their lung disease over 2 years. Lung compliance was reduced in those with impaired oesophageal peristalsis and
low LOS pressure, compared with those with normal motility or those with impaired peristalsis alone.

Proximal and distal reflux recorded by pH monitoring correlated with lung function impairment. There were laryngeal changes in reflux, proximal reflux by 24-h pH testing, and evidence of aspiration by 99-tecnium sulphur colloid scan.

The association between oesophageal dysmotility and pulmonary disease may be a cause–effect relationship or simply two manifestations of scleroderma that evolve together.\textsuperscript{80}

High-frequency ultrasound images of the oesophageal wall may be useful to follow up thickness of the oesophageal wall and presence of fibrosis.\textsuperscript{69}

Multiple combined intraluminal impedance and manometry recordings have shown that patients with scleroderma have severe impairment of bolus transit associated with severe ineffective motility, similar to that observed in achalasia.\textsuperscript{7} Impedance planimetry demonstrated that patients with scleroderma have increased cross-sectional areas but normal distensibility.\textsuperscript{81}

Finally, scleroderma patients with severe gastro-oesophageal reflux have delayed gastric emptying that parallels the severity of oesophageal hypomotility.\textsuperscript{82,83}

**Treatment**

Patients with scleroderma and oesophageal involvement should be treated (1) to control the primary disease in order to stabilise the process, avoiding further oesophageal damage, and (2) to control GORD. Additionally, treatment of dysphagia and prevention of nutritional deficits are indicated when appropriate. It must be emphasised that early recognition of oesophageal dysfunction is important because patients may be asymptomatic for a long time despite the presence of oesophageal motor abnormalities. This recognition can prevent the development of serious complications, such as oesophageal strictures and Barrett’s metaplasia. Finally, current therapeutic modalities for GORD in patients with scleroderma include lifestyle modifications and medical treatment. There are two main therapeutic categories: (1) antisecretory agents, such as proton pump inhibitors, and (2) prokinetic agents, including domperidone, erythromycin, metoclopramide, cisapride (if there are no cardiac contraindications) and tegaserod. Partial fundoplication is considered as an alternative after failure of medical therapy. When surgery is indicated, partial fundoplication is often preferred in order to decrease the risk of postoperative dysphagia. Reports on results of antireflux surgery in scleroderma are controversial. Satisfactory outcomes have been published in scleroderma patients with aperistalsis and troublesome symptoms of gastro-oesophageal reflux,\textsuperscript{84} whereas other studies have suggested very limited success of surgery in these patients.\textsuperscript{85}

**SEVERE INEFFECTIVE OESOPHAGAL MOTILITY**

Ineffective oesophageal motility (IOM) designates a manometric pattern of peristaltic failure characterised by the presence of distal oesophageal contractions of very low amplitude (less than 30 mmHg) and/or non-transmitted proximal contractions. The definition of IOM is based on the concept that pressure waves in the distal oesophagus, with amplitudes lower than 30 mmHg, are associated with failure of bolus clearance measured either radiologically\textsuperscript{86} or scintigraphically.\textsuperscript{87} This manometric pattern was previously considered part of non-specific oesophageal motor disorders.\textsuperscript{88} Several
studies have shown that IOM is common in GORD, and most have proposed an important role of IOM for delayed oesophageal clearance after reflux. IOM is considered to be the cause of increased acid exposure, extra-oesophageal symptoms and dysphagia both before and after antireflux surgery. IOM can also be observed in patients with dysphagia without evidence of GORD.

**Epidemiology**

IOM is the most prevalent oesophageal motor disorder in GORD, being diagnosed in 20–50% of patients. In a large series of consecutive patients with reflux disease, IOM was diagnosed in 21% of patients, and its presence was associated with heartburn and respiratory symptoms. In a group of patients with respiratory symptoms associated with reflux, IOM was found in 53% of asthmatics, 41% of chronic coughers and 31% of those with laryngitis. The majority of GORD patients diagnosed with IOM have between 30% and 70% of their swallows followed by ‘ineffective contractions’, whereas a more severe form, with more than 80% of abnormal contractions, is less frequent and may represent 20–40% of all GORD patients with IOM. IOM was observed in approximately 30% of patients with non-obstructive dysphagia without GORD.

**Pathogenesis and pathophysiology**

Although the pathogenesis of IOM is not completely understood, data from experimental models of oesophagitis, in-vitro human tissue and a positive response to prokinetic drugs suggest impaired cholinergic stimulation as the main defect. To date, it is not completely clear whether IOM is a primary motor disorder or a secondary abnormality due to chronic inflammation. Experimental studies have shown that acute oesophagitis-associated oesophageal hypomotility can disappear after spontaneous healing. In patients with chronic erosive GORD, however, healing of oesophagitis with medical or surgical treatment is not associated with complete recovery of oesophageal dysmotility, suggesting a secondary, irreversible motor abnormality or a primary phenomenon. The reversibility of GORD-associated oesophageal hypomotility depends on the mechanism involved, i.e. impaired neuromuscular control, extensive fibrosis or severe muscle hypotrophy. Inflammatory mediators, such as interleukin-6 and platelet activating factor, produced during oesophagitis can diffuse through the oesophageal wall and reduce acetylcholine release from excitatory myenteric neurons to circular smooth muscle. Abnormal secondary peristalsis observed in GORD patients can be due to impaired cholinergic excitation, but also to a defective response to oesophageal distension involving peripheral mechanoreceptors on the afferent part of the reflex.

The authors recently tested the reversibility of mild and severe IOM using edrophonium. Approximately half of the patients with severe IOM reverted to mild IOM or normal peristalsis, suggesting that adequate cholinergic stimulation can improve oesophageal motility in those patients with partially preserved neuromuscular structures.

In spite of its high prevalence, the functional and clinical relevance of IOM remains controversial. IOM has been blamed as the cause of abnormal oesophageal clearance and increased acid exposure, extra-oesophageal symptoms and dysphagia both before and after antireflux surgery. Although a causal relationship has never been proven, prokinetic therapy has frequently been proposed to improve oesophageal peristalsis as part
of GORD treatment. In recent studies, the authors analysed the association between different degrees of IOM and prolongation of acid clearance and increased oesophageal acid exposure.\textsuperscript{101,112} The results showed that only severe IOM is associated with longer oesophageal clearance and the highest acid exposure, mainly in supine periods.

**Diagnosis**

IOM is a non-specific manometric diagnosis in the investigation of patients with GORD or patients with non-obstructive dysphagia. The classical criteria for IOM, as published by Leite et al,\textsuperscript{71} include hypocontraction in the distal oesophagus, with at least 30\% of wet swallows exhibiting any combination of the following abnormalities: (1) non-transmitted contractions (not propagated down the oesophagus), and/or (2) low-amplitude contractions (peristaltic contractions with amplitude \textless 30 mmHg). Other proposed characteristics, although not widely accepted, include simultaneous contractions with amplitude \textless 30 mmHg or absent peristalsis.\textsuperscript{1}

A recent study using HFIUS detected increased oesophageal wall thickness in half of the patients with IOM, similar to that observed in other primary motor disorders. Based on these results, the authors suggested that IOM is an heterogeneous group with different pathophysiological mechanisms, i.e. reflux disease vs oesophageal outlet obstruction.\textsuperscript{19}

IOM is defined by data obtained using standard manometry. At present, there are no data from HRM studies refining the diagnosis of IOM.

The combination of oesophageal manometry and impedance allowed re-assessment of the functional impact of ineffective oesophageal contractions.\textsuperscript{7} A recent study using these techniques indicated that one-third of patients with manometric diagnosis of IOM had ‘effective’ transit for both liquid and viscous swallows.\textsuperscript{98} Similar findings were reported by Nguyen et al,\textsuperscript{113} suggesting that the definition of IOM should be adapted to functional implications and should only be considered in patients with severe hypomotility and impaired bolus transit.

**Treatment**

Prevention of IOM may be achieved by adequate control of gastro-oesophageal reflux. Once established, IOM seems to be unmodified after antireflux surgery,\textsuperscript{105} oral prokinetic therapy\textsuperscript{114,115} or acid-suppressive medications.\textsuperscript{107,108}

A recent study found that GORD patients with mild IOM were very similar to those without IOM, i.e. equal levels of acid exposure, average clearance times, frequency of hiatus hernia and fasting basal LOS pressure.\textsuperscript{101} The results suggested that the presence of few ineffective contractions in a patient with GORD is unlikely to be an ‘independent’ cause of prolonged clearance and increased acid exposure. Targeting those few low-amplitude contractions with prokinetic agents will probably fail to produce a positive therapeutic effect.

However, in the process of developing treatment strategies in GORD, testing the reversibility of severe IOM in patients with oesophagitis could be useful to predict the response of these patients to new prokinetic drugs. For example, stimulation of oesophageal mucosal afferent pathways by adding capsaicin to food was reported to improve the motor performance of the oesophageal body in patients with severe IOM.\textsuperscript{116} Furthermore, intravenous administration of edrophonium reverted the hypomotility in half of the patients with severe IOM, suggesting preserved neuromuscular structures.\textsuperscript{101}
Non-achalasic motor disorders have variable prevalence but they may be associated with invalidating symptoms such as dysphagia, chest pain and GORD. DOS has a low prevalence but is associated with chest pain and/or dysphagia. The oesophageal wall is thicker and there is a functional impairment of intrinsic inhibitory neurons and/or a possible subtle outlet obstruction. Symptoms may be due to prolonged contractions (circular and/or longitudinal muscle) inducing ischaemia or hypersensitivity. The diagnosis is manometric, and combined impedance and manometry shows either low-amplitude contractions with abnormal bolus transit or high-amplitude contractions with normal bolus transit. Treatment is mainly pharmacological and includes antireflux therapy, muscle relaxants and antidepressives.

Oesophageal involvement can occur in 50% of patients with scleroderma. The pathophysiology includes neuropathy, myopathy and fibrosis mainly affecting the smooth muscle of the oesophagus. The main manometric findings are non-specific and include feeble or abolished peristalsis in the smooth muscle of the oesophagus and hypotensive lower oesophageal sphincter. Severe hypomotility promotes increased gastro-oesophageal reflux. Endoscopy and pH-metry are important for evaluation of GORD. Oesophageal hypomotility and reflux may contribute to pulmonary disease by micro-aspiration of acid and by vagal stimulation from oesophageal acid causing bronchoconstriction. Patients with scleroderma and oesophageal involvement should be treated (1) to control the primary disease in order to stabilise the process, avoiding further oesophageal damage, and (2) to control GORD with lifestyle modifications, proton pump inhibitors and prokinetic agents. Surgery is indicated with failure of medical therapy, and partial fundoplication is often preferred in order to decrease the risk of post-operative dysphagia.

IOM designates a manometric pattern of peristaltic failure. This manometric pattern was previously considered part of non-specific oesophageal motor disorders. IOM is common in GORD (diagnosed in 20–50% of patients) and is considered to be the cause of increased acid exposure, extra-oesophageal symptoms and dysphagia. Impaired neural cholinergic stimulation is the main pathophysiological defect. However, recent studies with HFIUS suggest that IOM is an heterogeneous group with different pathophysiological mechanisms, i.e. reflux disease vs oesophageal outlet obstruction. Despite its high prevalence, the functional and clinical relevance of IOM remains controversial. Recent studies with combined impedance and manometry have shown that only severe IOM (>80% of ineffective contractions) is associated with longer oesophageal clearance and the highest acid exposure, mainly in supine periods. To date, prokinetics have failed to produce permanent regression of IOM. However, better selection of patients for prokinetic treatment can be achieved by a bolus transit test and a positive response to cholinergic stimulation.

**Practice points**

- Motor disorders of the oesophagus must be investigated in patients with non-obstructive dysphagia, non-cardiac chest pain and GORD symptoms.
- The importance of manometric changes (standard or HRM) should be evaluated in terms of impairment of bolus transit or simultaneous pain episodes.
- Oesophageal muscle hypertrophy is frequently observed in these patients, suggesting oesophageal outlet obstruction that can be treated pharmacologically or with dilations.
- Mild and moderate ineffective oesophageal motility do not represent a significant clinical problem in GORD and should not be considered a contra-indication for antireflux surgery.

**Research agenda**

- Use of new diagnostic techniques to reclassify oesophageal motor disorders in terms of complete or segmental abnormalities, thickness of the oesophageal wall, impaired, exaggerated or unco-ordinated contraction of the longitudinal muscle layer, trans-sphincteric pressure gradients, preservation of liquid and solid bolus transit.
- Functional and morphological evaluation of the myenteric inhibitory innervation to the oesophagus in patients with DOS and segmental aperistalsis observed in HRM.
- Evaluation of proximal acid and non-acid reflux in patients with oesophageal scleroderma with severe hypomotility and suspicion of bronchial aspiration.
- Evaluation of new NO donors and/or smooth muscle relaxants in patients with spastic disorders and prokinetic agents in patients with hypomotility, based on acute response during laboratory studies.

**REFERENCES**


