Invited Review

Approaches to driving the evolving understanding of lower oesophageal sphincter mechanical function

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Abstract

This article reviews and places into context the development of lower oesophageal sphincter (LOS) manometry, the key technique for researching the mechanics of this region. The first of two major challenges, being able to record sphincter pressure accurately with generally available equipment, was solved by the advent of perfused manometry in the 1960s. The other main challenge was to achieve reliable, continuous recording of LOS pressure, despite the constant movements of the LOS relative to the manometric catheter. Though well documented, this challenge is still poorly understood and prioritised, as many clinical/diagnostic and research manometric studies use methods for LOS manometry that are invalidated by LOS movement. There are two techniques that can record continuously from the LOS, despite its movements: high resolution manometry (HRM), which uses multiple point pressure sensors spaced at 1 cm interval or less, and the sleeve, which is a single long sensor. HRM provides valuable additional information on the varied topography of pressure patterns across the gastro-oesophageal junction and how this can change in an individual, second to second. HRM especially, but also sleeve manometry continue to advance understanding of the mechanics of gastro-oesophageal reflux, to unravel the mysteries of the mechanics of hiatus hernia and the diaphragmatic hiatus, to define why antireflux surgery fails or causes dysphagia, to recognise patients with dysphagia due to isolated defects of LOS relaxation and to test novel therapies for reflux disease directed at LOS function. Ample evidence now exists that accurate monitoring of LOS and gastro-oesophageal junction pressures is important for the diagnostic assessment of many patients and for advancing research into several aspects of the mechanical function of the LOS and its surrounding structures. This evidence now needs to be better reflected in the methods used for routine clinical practice and research.

Key words: lower oesophageal sphincter, mechanics, manometry, reflux

Introduction

The growth of understanding about lower oesophageal sphincter (LOS) mechanical function in humans can be broadly divided into four major steps which in practice have been overlapping.

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Firstly, initial insights derived from animal studies helped focus efforts directed at recognising and understanding LOS function in humans. Secondly, it was necessary to develop techniques that were capable of signalling LOS pressure reliably. The third challenge was to develop approaches that solved the potentially confounding effects of the mobility of the lower oesophageal sphincter relative to an intraluminal recording probe. Once solutions had been developed which were able to address these challenges, approaches were developed which have given good insights into mechanical functioning of the sphincter through detailed spatial analyses of oesophagogastric junction pressures and correlations of LOS pressure with occurrence of flows across this region.

This review summarises the development of approaches to monitoring of lower oesophageal sphincter mechanical functioning in humans that are now capable of providing detailed insights into the mechanics of flow across the lower oesophageal sphincter which are relevant for both patient management and clinical research.

**Initial insights from studies in animals**

*Primitive manometry*

By the early 1900s, observations in animals led to general agreement that there was a sphincter that controlled flows between the oesophagus and the stomach. The first convincing observations of LOS function in animals, carried out in the late 1800s, were quite indirect, or used very primitive measures of motor function at the gastro-oesophageal junction, usually performed during acute experiments in anaesthetised animals (Ingelfinger, 1958). Notable among these studies were those of Langley in the rabbit which demonstrated that a tonic contraction of the most distal part of the oesophagus provided sustained resistance to flow of water into the stomach. This resistance was measured as a sustained head of pressure when the oesophagus was filled with water and sealed around a catheter (Fig. 1). With this methodology, Langley (1898) provided the most convincing evidence then available that electrical stimulation of the vagus caused inhibition of a measurable, tonic resistance to the flow of liquid from the oesophagus into the stomach.

*Early fluoroscopic observations*

Walter B Cannon, Professor of Physiology at the Harvard Medical School for most of his career, was the inventor of gastrointestinal X-ray fluoroscopy, and used this technique for studying the mechanical function of the gut in animals. His pioneering observations were described in his monograph, published in 1911 entitled “The Mechanical Factors of Digestion” (Cannon, 1911; Dent, 2006). Notably, fluoroscopy enabled Cannon to make his observations in awake, trained animals during both fasting and after food. Chapter 4 of his monograph deals with activities of the “cardia” which we now call the lower oesophageal sphincter (LOS). This chapter starts with the following text: “The thickened band of circular muscle at the junction of the oesophagus with the stomach—the cardiac sphincter or cardia—has the function of preventing the passage of material back into the oesophagus” (Cannon, 1911). These words leave no room for doubt about the existence of an LOS. It would have been reasonable to
Fig. 1. Schematic of the method used by Langley (1898) to monitor LOS function in the rabbit. The oesophageal body was sealed around a cannula connected to a water reservoir/manometer. The water pressure required to initiate flow across the LOS indicated the tone of the LOS.

generalise this to humans, yet more than 50 years after Cannon reported his observations, there was still argument as to whether there was such a thing as an LOS in humans since, at that time, there was no anatomical evidence of a sphincter in humans and physiological studies were conflicting. This conflict arose from not only the limitations of recording methods that were used for studies in humans, but also inadequate understanding of these limitations by those who used these techniques, or attempted to interpret data gathered with them.

Cannon’s conviction about the existence of an LOS was supported by his knowledge of the prior literature (Cannon, 1911; Ingelfinger, 1958) as well as being strongly reinforced by his own fluoroscopic observations. In his monograph he wrote the following: “In 1902 ... I noted repeated regurgitation from the stomach into the oesophagus .... The animal lay comfortably on a holder, unanaesthetised, and was examined by means of the X-rays .... Each regurgitation ... was followed at once by a peristaltic wave which pushed the escaped material back again into the stomach. Soon after it was thus restored, the cardia again relaxed and it again rushed out ...” (Cannon, 1911). This elegantly worded description not only captures the concept of gastro-oesophageal competence that is not easily explained by anything other than the action of a sphincter, but also introduces the concept of effortless “spontaneous” episodes of gastro-oesophageal reflux, with subsequent clearance of refluxate back into the stomach. These observations of the intermittency of effortless episodes of gastro-oesophageal reflux were largely forgotten in the ensuing 80 years of research into mechanisms of gastro-oesophageal reflux in humans.
The challenge posed by lower oesophageal sphincter manometry

During the first half of the 20th century, researchers attempted to record directly from the LOS with luminal probes designed to detect the “squeeze” or active closure forces of the sphincter. Recording of in vivo LOS function required two major capabilities—reliable measurement of the strength of LOS squeeze and capture of how this squeeze varied from second to second. It was also highly desirable that, for investigation of many aspects of LOS function, recording methods were suitable for use in humans and awake animals. Early in the 1900s, it was recognised that intraluminal manometry was the method of choice, but reliable techniques for monitoring of LOS pressure have been available only in the last 20 years.

Development of techniques capable of reliable signalling of sphincter pressure

Evolutions of non-perfused manometry

During the early 1900s, initial attempts at LOS manometry in animals used latex balloons connected to a simple mechanical recording device (Ingelfinger, 1958). Initially, most researchers used quite large balloons which straddled the sphincter. Maintenance of the balloon in position required a “railroad” approach with the tip of the recording catheter being passed through and held at a gastric stoma, making this a clumsy, invasive approach restricted to animals (Carlson and Luckhardt, 1914; Carlson et al., 1922). This method gave only a semi-quantitative recording of LOS activity, but despite this, insightful data were gathered on the vagal control of the LOS. The clumsiness, lack of spatial resolution of large balloons and the need for absolute pressure measurements led to use of miniature balloon catheters in both animal and human studies (Botha et al., 1957; Ingelfinger, 1958; Code et al., 1962). With hindsight, such catheters performed relatively well in detecting LOS pressure, when they were accurately positioned within the sphincter, but they were soon discarded in favour of bundles of water-filled, open-tipped or side-opening non-perfused catheters (Brody et al., 1940; Quigley et al., 1952). Unfortunately, as subsequent testing in a model sphincter showed, such catheters are inferior in their ability to signal sphincter pressure compared to a miniature balloon (Pope, 1967). Probably, the main factor that led to this ill-informed switch of manometric technique was the difficulty of making, positioning and passing balloon manometric catheters. It is remarkable that there were no formal attempts to evaluate the accuracy of non-perfused manometric catheters for measurement of sphincteric pressures before they were introduced into general use.

The major inaccuracy of non-perfused catheter manometry, caused by mucosal plugging of the side hole, especially within sphincters, was only revealed after they had been used quite extensively to gather data that when published, caused only confusion due to conflicting results. The first rigorous insights on the limitations of non-perfused catheters came from the validation studies of constant perfusion manometry, published in 1966 and 1967 (Harris et al., 1966; Pope, 1967; Winans and Harris, 1967).
Definition of the requirements for adequate sphincter manometry

Recognition of the need for perfusion of side holes

Demonstration of the major inaccuracies of non-perfused manometric catheters explained the conflicting published data on the existence of the LOS in humans. The finding that constant perfusion manometry and intraluminal transducers were able to detect sphincter pressure with accuracy (Harris et al., 1966; Pope, 1967; Winans and Harris, 1967) led to an almost euphoric blossoming of clinical and research evaluations of LOS function in humans with these methods.

Slow parallel development and adoption of intraluminal transducers

 Intraluminal transducers convert pressure to an electrical signal within the lumen at the site at which the pressure is generated. This method depended on miniaturisation and sealing of transducers and was developing in parallel with the methods discussed previously, which use external pressure transducers. A description of an intraluminal transducer for use in the gut was first published in 1943 (Wetterer, 1943). Adoption of this method was slow, even though Code and Schlegel (1958) demonstrated that an intraluminal transducer signalled model sphincter pressure with accuracy. Factors that impeded use of intraluminal transducers were their fragility, high cost, size, sealing them from the luminal environment and the difficulties of making probes with 3 or more transducers. Gradually, technical development has reduced the limitations of intraluminal transducers, which have the major advantage of signalling pressure accurately without the need for perfusion. Measurement probes are now available which have a diameter that is well tolerated in adults with up to 36 intraluminal transducers (Pandolfino et al., 2006a) (see below). Cost and susceptibility to damage are now less of an issue.

 All currently marketed intraluminal transducers are "point" sensors—that is, like perfused side holes, they detect pressure from a small length of the lumen of about 2 mm. The implications of this pressure sensing pattern to LOS manometry are substantial, as discussed below.

Understanding and dealing with lower oesophageal sphincter mobility

 The word "euphoric" was used advisedly above, since very few researchers and clinical oesophageal laboratories recognised the crucial impacts of the mobility of the LOS relative to a point pressure sensor, which, to give valid data, must record from the narrow zone of maximum LOS pressure. This zone represents a target about 3–4 mm wide in adults.

 The mobility of the LOS relative to the manometric catheter was first demonstrated definitively in the cat by Dodds and colleagues by use of simultaneous fluoroscopy and manometry (Dodds et al., 1974). Two major causes of LOS mobility relative to an anchored side-hole catheter were documented. Firstly, each quiet inspiration caused a downwards movement of the LOS large enough to displace the recording side hole away from the zone of maximum LOS pressure. Secondly, and more importantly, swallowing produced complete displacement of the recording side hole from the sphincter into the stomach, because of upwards traction on the gastro-oesophageal junction produced by contraction of the oesophageal body.
Generalisation of the data of Dodds et al. (1974) on LOS mobility to humans was very reasonable and supported by earlier fluoroscopic studies of movements of the human gastro-oesophageal junction (Berridge et al., 1966). Mobility relative to a manometric catheter in humans of a similar degree to the cat was eventually formally confirmed in manometric/fluoroscopic studies by Kahrilas et al. (1995). Data gathered with the recently developed technique of high resolution manometry (see below) further document the mobility of the LOS relative to a manometric catheter.

Remarkably, many oesophageal manometric laboratories involved in clinical diagnosis and research continue to use manometric methods that fail to compensate adequately for the inaccuracies caused by LOS movements, more than 30 years after this problem was prominently documented. Most important is the failure to recognise that single-channel side-hole or intraluminal transducer recordings are an invalid approach for measurement of all forms of LOS relaxation.

Approaches to dealing with lower oesophageal sphincter mobility

When a single manometric side hole or transducer is stationed with the aim of recording continuously from the zone of maximum LOS pressure, virtually all manometrists recognise that the recorded pressure is a mixture of real sphincter pressure changes and artefacts due both to cyclical respiratory-induced movements and gradual drift of the resting position of the recording point from the centre of the sphincter (Dent, 1976) (Fig. 2). Such drift can only be recognised by altering the manometric catheter position, which in itself usually disturbs sphincter pressure by causing swallowing. Implicit to derivation of values for LOS pressure from a single anchored focal sensor recording is the need to make judgements on which bit of a squiggly line is truly representative of maximum LOS pressure. In the absence of clear indicators, this judgement is very uncertain and so the data derived very open to interpretative error, or worse, observer bias.

In acute studies in animals, transfixing the catheter at the LOS with a pin has solved the problem of LOS mobility (Goyal and Rattan, 1976). This approach has limited applicability and other significant drawbacks.

In 1956, Fyke and colleagues (Fyke et al., 1956) advocated the use of the station pull-through of manometric sensors across the LOS to ensure that LOS pressure was at least sampled reliably by the sensor passing through the region of maximum pressure. Since then, this method has been in wide use, with some adaptations such as slow continuous or rapid pull-through. This approach is now obsolete, not only because of the existence of techniques that are able to monitor LOS pressure but also because pull-through cannot address the challenge for recording LOS relaxations, is poorly tolerated and likely to influence LOS pressure, and can only provide a limited number of samples of LOS pressure which can be highly variable over short time periods (Dent et al., 1980).

Manometric techniques that can cope with sphincter movement

The needs for technically adequate assessment of LOS motor function demand that maximum LOS pressure be recorded continuously both during and between swallowing. Since the LOS cannot usually be anchored to a manometric catheter, effective monitoring of its
Fig. 2. The 4 panels plot values of LOS pressure recorded during separate 5-minute period with the sleeve — and a perfused side hole — in an anaesthetised dog (Dent, 1976). No swallowing occurred, but bold arrows indicate deep breaths. At the start of each 5-minute period, the manometric catheter was positioned so that the side hole was in the zone of maximum sphincter pressure and then anchored at the mouth. No adjustments of catheter position were made during each 5-minute period. The two methods were in excellent agreement in period 3, but in the other periods, after reasonable initial agreement, the side hole recorded substantially lower levels than the sleeve, especially in later parts of the periods, suggestive of progressive displacement, despite the immobility of the dog. Deep breaths were sometimes associated with the start of persistent presumed side hole displacement. (Reprinted from Gastroenterology, Vol 71, Dent, J. "A new technique for continuous sphincter pressure measurement" 263–267 (1976), with permission from the American Gastroenterology Association).

pressure needs to be achieved despite the movements discussed above. This requirement was first met with a single long sensor, the sleeve (Dent, 1976) and more recently by the use of multiple closely spaced focal sensors, a technique now known as high resolution manometry (Pandolfino et al., 2005) (Fig. 3).

The perfused sleeve signals the greatest pressure anywhere along its length, so that, provided the sphincter does not move beyond its span, true maximum LOS pressure is signalled continuously (Dent, 1976). For adult humans, a 6 cm sleeve length appears usually adequate, though some episodes of transient LOS relaxation cause an upwards excursion of the LOS that can exceed the length of the sleeve (Pandolfino et al., 2006). A validation study and an extensive literature support the utility of the sleeve for monitoring of LOS pressure in both humans and animals (Dent, 1976; Mittal et al., 1995). The sleeve enabled recognition of transient LOS relaxations and their relationship to gastro-oesophageal reflux in healthy subjects and reflux disease patients (Dent et al., 1988; Mittal et al., 1995), but there has been relatively little direct
evaluation of the ability of the sleeve to signal LOS pressure changes in response to swallowing and abnormalities of this (Shi et al., 1998).

Over the years, researchers have been attracted by the option of an array of closely spaced focal manometric sensors to record from the LOS to ensure that maximum pressure is captured. For instance, Pert and colleagues reported on this approach (Pert et al., 1959), but the number of channels needed and other challenges made this approach impractical. High resolution manometry (HRM) only became a feasible approach with the development of computer-based polygraphs which could display and store data from unprecedented numbers of recording channels and implement novel data displays and analyses (Clouse et al., 2000). Manometric probes had to develop also; this happened for perfused manometry in the mid 1990s, when miniaturisation of manometric channels enabled development of manometric catheters of acceptable diameter which had at least 21 measurement channels (Clouse et al., 2000) (Fig. 3). In the last 3 years, experience has been building rapidly with the use of a manometry probe that has 36 intraluminal transducers spaced at 1 cm intervals interfaced with a purpose-designed computer display and analysis system (Pandolfino et al., 2006a) (Fig. 4). The recording points on the transducer probe span from the distal pharynx to the upper stomach and have a spatial resolution that enables effective capture of the LOS pressure profile no matter how much it moves relative to the catheter. The chain of recording points allows reliable correlation of LOS motor events with pharyngeal and oesophageal body pressure events.
Mechanical function of lower oesophageal sphincter

Development insights into lower oesophageal sphincter mechanical functioning

Control of flows in both directions is the key mechanical function of the LOS. As Cannon (1911) demonstrated, fluoroscopy alone can be very informative, but the mechanical activity of the LOS can only be deduced, on the basis of observed flows. Technically adequate simultaneous monitoring of pressure events between the pharynx and upper stomach enables direct evaluation of LOS motor activity, from which mechanics can frequently be inferred. Most is gained however by combining this manometric approach with recognition of trans-sphincteric flows demonstrated either fluoroscopically, or by oesophageal pH (Dent et al., 1980) or impedance monitoring (Sifrim et al., 2001) or by combinations of these three techniques.

Understanding abnormal resistance to flow into the stomach from the oesophagus

Achalasia is the most important and treatable primary cause of impeded trans-sphincteric flow which arises mainly from impaired relaxation of the LOS in response to swallowing (Clouse et al., 2000; Hirano et al., 2001; Staiano and Clouse, 2001). Use of the sleeve sensor and HRM has led to recognition of patients who complain of dysphagia who may have virtually normal oesophageal body peristalsis and not infrequently no oesophageal dilatation, but mechanically significant impairment of LOS relaxation (Shi et al., 1998; Clouse et al., 2000; Hirano et al., 2001;
Fig. 5. High resolution manometric plot of a swallow motor response showing the manometric pattern generated by a slipped fundoplication wrap which is below the level of the LOS. The diaphragmatic hiatus is probably mainly at the level of the slipped wrap. This could be clarified with physical manoeuvres that cause vigorous diaphragmatic contraction. (Kindly provided by Dr. G. Hebbard).

Staiano et al., 2001). Such patients who are thought to have variants of achalasia respond well to LOS-disruptive procedures (Hirano et al., 2001). HRM in patients who have usually little if any oesophageal dilatation and varying abnormalities of oesophageal body function has shown that the orad excursion of the LOS during swallowing is preserved (Clouse et al., 2000; Hirano et al., 2001; Staiano et al., 2001; Fox et al., 2004), explaining why “conventional” assessment of swallow-induced LOS relaxation with a single stationed side hole or transducer fails to detect the impaired relaxation (Fig. 4). HRM has been used recently to define normal patterns of swallow-induced LOS relaxation in considerable detail, enabling better recognition of defects of this function (Pandolfino et al., 2006b).

Insights into antireflux surgery

Technically adequate assessment of gastro-oesophageal junction pressures is important for understanding the dysphagia caused by a “too tight” antireflux surgical procedure. First sleeve sensor and then HRM studies have shown that antireflux surgery causes a minor impairment of the completeness of the swallow-induced reduction of gastro-oesophageal junction pressure (Ireland et al., 1993; Clouse et al., 2000) and that persistent, troublesome post-surgical dysphagia can be related to excessive impairment of this swallow relaxation response (Ireland et al., 1993; Scheffer et al., 2005). HRM also has the potential to be able to determine whether dysphagia is related to a too tight fundic wrap or a constrictive diaphragmatic hiatus (Kahrilas et al., 2000). HRM is not only a major advance in the assessment of dysphagia after antireflux surgery, it is also a powerful tool that now needs to be exploited systematically to define the mechanics of failed control of reflux (Fig. 5). The conceptual development and animal testing of novel endosurgical
antireflux procedures would be greatly facilitated if HRM were used as a tool for this research.

**Dissection of the mysteries of hiatus hernia**

The spatial resolution of HRM is sufficient to allow monitoring of the pressure profile across even small hiatus hernias (Fox et al., 2004) (Fig. 3). This allows analyses not possible previously by showing how gastric, diaphragmatic hiatal, hiatal sac, LOS and distal oesophageal body mechanics vary among patients (Pandolfino et al., 2003) and change from moment to moment (Bredenoord et al., 2006). Such studies are building on those of Mittal and colleagues with the sleeve and luminal electromyography which have clarified the significant role that contractions of the normally-positioned diaphragmatic hiatus play in bolstering the antireflux action of the LOS itself (Mittal and Balaban, 1997).

**Definition of mechanisms of gastro-oesophageal reflux**

The ability to monitor LOS pressure with the sleeve and the occurrence of reflux with pH monitoring enabled analysis of LOS motility at the time of acid reflux. This resulted in recognition of transient LOS relaxation as the most prevalent among several mechanical patterns associated with reflux episodes in patients with reflux disease (Dent et al., 1988; Mittal et al., 1995; Van Herwaarden et al., 2000). The sleeve has become an important tool for development of novel antireflux drugs directed at the LOS, but, as explained above, HRM is the only technique which can monitor and identify the pressures produced by all of the individual mechanical components around the gastro-oesophageal junction (Figs. 3 and 5). HRM also tracks dynamic variations of gastro-oesophageal junction anatomy, including its descent due to diaphragmatic traction with respiration (Pandolfino et al., 2006a) and elevation, ascribable to oesophageal longitudinal muscle contraction (Clouse et al., 2000; Hirano et al., 2001; Staiano and Clouse, 2001; Fox et al., 2004). When combined with fluoroscopy or pH monitoring and/or impedance monitoring, HRM is a powerful approach for understanding the detailed mechanics of individual episodes of gastro-oesophageal reflux. This approach now needs to be applied systematically to definition of LOS mechanical antireflux function at rest and during physical straining according to patterns of anatomical disruption of the gastro-oesophageal junction.

**Conclusions**

Insights into the mechanical function of the LOS have developed slowly because of limitations of the manometric methods that have been used by investigators since the early 1900s, and because of the publication of misleading data and commentary due to failure to adequately recognise these limitations.

During the last 50 years, systematic research has revealed the technical challenges of manometric assessment of the LOS and the structures around it. These challenges continue to be underestimated by many, even years after some were well defined. Unreliable measurement techniques continue to be used in both clinical diagnostic studies and in research studies and continuing publication of such data creates avoidable confusion.

Research into the challenges of manometric assessment has guided the development of
measurement approaches, so that technically valid monitoring of LOS pressure is now possible. High resolution manometry is a “breakthrough” method; available data already indicate that, when used for clinical diagnostic assessment of function at the gastro-oesophageal junction, it provides clinically important information that cannot be obtained in any other way. Especially when combined with measurement of trans-sphincteric flows, HRM is a potent tool for advancing the understanding of the mechanics of LOS function. Hopefully, the convincing demonstrations of movements of the LOS provided by HRM colour plots will lead to an acceleration of the abandonment of LOS manometry with a single focal-recording sensor.

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