HIGH RESOLUTION OESOPHAGEAL MANOMETRY IN THE INVESTIGATION OF RESPIRATORY SYMPTOMS

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High Resolution Oesophageal Manometry in the Investigation of Respiratory Symptoms

Background: It has been suggested that gastro-oesophageal reflux and aspiration are common precipitants in respiratory diseases such as asthma, COPD, and interstitial lung disease. Several studies have indicated reduced oesophageal motility as a factor in aspiration and poorly controlled gastro-oesophageal reflux causing respiratory symptoms, however, none have provided evidence that the motility profile of this group of patients differ from GORD sufferers exhibiting more typical symptoms. Recent studies have also highlighted the importance of the gastro-oesophageal pressure gradient (GOPG) in the prevalence of reflux.

Method: High Resolution Oesophageal Manometry (HRM) was performed in 121 patients, 61 of whom presented primarily with unexplained respiratory symptom (Group A). An age and sex matched control group was chosen from patients presenting with dyspepsia (Group B). The HRM findings of 61 patients (38 female), mean age 56, range (18-81) with respiratory symptoms were compared with the those of 60 suspected gastrooesophageal reflux disease (GORD) patients (39 female), mean age 57, range (19-81). Respiratory patients complained predominantly of chronic cough (50), or breathlessness (11).

Results: Mean LOS and UOS resting pressures were similar between the two groups. There was a significant difference in the number of intact peristaltic swallows with a larger number of intact swallows in Group B (58% vs 43%, P=0.03) than in Group A. Intraoesophageal pressure was significantly lower during inspiration in group A (-11.5mmHg vs -8.7, p=0.001). Consequently, a significantly higher GOPG was found in group A (46mmHg vs 33mmHg, $p<0.01$).

Conclusion: Using HRM, we have demonstrated a higher prevalence of oesophageal dysmotility in patients with unexplained respiratory symptoms than those with typical manifestations of GORD - a group in which reduced oesophageal motility is already widely documented. As well as this, we have shown that those with unexplained respiratory symptoms exhibit higher inspiratory GOPGs. Theoretically, our findings support the hypothesis that oesophageal dysmotility and an increased inspiratory GOPG could encourage both acid and non-acid aspiration and thus provoke respiratory symptoms such as cough and breathlessness.

ABBREVIATIONS

GOPG – GASTROOESOPHAGEAL PRESSURE GRADIENT
GOR – GASTROOESOPHAGEAL REFLUX
GORD – GASTROOESOPHAGEAL REFLUX DISEASE
HRM – HIGH RESOLUTION OESOPHAGEAL MANOMETRY
IRP – INTEGRATED RELAXATION PRESSURE
LOS – LOWER OESOPHAGEAL SPHINCTER
TLOSR – TRANSIENT LOWER OESOPHAGEAL SPHINCTER RELAXATION
UOS – UPPER OESOPHAGEAL SPHINCTER

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CHAPTER 1 – INTRODUCTION

The function of the oesophagus is relatively uncomplicated – it transports swallowed food from the mouth to the stomach. To meet its functional requirement, its design is simple; a muscular tube that is protected at each end by a lower and an upper sphincter.

Following the voluntary initiation of a swallow, the two sphincters relax and open in sequence and a peristaltic wave sweeps behind the swallowed bolus autonomously. Neuromuscular control mechanisms ensuring successful functioning of the two sphincters and oesophageal peristalsis are complex; fine coordination of the muscles and nerves at the level of the central and peripheral nervous system are required to guarantee the process.[1]

Abnormal motor activity in the oesophagus can result in a variety of complaints such as difficulty of swallowing, chest pain and acid reflux[2]. These problems can be diagnosed by oesophageal manometry which involves the trans-nasal passage of a pressure sensitive catheter in to the stomach - allowing for motor function assessment of the upper oesophageal sphincter (UOS), oesophageal body and lower oesophageal sphincter (LOS). Pressure sensitivity is achieved using a series of sensors located either within, or fixed directly to the catheter.

For several decades conventional oesophageal manometry has been the test of choice to assess oesophageal motor function, however, the accuracy of conventional manometry with as few as 3-5 sensors is limited by poor spatial resolution and can be complicated to interpret. This is largely due to the fact that the space between each sensor can be up to 5 centimetres; each section of the oesophagus therefore requires a separate evaluation with sections needing to be assembled to ascertain the overall motility profile within the oesophagus.

Conventional manometry endeavours to measure a number of physiological mechanisms within the oesophageal lumen. These measurements are used to evaluate the strength

and co-ordination of the contractions. Typically, the following measurements and observation are taken:

- lower oesophageal sphincter resting pressure
- upper oesophageal sphincter resting pressure
- relaxation of the lower oesophageal sphincter
- relaxation of the upper oesophageal sphincter
- peristaltic integrity, i.e. is the peristalsis intact/weak/failed

The recent introduction of high resolution manometry (HRM) for the study of oesophageal motor function has simplified the performance of oesophageal manometry, and uncovered previously unidentified patterns of normal and abnormal oesophageal motor function.

Whereas conventional manometry employs catheters with 3-5 unidirectional sensors, usually with a posterior orientation, HRM catheters, depending on their configuration can utilise up to 36 circumferential sensors spaced at one-centimetre intervals. Solid-state and water-perfused systems are available, the latter uses a catheter composed of a bundle of thin polyvinyl tubes with outward facing side holes, which function as point pressure sensors. A low-compliance pneumohyrdaulic pump slowly perfuses each of the tubes with water. The sensors in each of the side holes convert the reverberation they detect to an electrical signal via a volume displacement transducer. Since water perfused catheters can house fewer pressure sensors, solid-state catheters are often favoured.

Pressure data from each of the available sensors on the HRM catheter are presented as colour contour plots, or oesophageal pressure topography, rather than simple line graphs. This influx of data has necessitated the development of new tools for analysing and classifying oesophageal motor patterns. The current standard and still developing approach to do this is the Chicago Classification Version 2 .0.[3]

The technical theory of HRM can be illustrated using line graphs produced by the conventional method of manometry during a peristaltic wave sequence.

Figure 1:

During conventional oesophageal manometry, each of the pressure sensors illustrated in figure 1 record the pressure of the contraction of the muscle layers as the peristaltic sequence passes through the oesophagus. These are then converted in to a real time individual graph of pressure as demonstrated to the left in figure 1.

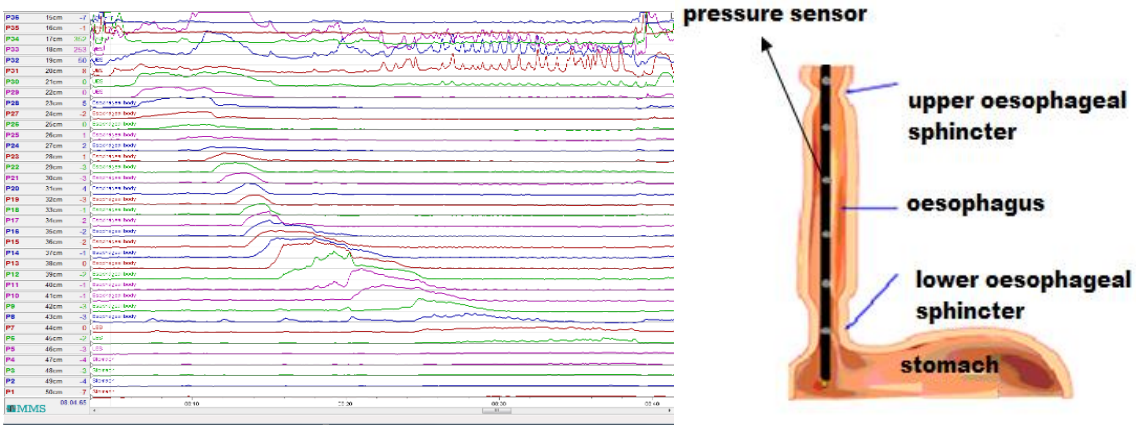


Figure 2: A recording from one sensor within the oesophagus during a peristaltic wave sequence

Every pressure level is designated a different colour, creating a 'colour bar' which can be observed at the top of the image.

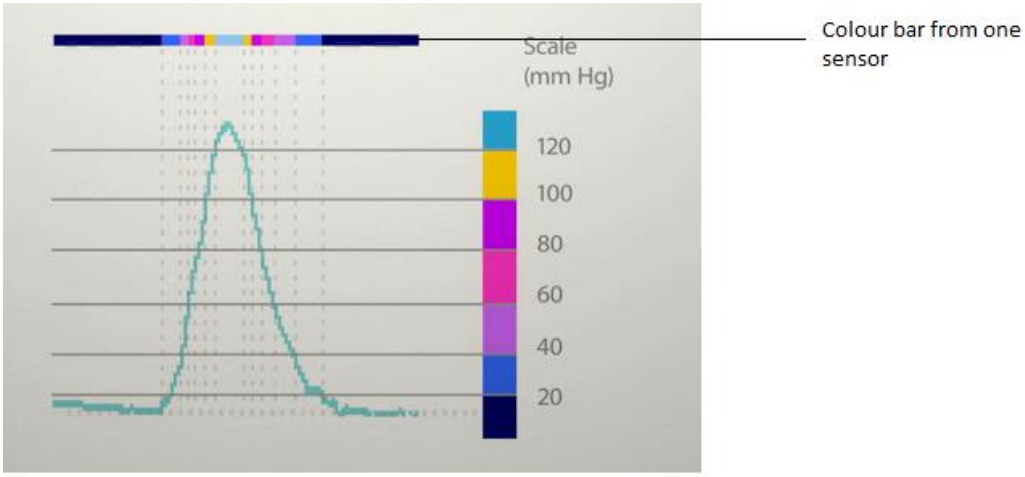


Figure 3: Pressure traces from 4 of the 36 pressure sensors during a peristaltic wave sequence

The software converts the pressure trace from each sensor in to individual 'colour bars'

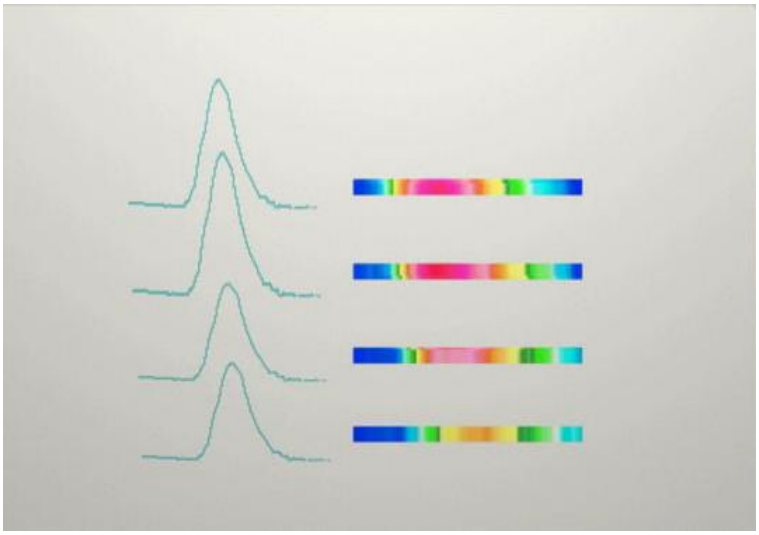
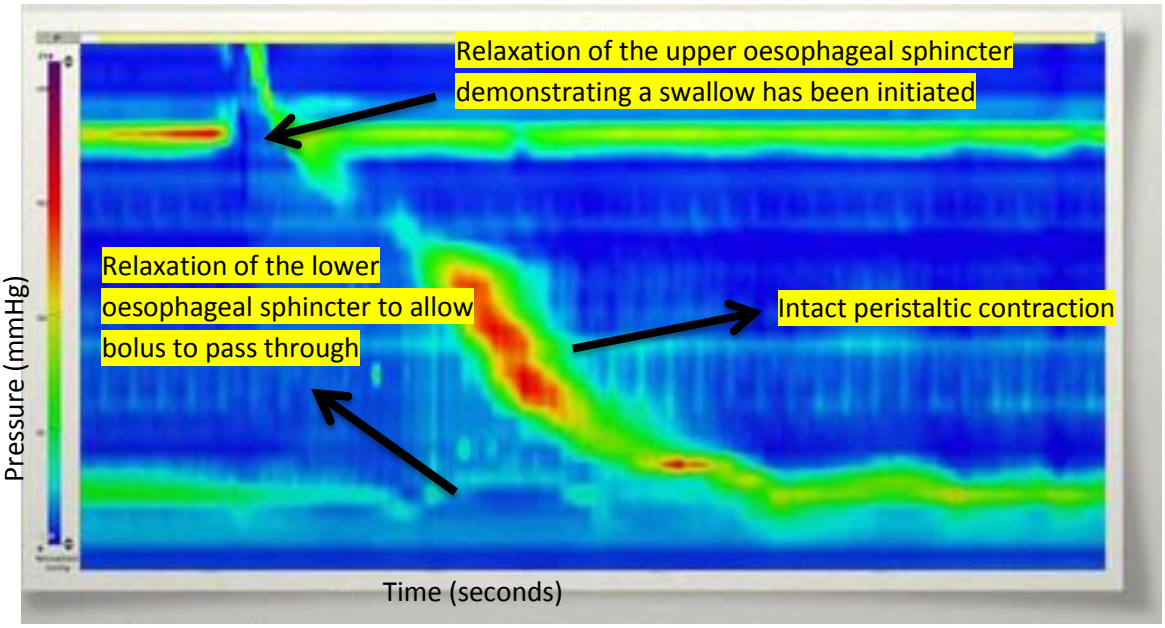


Figure 4: Final colour plot demonstrating an intact peristaltic contraction with normal relaxation of the upper and lower oesophageal sphincters.

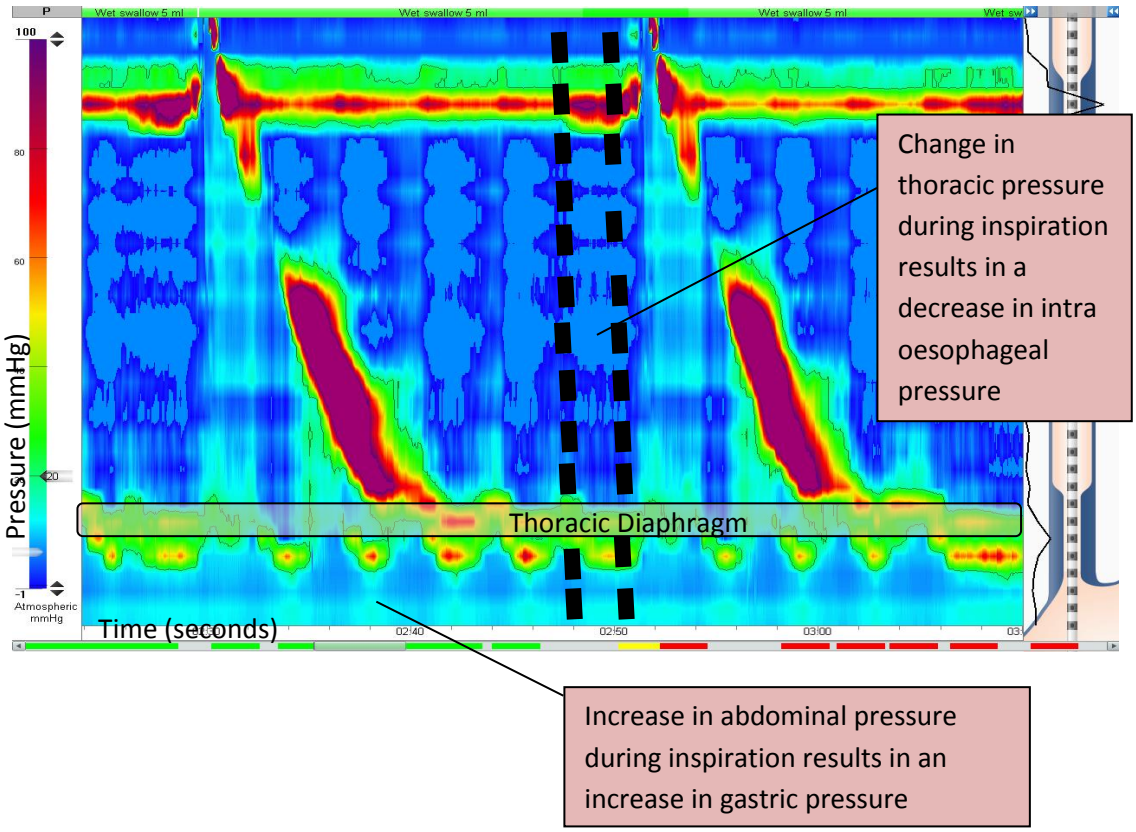
Gaps in the data are interpolated resulting in the final contour plot. Interpolation describes the process by which algorithms provide estimated pressures between actual sensor data, which gives the appearance of continuous pressure information along the entire length of the luminal axis at any given point.



The association between oesophageal motor abnormalities diagnosed with conventional manometry, and respiratory complaints was described by Kastelik et al (2003)[4]. This study was among the first to indicate a high prevalence of manometric abnormalities in patients presenting with chronic cough. Most recently, Vardar et al (2013)[5] used HRM to obtain a detailed evaluation of pharyngeal and oesophageal motility in chronic cough patients. This revealed a high prevalence of changes to UOS and oesophageal motility in this group of patients that are associated with impaired bolus clearance. Whilst an association between chronic cough and oesophageal dysmotility has been established by these authors, the link has rarely been investigated using HRM. There is also a paucity of theories or recommendations as a result. Furthermore, the association between dysmotility in the oesophagus and a broader range of respiratory complaints has not yet been explored in detail using HRM.

An increase in the number of sensors available in HRM compared to conventional manometry does not solely benefit the investigation of oesophageal motor activity. As well as facilitating the development of new tools for analysing oesophageal motor patterns, the introduction of HRM has highlighted previously unexplored phenomenon during the dynamic process of respiration. Due to the close spacing and substantial number of pressure recording sites, and given that the manometry catheter traverses the diaphragm, it is now possible to determine the pressure profile of both thoracic and abdominal cavities during respiratory cycles simultaneously making it easier and more accurate to visually identify and measure where these changes occur.

Figure 5: Decrease in thoracic pressure during inspiration



The principal aim of this study is to examine and compare the oesophageal motility in patients with unexplained respiratory symptoms, and those with typical dyspeptic symptoms. The study will also explore some of the manometric artefacts associated with the respiratory cycle such as changes in intragastric and intraoesophageal pressure. This will enable a calculation of the gastrooesophageal pressure gradient (GOPG) which refers to the gradient produced by the pressure profiles of the thorax and abdomen and their subsequent effect on oesophageal and gastric pressures. As well as comparing the GOPG of each of the groups, the study will also compare the effect of inspiration on the augmentation of the LOS.

To date, many of the researchers exploring the relationship between respiratory symptoms and oesophageal function have focussed their attention on providing comparisons between GOR and oesophageal motility in healthy subjects, and those with

respiratory symptoms. None of the current literature has explored the difference in GOPG between those with primarily respiratory symptoms to those with GOR symptoms which may point to a different gastro-oesophageal reflux mechanism. Also, by comparing respiratory symptoms to those with suspected GORD (a group frequently found to have suboptimal oesophageal motility) as opposed the healthy volunteers – the investigation hopes to demonstrate whether oesophageal function is comparable between the two groups.

Investigation hypotheses

Hypothesis 1:

Patients with a respiratory symptom as their primary presenting complaint show a greater degree of oesophageal dysmotility than patients presenting primarily with a typical GORD symptom such as heartburn, chest pain or regurgitation.

Hypothesis 2:

Patients with a respiratory symptom as their primary presenting complaint show an increased GOPG when compared to patients presenting primarily with a typical GORD symptom such as heartburn, chest pain or regurgitation.

CHAPTER 2 LITERATURE REVIEW

Gastro-oesophageal reflux (GOR) describes the retrograde flow of gastric contents in to the oesophagus. This can cause symptoms such as heartburn, epigastric pain and regurgitation[6,7,8]. Gastro-oesophageal reflux disease (GORD) is often suspected when the above symptoms become troublesome and frequent. They can usually be confirmed by a combination of laryngeal examination, empiric proton pump inhibitor trail and oesophageal pH monitoring[9]. Chronic reflux observed in GORD is the main cause of Barrett's oesophagus[10] which is a columnar-cell metaplasia that replaces the innate squamous-cell epithelium of the oesophageal mucosa.[11]

GORD can also be a compounding factor in the control of a number of respiratory diseases. Raghu et al[12] demonstrated that GOR is highly prevalent in a large and well-defined population of patients with established idiopathic pulmonary fibrosis; although the majority of patients with idiopathic pulmonary fibrosis are asymptomatic. In addition, not only was it found that the asthmatic patient is more likely to have GORD as compared to the general population; GORD is recognised as a potential trigger in many cases of severe asthma[13].

In the last decade several studies have indicated that transient lower oesophageal sphincter relaxations (TLOSRs) represent the main mechanism of all types of GOR, with the majority demonstrating a high proportion of TLOSRs associated with acid reflux in GORD patients as opposed to controls[14,15,16,17]. TLOSR describes the spontaneous relaxation of the LOS and inhibition of the crural diaphragm usually as a result of gastric distension[18]. Relaxations occur independently of swallowing and are not accompanied by peristalsis. An investigation of 15 healthy volunteers indicated a large number of TLOSRs, 79% of which also demonstrated relaxation of the upper oesophageal sphincter. The authors speculate that this is due to rapid changes in intraoesophageal pressure[19], and could be an important factor in understanding the link between GORD and extra oesophageal manifestations of the disease such as cough.

Cough and Gastrooesophageal reflux

Chronic cough is defined as a cough that lasts for over 8 weeks [20]. GOR in addition to other pathologies is thought to be a common cause of chronic cough in all age groups[21,22,23,24]. Given that very few patients with GOR related chronic cough exhibit typical reflux-type symptoms described above [25,26] GOR related cough is difficult to diagnose. This necessitates the use of a number of diagnostic tools to establish an association. Oesophageal manometry, 24-hour oesophageal pH-metry and symptomatic response to empirical treatment with proton pump inhibitor (PPI) drugs - which directly reduce gastric acid secretion - are among the assessments employed in the diagnostic evaluation of patients with unexplained cough. The association between GOR and chronic cough is often rejected in a patient if, in the absence of typical reflux symptoms, those with a normal 24 hour pH-metry investigation have an inconclusive response to PPI treatment.

Faruqi et al[27] conducted a study to determine the value of the PPI esomeprazole in chronic cough patients compared to placebo. The results indicated that esomeprazole did not have a clinically important effect greater than placebo in this group of patients; however the investigation was conducted with only a small sample of 50 patients. A meta-analysis carried out by Chang et al [28] also indicated that there is insufficient evidence to conclude definitely that GOR treatment PPI is universally beneficial for cough associated GORD, with most studies pointing to negative findings or indicating no significant difference from placebo. This suggests a marked placebo effect in the treatment of cough with PPI.

The diagnostic yield of oesophageal pH monitoring in patients with chronic cough was explored by Bogte et al [29] who found that 20% of their study population displayed a positive symptom association probability for GOR related cough. The authors concluded that since positive findings were not infrequent and had diagnostic and therapeutic consequences; pH-metry was a useful tool in the investigation of cough patients. However, this outlook was not supported by Mainie et al [30] who concluded that unexplained symptoms and poor response to PPI in cough patients could be explained by

oesophageal distension from weakly acidic reflux which would not be detected by conventional pH-metry.

Blondeau et al[20] also argued that the criteria for the diagnosis of suspected GOR related cough were insufficient to disregard GOR as the cause in some patients. This group utilised oesophageal pH impedance, a relatively new technique to improve the detection and quantification of acid GOR with the direct benefit of weakly and non-acidic reflux recognition. The results identified weakly acidic reflux as a potential mechanism for cough in 24/100 patients. This demonstrated an association with GOR and cough in a group in which the idea would have been disregarded using the standard diagnostic criteria for acid reflux, and supports the conclusion of a review carried out by Sifrim et al [31] who determined that impedance monitoring was the only recording capable of achieving high sensitivity for detection of all types of reflux.

Pathophysiological mechanisms

The literature suggests that there are 3 main mechanisms by which reflux may provoke cough. All of the mechanisms described act by directly triggering cough events or via sensitization of the cough reflex meaning that coughing is provoked by what would usually be tolerable environmental stimuli i.e. patients that describe cough as a result of exposure to changes in temperature and aerosols. [32]

Pathophysiological mechanisms

1. Microaspiration

There are a number of theories surrounding the mechanism of GOR related cough. Smith and Houghton [33] postulate that the acidity of refluxate is not of major importance in the mechanism of reflux-induced cough. These authors hypothesised that any type of gastric secretion or refluxed material could be aspirated. This theory is supported by Mays et al[34] who found that small tracheobronchial aspirations of gastric secretions over a long period of time might cause interstitial pulmonary fibrosis. However, in one study[35] the gastric enzyme pepsin was used as a marker to explore the theory of microaspiration in chronic cough. These authors compared the amount of pepsin in the lungs of a group of unselected chronic cough patients, and a control group of healthy volunteers and found

that patients with chronic cough did not have significant amounts of reflux into their proximal oesophagus or a significant amount of pepsin in their airways, despite having more reflux when compared with healthy volunteers. Furthermore, patients with abnormal levels of reflux had no more pepsin in the airways compared with those with physiological levels of reflux. Interestingly Rosen et al[36]did find an association between the number of non-acid reflux events and airway-pepsin positivity in a paediatric population using a group of chronic cough/asthma sufferers.

Pathophysiological mechanisms

2. Oesophageal-bronchial reflex.

Convergence of afferents of the vagus nerve from the respiratory tract and oesophagus in the same part of the brain stem has highlighted the existence of an oesophageal-bronchial reflex[37 38]. Ing et al[39] supported this theory by conducting a study in which acid was infused in to the oesophagus of patients with chronic cough to determine the response of the oesophageal-bronchial reflex. This group of authors found that infusion of acid in to the distal oesophagus resulted in an increased the frequency of coughing when compared to infusions of normal saline. Contrarily, in a similar study with fewer subjects Irwin and colleagues[40] noted that oesophageal acid and saline provoked cough at the same frequency, concluding that acidity of refluxate in the distal oesophagus may not be the sole cough mediator. Further to this, Rosztocy et al[41] found that individuals with an oesophageal-bronchial response to acid exposure were more likely to have an acid-sensitive esophagus, suggesting a potential element of hypersensitivity in this subgroup.

Along with other outcome based studies[42 43], Ziora et al[44] demonstrated an increased threshold for cough in patients that had undergone laparoscopic fundoplication and postulated that this was highly likely to be as a result of a weakening of the oesophageal-bronchial reflex. It is important to note however, that approximately 70% of this study group exhibited other typical symptoms of reflux aside from cough – typical reflux symptoms have been shown to respond better to both medical and surgical intervention.[45]

Pathophysiological mechanisms

3. Extra-oesophageal reflux

When the effects of refluxed gastric contents extend beyond the oesophagus itself, this is referred to as extra-oesophageal reflux. Laryngopharyngeal reflux specifically refers to incidence of gastro-oesophageal reflux events, which continue proximally up the oesophageal body breaching the upper oesophageal sphincter to reach the larynx. This can result in cough through direct activation of the receptors in the larynx[4647] but can also lead to chronic sensitivity of the mucosa in this area, since exposure of the mucosa to harmful components of gastric contents is thought to lead to the sensitization of peripheral nerves mediating cough[48]. Laryngopharyngeal reflux is difficult to diagnose. Whilst pH or impedance testing is successful in quantifying reflux events in the oesophageal body, there is no 'gold standard' test to confirm its presence in the pharynx and larynx. This is due to the fact that in the oesophageal body, baseline impedance levels remain relatively stable due to the close contact of the impedance or pH sensors to the oesophageal mucosa. Given that the pharynx and larynx are air-filled cavities, the baseline impedance is unstable, and pH sensors can dry out[33] [49]. A number of observational studies have described a high prevalence of GORD and improvement in suspected reflux laryngitis and its associated symptoms on PPI anti reflux therapy in 60-100% of patients [50] [51]

Oesophageal dysmotility

Oesophageal dysmotility may also play a role in the pathophysiology of chronic cough. In GORD associated with typical symptoms, an increased level of esophageal acid exposure has been shown to correlate with disordered oesophageal motility[5253]. Ribolsi et al [54] used HRM and 24hr impedance/pH to investigate patients with GORD and found that patients with pathological numbers of large breaks in their peristaltic profile (>20% swallows with >5cm breaks) demonstrated prolonged reflux clearance times and higher acid exposure time in the oesophagus than those without breaks.

Knight and colleagues[55], explored the esophageal motility of 112 consecutive patients with extraoesophageal manifestations of gastrooesophageal reflux with a broad symptom

spectrum including hoarseness, globus pharyngeus and chronic cough. This study demonstrated a high prevalence of suboptimal oesophageal motility in patients with extraoesophageal manifestations of GER with less than adequate motility present in 73% of the study population. Only one of the healthy control group displayed substandard motility on manometry. However, this group used a conventional manometry catheter to assess their subjects with only 4 transducers spaced at 5cm intervals. As well as this the broad spectrum of symptoms included meant that there were a limited number of participants in each distinct sub-type.

Kastelik and colleagues[4] looked specifically at the oesophageal motility in patients with the primary presenting complaint of chronic cough. The authors found that oesophageal dysmotility was common in patients with GOR related chronic cough. They noted that 67% of chronic cough patients had abnormal oesophageal manometry. Furthermore, oesophageal dysmotility was the only oesophageal abnormality found in one-third of patients. Kastelik et al[4] describe a high prevalence of hypotensive LOS with low LOS pressure the single most common manometric abnormality in patients presenting with chronic cough. This is in contrast to Fouad et al[56] who reported a normotensive LOS among their two study groups when comparing those with extraoesophageal manifestations of reflux and those with typical GORD symptoms).

Unlike the Kastelic group[4] who opted for a control group of healthy volunteers, Fouad et al[56] compared patients presenting solely with heartburn (excluding those exhibiting extraoesophageal manifestation of GOR) to a group of cough patients. Comparison of the manometric profiles in the two groups demonstrated that ineffective oesophageal motility was a common abnormality seen in both of the groups, however, interestingly, ineffective oesophageal manometry was significantly more prevalent in patients with chronic cough. Although these studies point to a previously undiscovered association between cough and oesophageal dysmotility, each was carried out using conventional manometric techniques, the outcomes of which are thwarted by a lack of standardised methods of defining oesophageal motility.

The introduction of HRM catalyzed the assembly of a standardised protocol for the performance and interpretation of oesophageal motility testing [57]. Vardar et al[5] utilized

HRM and 24 hour pH-metry to assess the upper oesophageal sphincter, esophageal motility, and oesophageal acid exposure in patients with chronic cough. The results indicated 68% of the cough group exhibited pathological reflux with 38% found to have a positive symptom association probability for reflux-cough. The SAP positive subgroup was compared to the remaining group of participants comprised of healthy controls, and cough patients with a negative reflux cough SAP. Those with a positive SAP were found to have significantly less effective peristaltic contractions and thus abnormal oesophageal motility compared to the rest of the study population. Upper oesophageal sphincter resting pressure was normal in all groups.

Gastro-oesophageal pressure gradients

The gastro-oesophageal pressure gradient (GOPG) refers to the gradient created by the pressure profiles of the thorax and abdomen and their subsequent effect on gastric and oesophageal pressures. The literature also commonly refers to this phenomenon as the transdiaphragmatic pressure, the transdiaphragmatic gradient and some inversely label it the thoraco-abdominal gradient. Though the terms vary, the gradient represents the difference between the intragastric and the intraoesophageal pressure and is generated by calculating the abdominal pressure minus the thoracic pressure (or thoracic minus gastric for the inverse thoraco-abdominal gradient).

A limited number of authors have examined GOPGs; each group has explored the influence of the gradient on marginally different parameters. The majority have shown that an elevated GOPG is associated with an increased number of reflux events.

Frankhuisen et al[58] used HRM to explore and compare GOPGs in patients with GORD and healthy controls. These authors measured the GOPG at the start of a TLOSR and at 180, 60, and 10 seconds prior. They found that the GOPG was markedly increased in GORD patients compared with that of control subjects (9.9 mmHg and 7.5 mmHg, respectively; $p<0.05$). Elevated GOPG was caused by increased intragastric pressure in the GORD group who were found to have a significantly higher intragastric pressure than controls. No difference was found between the groups in relation to their intrathoracic pressure.

Similarly, Ayazi et al[59] aimed to investigate why some patients with a manometrically normal LOS and no hiatus hernia still displayed a high level of oesophageal acid exposure on pH testing. Using a group of participants with typical reflux symptoms and a confirmed normal LOS resting pressure, the authors demonstrated that those with an abnormal DeMeester score had a significantly higher GOPG than those with a normal DeMeester score. However, Ayazi et al used an 8-channel water perfused catheter to assess their participants; a study carried out by Florrisen et al[60] concluded that water-perfused manometry systems are disadvantageous in assessing rapidly changing physiological pressures, given the limited frequency response and the fact that they are prone to artefacts due to movement of the connecting tubing or air bubbles in the system.

Contrary to the findings of Ayazi et al, De Vries et al[61] found no direct influence of GOPG on oesophageal acid exposure in a study of 149 GORD patients to determine the effect of GOPGs and their relationship with hiatal hernia, BMI and oesophageal acid exposure. The results of the investigation indicate that BMI and age independently predict the GOPG in this group most likely as a result of increased intragastric pressure. However, the authors elected to use BMI as a measure of obesity, recent reports suggest that the circumference of the waist in a more reliable indicator of the increased risk of GORD in the obese.[62 63]

Scheffer et al[64] also compared the GOPGs between a group of GORD patients (confirmed by the presence of Los Angeles A oesophagitis on recent endoscopy or abnormal 24-hour ambulatory pH monitoring) before and after fundoplication and a group of healthy controls. Their findings indicated that the GORD group had significantly higher GOPGs before TLOSRs accompanied by an acid reflux event when compared to controls. They also demonstrated that the GOPG decreased in GORD patients after fundoplication. Unlike other investigators of GOPG Scheffer et al[64] did not provide a comparison of the effect of inspiration/expiration on the GOPG of their two groups but did demonstrate a significant difference in GOPG overall with a higher gradient evident in the GORD group. However, the vastly different mean ages of the two study populations (GORD 50 years of age; Control 28 years of age) could influence the results since it was recently

demonstrated that age influences the inspiratory GEPG by decreasing intraoesophageal pressure. De Vries et al demonstrated that each added year of age caused inspiratory oesophageal pressure to decrease by 0.06mmHg. As well as this, the catheter configuration of perfused side holes rather than circumferential sensors employed in this study do not allow accurate analysis of very rapid variations of pressure and leave the sensors vulnerable to artefact as a result of contact with the oesophageal and gastric mucosa.

As demonstrated, the effect of fluctuating GOPGs has been investigated in GORD by several authors. Many have concluded that their findings may have a considerable impact on reflux associated with increased ventilatory effort that occurs in some respiratory diseases. However, there still remains a paucity of literature in this area.

One group elected to investigate inspiratory GOPGs in the respiratory field by assessing the relationship between the gradients and reflux in cystic fibrosis (CF) patients when compared to healthy controls[65]. Unlike Frankhuisen et al[58], these authors found no difference between the intragastric pressure during inspiration in their groups, however, there was a significant difference in the inspiratory GOPGs of the two groups with a higher inspiratory gradient in the CF group as a result of the significantly lower intraoesophageal pressure in the inspiratory phase of respiration. Additionally, participants of the CF group showed significantly more reflux episodes that started during inspiration than in expiration, whereas in healthy subjects, reflux occurred equally in both respiratory phases. There were a number of limitations in this investigation; unlike other researchers of GOPG and reflux, Pauwels et al[65] did not monitor ambulatory pH over a 24 hour period, instead electing to detect reflux events using impedance manometry. This limited the time available to assess reflux events to around 3 hours. Although the findings of the study suggest the possibility of an altered mechanism of reflux in this group, and potentially other groups with altered ventilatory efforts, the limited reflux data and small sample size (n = 12) may result in a lack of statistical representation of this phenomenon.

The crural diaphragm

The thoracic diaphragm consists of two functionally distinct parts: costal parts, and crural parts. Costal diaphragm fibres originate from the lower inner rib borders and the lower end of the sternum. Crural fibres originate from the first three lumbar vertebrae forming two muscle bands, the left and the right crura[66]. The crural portions of the diaphragm have no direct rib cage attachments however both the costal and crural fibres converge in to a common central tendon. During inspiration, costal and crural diaphragmatic muscle fibres contract, pulling the central tendon down. This causes the diaphragm to flatten which increases the vertical dimension of the thoracic cavity which sequentially results in a decrease in lung pressure in comparison to the atmosphere; air therefore rushes in to the airway. [1]

Numerous structures pass around or through the diaphragm. The oesophagus passes through the musculature of the right crus of the diaphragm which surrounds the oesophageal hiatus; the section of the oesophagus that passes through the oesophageal hiatus contains the oesophagogastric junction. Anatomically therefore, the LOS and the crural diaphragm are superimposed on to each other[1].

The close positioning of the LOS and crural diaphragm has been the subject of intense investigation over the last 50 years; with many authors exploring the influence of the respiratory cycle on the behaviour of the crural diaphragm and LOS using oesophageal manometry techniques. Boyle et al[67] investigated respiratory induced pressure oscillations at the level of the lower oesophageal sphincter in cats and concluded that the oscillations observed during inspiration in the cat LOS were primarily the result of active diaphragmatic contraction. Dodds et al[68] disputed this finding proposing that perceived increase in pressure observed at the LOS of cats in their own similar study was merely artefact caused by relative movement of the LOS over a fixed intraoesophageal catheter.

Subsequent investigators have sought to explore the effect of diaphragmatic contraction on the lower oesophageal sphincter in human subjects, with most concluding that the crural diaphragm plays a distinct role in the body's anti reflux mechanism[69]. The best evidence for this comes from a study that elected to perform conventional manometry in a group of ten patients with prior oesophagogastrectomy following cancer in the distal

oesophagus[70]. The manometric profile of this group showed a sphincter-like high pressure zone at the thoracoabdominal junction even after surgical removal of the lower oesophageal sphincter strongly indicating the active involvement of the crural diaphragm.

Mittal et al[71] examined the electrical and mechanical activity of the human LOS during diaphragmatic contraction, concluding that while LOS tone is a property of the smooth muscle sphincter, the striated muscle crural diaphragm is selectively and rapidly activated during respiration inspiration. Inspiration in the group of healthy volunteers recruited for this study was shown to be directly related to LOS augmentation; however, the slow response rate of the water perfused catheter used meant that only activity at the LOS produced by controlled respiratory manoeuvres could be assessed rather extemporaneous tidal breathing.

As is indicated by Mittal et al[72], measuring the contribution of the crural diaphragm to the oesophagogastric junction is challenging for a number of reasons. Firstly, as the LOS and crural diaphragm are anatomically superimposed on each other, it is difficult to distinguish whether the intraluminal pressure is related to LOS or crural diaphragm contraction. Secondly, due to the limited spatial resolution of most of the catheters employed in the studies to date, it is likely that craniocaudal movements of the diaphragm during tidal breathing have caused difficulties in maintaining the limited number of available pressure sensors directly in the region of the oesophagogastric junction. As well as this, because the crural diaphragm is a skeletal muscle, its rapid contractions require high-fidelity pressure sensors with a rapid response to record its activity. Previous studies [68,67,72,74] have been hampered by low frequency response catheters requiring sustained inspiratory manoeuvres to mimic the mechanism of tidal breathing.

Using HRM, Pandolfino et al [73] analysed the crural diaphragm function of participants with and without GORD. GORD patients had significantly less inspiratory augmentation of LOS pressure compared with controls. The authors found that the only independent predictor of GOR as a categorical outcome in a logistic regression analysis was impaired crural diaphragm function as indicated by reduced augmentation of LOS pressure during inspiration. This finding is supported by the work carried out by Souza et al [74] who

studied the effect of inspiratory muscle training on the prevalence of gastrooesophageal reflux. These authors hypothesised that since the crural diaphragm is an inspiratory striated muscle, its function may be modified by training. The group demonstrated that the oesophagogastric junction resting pressure increased significantly after inspiratory muscle training, also reducing the number of transient lower oesophageal sphincter relaxations (TLOSRs). Proximal progression of reflux was also reduced.

CHAPTER 3 - METHODOLOGY

Participants

Group A:

An initial group of individuals were selected on the basis that they had exhibited unexplained respiratory symptoms for over 8 weeks that could potentially be due to oesophageal dysfunction. All had therefore been referred the Department of GI Physiology with a primary complaint of a respiratory nature i.e. cough, wheeze, breathlessness. All participants had been referred for HRM between the years 2011-2014. All participants were investigated using HRM; some also underwent 24 hour ambulatory pH-metry.

Group B:

Individuals who had been referred to the Department of GI Physiology with a primary complaint of a gastrointestinal nature i.e. heartburn, regurgitation and non-cardiac chest pain, who had attended for HRM and 24 hour ambulatory pH-metry between the years 2011-2014 were age and sex matched to group A participants.

The relevant clinical history of each of the participants was reviewed to determine their suitability. Group B potential participants were excluded if their clinical history suggested the existence of any respiratory symptoms such as cough, wheeze, or breathlessness. Those who were found to have a pre-existing chronic respiratory illness were also excluded.

Equipment

HRM was performed using a solid-state catheter (UniTip: UniSensor AG, Switzerland) incorporating 36 microtransducers each of which measured circumferential pressure by means of a unidirectional pressure sensor embedded within silicone gel. Each of the 36 sensors were spaced at 1cm intervals.

Before each study, the catheter was immersed in warm water for at least three minutes to pre-soak the sensors in order to reduce artefact resulting from temperature changes in vivo. Sensors were calibrated to atmospheric pressure under 1cm of water. Data acquisition, online visualisation and signal processing were performed using a commercially available manometric system (Solar GI HRM v 2.04, Medical Measurement Systems (MMS), Enschede, Netherlands).

Protocol

Each participant was instructed to stop the following medications prior to investigation.

7 days before investigation

Any proton pump inhibitor such as:

- omeprazole
- lansoprazole
- rabeprazole
- esomeprazole
- pantoprazole

3 days before investigation:

Any Histamine H2 -receptor antagonist or drugs listed here:

- ranitidine
- cimetidine
- nizatidine
- famotidine
- domperidone
- metoclopramide

- mebeverine
- alverine citrate
- buscopan or baclofen

Participants were asked to remain nil by mouth from 4 hours prior to the procedure. Prior to catheter insertion, a visual examination of the nasal passages was performed and the ability of the participant to understand simple commands was confirmed.

All test manoeuvres were performed in accordance with departmental guidelines and using departmental protocol (see appendix 1). To perform the study, lubricating gel was applied to the end of the catheter before it was inserted trans-nasally in to the stomach.

The catheter was advanced until both the upper and lower oesophageal sphincters were visualised on the computed display unit. Participants were asked to take an exaggerated breath in to ensure the catheter had traversed the LOS entirely. This was confirmed by an increase in gastric pressure, and a decrease in oesophageal pressure. The catheter was secured in position and the depth of the catheter from the nares noted. Following a 3 minute 'acclimatisation' period for the purposes of familiarisation, the following procedures were performed.

- 10 x 5ml swallows of water (each 5ml water bolus was separated by at least 20 seconds to allow evaluation of each peristaltic sequence).
- A multiple rapid swallow - 5 x 2ml swallows of water (in rapid succession, allowing time to observe a 'clearance contraction')
- Some studies included 5 single swallows of bread separated by a 20 second interval.

<u>24 hour pH-metry</u>

All group 2 participants and some of group 1 participants also underwent 24hour pH-metry using one of the following devices

- Mk3 single-channel Digitrapper, (Synectics Medical, UK)

- Orion II Ambulatory pH Measurement System (MMS, Enschede, the Netherlands)

24 hour pH catheter placement took place immediately after HRM investigation. For each participant the upper border of the LOS was noted using the information available from the HRM procedure. In all participants the 24 hour pH catheter was inserted trans-nasally in to the stomach. The catheter remained in the stomach to ensure a suitable gastric pH reading (<4). When confirmation of a gastric pH of less than 4 was established on the visual display unit, the catheter was withdrawn so that the pH sensor was resting 5cm above the upper border of the LOS and was secured in place. Verbal and written instructions were given to each participant regarding the operation of the monitoring device.

Consent

Each of the participants gave written permission to undergo the study and for their investigation data to be used for research purposes at the time of study (see appendix 2).

Analysis of HRM measurements

Historical investigations from the selected participants were retrospectively analysed in-line with the study protocol and Chicago Classification Criteria (version 2.0).

Before calculation of the results for the LOS resting pressures and IRP it was necessary to set the gastric baseline. LOS resting pressure and IRP measurements are taken relative to gastric pressure. In each participant the gastric baseline marker was placed distally to the horizontal high pressure zone denoting the lower border of the LOS in a position deemed least likely to be influenced by artefact.

Placement of upper and lower boarders of the LOS and UOS

Placement of the upper and lower borders of the LOS and UOS were vital to the accuracy of the figures generated by the report. Placement of the borders created a virtual ‘sleeve’ in which the sensors of the area could be combined to give the overall pressure profile of the particular location.

Upper border of LOS

The upper border marker of the LOS was placed where the high pressure zone of the LOS was visually intercepted by the peristaltic sequence creating an obtuse angle.

Lower border of LOS

The lower border marker of the LOS was placed at the most distal point of the horizontal high pressure zone, where the high pressure zone ended and was met by a lower gastric pressure.

Upper border of UOS

The upper boarder of the UOS was placed at the most proximal point of the horizontal high pressure zone.

Lower border of UOS

The lower border of the LOS was placed at the distal point of the horizontal high pressure zone where the high pressure zone ended and was met by the oesophageal body resting tone.

LOS resting pressure

A two second automated measurement of the LOS resting pressure within the e-sleeve created by placement of the upper and lower LOS borders was generated by the system software 'auto-analysis' tool. Measurement markers were placed during the end expiratory segment of the tidal breathing cycle nearest to the end of a 20 second peristaltic sequence. This is thought to be the area of the recording most characteristic of LOS resting pressure since it is not under the influence of crural diaphragm contraction which occurs on inspiration. The 2 second automated measurement window which is generated for each of the 10 5ml swallows of water was adjusted in line with this protocol. If there was not a suitable area for these measurements to be taken, the measurement box within the sleeve was deleted and the LOS resting pressure was taken as an average from the remaining suitable readings.

LOS at inspiration

LOS pressure during inspiration was measured in each of the participants. The point of peak inspiration was visually identified by the maximal augmentation and decent of the LOS. A one second measurement window of the LOS during peak inspiration was taken. This measurement was made on swallows 5 and 6 of the recording to allow for any physiological acclimatisation to the catheter. Two consecutive measurements were taken and an average of the two figures was generated to produce the final figure.

UOS resting pressure

A measurement of UOS resting pressure was taken in each patient. This was measured on the 5th swallow of 10 and measured the resting tone of the sphincter for 20 consecutive seconds. Markers were placed so as not to include any relaxation of the UOS as a result of swallowing.

IRP

An IRP measurement was taken in each patient. Markers for this measurement were placed within the borders of the LOS directly in line with the opening of the UOS indicating the start of a swallow. An IRP measurement was made on each of the 10 wet swallows.

Intraoesophageal and intragastric pressure during inspiration

Intraoesophageal and intragastric pressure during inspiration was measured at the peak of inspiration using the 'line information' tool which displayed the pressure of each of the 36 sensors simultaneously. Using this tool, the lowest intraoesophageal pressure during inspiration was identified and recorded. The intragastric pressure was taken 2cm below the lower border of the LOS.

Peristaltic integrity

The percentage of peristaltic, weak, and failed swallows of each participant were calculated in line with the Chicago Classification (Version 2.0)

- Peristaltic swallows were classified as such if there was less than a 2cm break in the peristaltic contraction.
- Weak swallows were classified as such if there was larger than a 2cm break in the peristaltic contraction.
- Failed swallows were classified as such if there was less than 3cm integrity of 20mmHg isobar distal of the proximal trough.

Break location

If a break of over 2cm was detected in the peristaltic sequence, the location of the break was recorded. The criteria for the position of the break were:

- Transition zone (a break in the transition between the striated and smooth muscle)
- Proximal oesophagus (a break in the proximal 3rd of the oesophagus)
- Mid oesophagus (a break in the mid-3rd of the oesophagus)
- Distal oesophagus (a break in the lower 3rd of the oesophagus)
- Multiple sites (breaks in more than one area of the oesophagus)

Multiple rapid swallow clearance

MRS clearance contractions were deemed to be ineffective if the clearance contraction had a break of 3cm or more.

Pressure inversion point

The pressure inversion point was determined and marked in each of the participants by paying close attention to the location along the recording segment at which cyclical pressure changes produced by respiration changed in phase by 180 degrees.

Hiatus hernia

The presence of a hiatus hernia was confirmed in participants whose pressure inversion point did not ensue within the LOS. This indicated that the LOS and diaphragm were not anatomically superimposed and therefore indicated the presence of a hiatus hernia.

Effective bread swallows

Historical investigations that included 5 consecutive successfully performed bread swallows were analysed. Bread swallows were deemed ineffective if the peristaltic contraction had a break of more than 2 cm.

24 hour ambulatory pH recording measurements

24 hour ambulatory pH recordings were analysed using a commercially available pH measurement system (Solar GI HRM v 2.04, Medical Measurement Systems (MMS), Enschede, Netherlands) and the following figures were recorded:

- % time <pH 4
- DeMeester score

Statistical analysis

Variables were summarised using mean, median, minimum, and maximum. To assess the impact of presenting complaint on the measured parameters student's t tests, chi-squared tests and a Mann-Whitney U test were used. Statistical analyses were performed using a commercially available software package (Microsoft Excel for Mac 2011, version 14.5.3 (150624)). A p value of <0.05 was considered statistically significant.

CHAPTER 4 – RESULTS

Of 88 patients referred for investigation of cough lasting >8 weeks between the years 2011-2014, 23 were investigated using a water perfused manometry system and were therefore excluded from the study. 3 solid-state studies displayed technical failure in >4 channels and were also excluded. Thus 69% were eligible for inclusion (Group A). A control group of 60 individuals with the primary presenting complaint of dyspepsia (including heart burn, regurgitation, and non-cardiac chest pain) (Group B) were selected. Relevant medical history of potential group B matches was reviewed and participants were excluded if history of cough, breathlessness, wheeze or respiratory disease were found.

Table 1: Group demographics and primary complaints

	Gender	Age range	Median age
Group A (n=61) (50 cough, 11 breathlessness)	38 Female	18-81	56
Group B (n=60) (56 heartburn, 4 regurgitation)	39 Female	19-81	57

Table 2: Group A – Primary and secondary complaints

Secondary complaint	Count
Asthma	11
Pulmonary Hypertension	2
Bronchiectasis	2
Chronic Obstructive Pulmonary Disease	2
Cystic fibrosis	2
Eosinophilic bronchitis	1
Pulmonary fibrosis	1

Table 3: Group B – Secondary complaints

Secondary complaint	Count
Post fundoplication	5
Barrett's Oesophagus	2

30% of group A had manometric evidence of a hiatus hernia, 30% of B also had manometric evidence of a hiatus hernia.

Oesophageal acid exposure

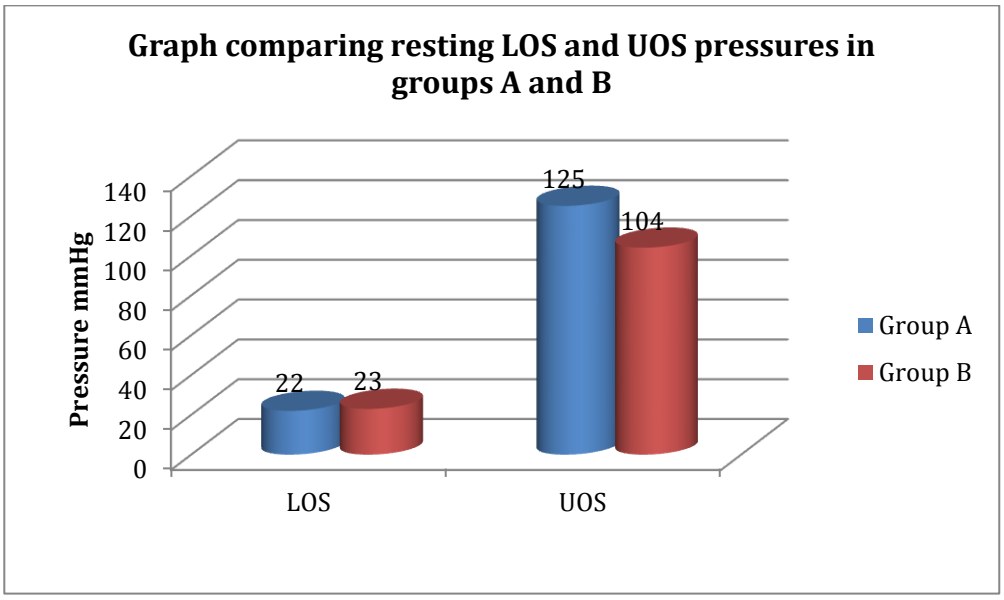
There was no statistically significant difference between the DeMeester scores of groups A and B, however there was a statistically significant difference found between the percentage of oesophageal acid exposure time with a higher percentage of acid exposure found in group B (6.9% vs 4.45, p=0.03). The upper limit of normal oesophageal acid exposure time is 4% of a given 24 hour study.

Table 4: Comparison of DeMeester scores

	Group A		Group B		Normal value
	Mean	Range	Mean	Range	
DeMeester score	16.1	0-43.8	22.6	0.3-79.8	14.72

Static pressures

There was no significant difference between two groups with regard to the upper oesophageal sphincter resting pressure. Group A demonstrated a slightly higher mean upper oesophageal sphincter resting pressure (125mmHg vs 104mmHg), however the difference was not statistically significant. LOS pressures were similar (Group A 22mmHg, Group B 23mmHg).



No difference was found in the integrated relaxation pressure (IRP) values of the two groups. IRP is a measure of how well the lower oesophageal sphincter relaxes upon swallowing, it measures the lowest four seconds of pressure (mmHg) in a 10 second window following a swallow. If the IRP is equal to or more than 15mmHg this can indicate outflow obstruction at the oesophagogastric junction.

Table 5: Comparison of IRP values

	Group A		Group B		Normal
	Mean	Range	Mean	Range	Value
IRP(mmHg)	11	0-37	10	1-26	15

Oesophageal Motility

The percentage of intact primary contractions with a 5ml water bolus was significantly lower in group A than group B (43% vs 58%, P=0.03)

The location of breaks in peristaltic integrity was similar, however, group B showed a higher prevalence of breaks in the oesophageal body transition zone where the striated muscle of the upper oesophagus intertwines with the smooth muscle of the lower two thirds of the oesophageal body.

Table 6: Comparison of break location

The break location was recorded to establish whether there was a particular area of the oesophageal exhibiting a weakness in either of the groups. Group B exhibited a higher prevalence of breaks in the transition zone. This is the area in which there is a cross over from striated to smooth muscle control .

	Proximal oesophagus	Mid oesophagus	Distal oesophagus	Transition zone	Multiple sites	100% Intact peristalsis
Group A (61)	8%	0%	2%	18%	54%	18%
Group B (60)	13%	2%	3%	33%	31%	18%

Bread swallows were successfully performed in 69% of group A and 100% of group B. There was no statistical difference between groups with the average number intact peristaltic bread swallows at 3/5 for each group.

Multiple rapid swallows were performed in all subjects. There was no significant difference between the two groups in the percentage of successful clearance contractions following the multiple rapid swallow sequence.

Table 7: Comparison of clearance contraction following multiple rapid swallows

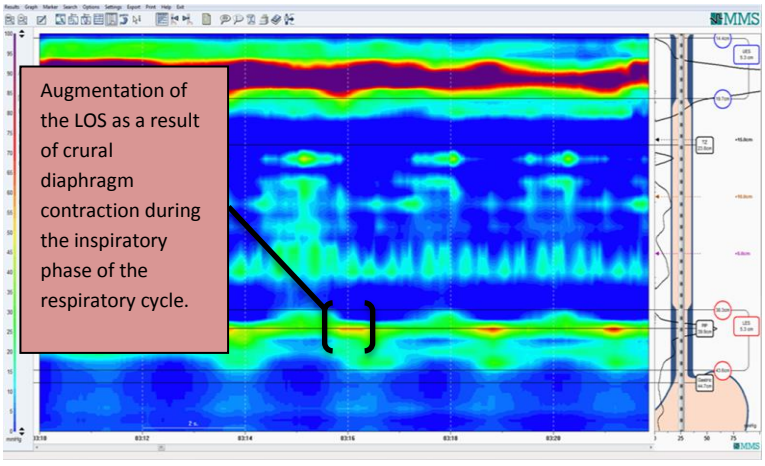
Failure of the oesophagus to produce a clearance contraction following multiple rapid swallows can indicate hypomotility of the oesophageal body and compromised neuromuscular function.

	Group A		Group B	
	Failed	Intact	Failed	Intact
Percentage of contractions (%)	52	48	50	50

Dynamic pressures

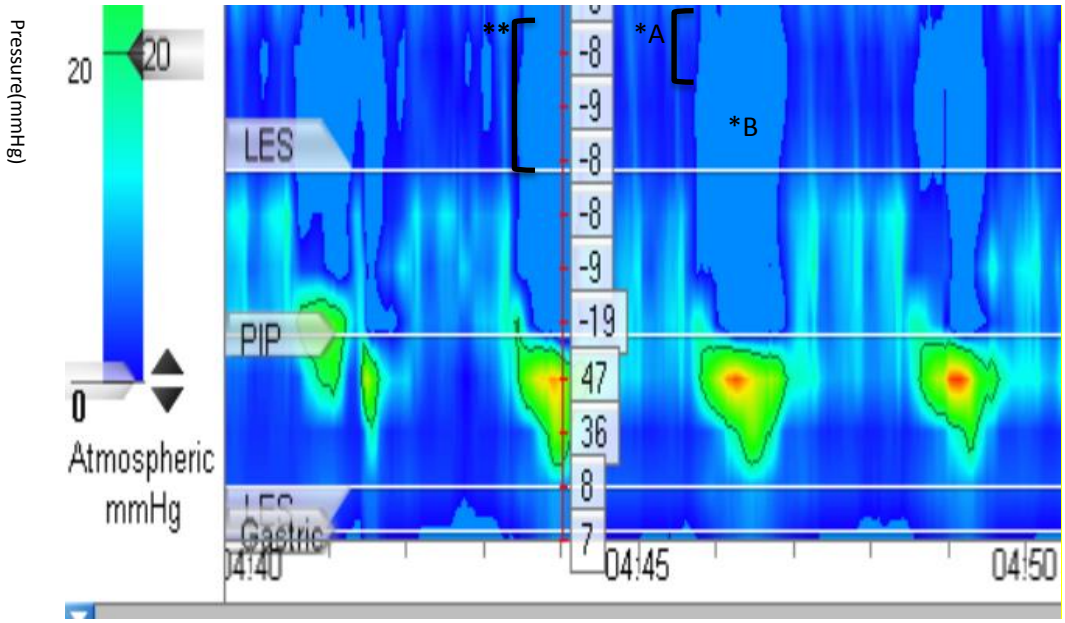
Augmentation of the LOS during inspiration was significantly higher in group A. (46mmHg vs 33mmHg, p=<0.01).

Figure 6: High resolution manometry trace (10 second window)



Intra oesophageal pressure during inspiration was significantly lower in group A (-11.5mmHg vs -8.7mmHg, p=0.001).

Figure 7: High resolution manometry trace showing distal oesophagus and LOS (10 second window)



*A Lighter blue indicating negative pressure excursion in the oesophagus during inspiration (** demonstrates pressures of 10/36 sensors during tidal inspiration).

*B LOS augmentation due to crural diaphragm contraction during tidal inspiration

Table 8: Comparison of intraoesophageal inspiratory pressure

	Group A		Group B	
	Mean	Range	Mean	Range
Intraoesophageal inspiratory pressure (mmHg)	-11.5	-23-0	-8.7	-21-4

4% of group A had an inspiratory GOPG higher than the augmentation of the LOS pressure during inspiration. 3% of group B had an inspiratory GOPG higher than the augmentation of the LOS pressure during inspiration.

No difference was found in intragastric pressure during the inspiratory phase of tidal breathing.

Table 9: Comparison of intragastric inspiratory pressure

	Group A		Group B	
	Mean	Range	Mean	Range
Intragastric inspiratory pressure (mmHg)	5.8	-3-18	5.8	5-19

The inspiratory GOPG (intra gastric pressure – intra oesophageal pressure) was significantly higher in Group A (P=0.01).

Table 10: Comparison of inspiratory GOPG

	Group A		Group B	
	Mean	Range	Mean	Range
Inspiratory GOPG	17.3	6-35	14.1	1-29

CHAPTER 5 – DISCUSSION

GOPGs

The most important original finding of this study is the significantly higher inspiratory GOPG in group A as a result of a significantly lower intraoesophageal pressure on inspiration. This is consistent with the findings of Pauwels et al[65] who demonstrated a higher inspiratory gradient in their CF group also as a result of a significantly lower intraoesophageal pressure in the inspiratory phase of respiration. Frankhuisen et al[58] provided a comparison of GOPG in GORD and healthy controls and also indicated an increased inspiratory GOPG in GORD sufferers. Conversely to the present study, this was as a result of increased intragastric pressure, with no difference found in the intraoesophageal inspiratory pressure. These findings point to a different process of GOPG induced reflux promotion in the respiratory symptom population compared to sufferers of GORD.

Although the present study was unable to associate reflux events with increased GOPG, the HRM-impedance methodology employed by Pauwels et al[65] enabled the group to reveal that significantly more of the reflux episodes observed in their CF group started during inspiration compared to expiration, whereas in healthy subjects, reflux occurred equally in both respiratory phases. This implies that incidence of TLOSRs pose more of a threat to those with an increased GOPG as a result of reduced intraoesophageal pressure on inspiration.

Oesophageal acid exposure

Unsurprisingly, acid reflux was more common in group B. The mean total oesophageal acid exposure time of group A was just above the upper limit of normal. Whilst there is only a marginal excess of acid demonstrated in group A it is plausible to theorise that reduced oesophageal motility could contribute to an untimely clearance of near-physiological amounts of reflux in these patients, promoting troublesome symptoms by

way of the mechanisms described in chapter 2. Unfortunately with only access to standard pH-metry – acid clearance time was not a parameter that could be measured; however, Ribosi et al [54] found that reduced motility in GORD patients was associated with prolonged reflux clearance times.

Oesophageal motility

Unlike Kastelik et al[4] who demonstrated a high prevalence (42%) of hypotonic LOS resting pressure in patients with chronic cough, the current results indicate that only 26% of group A demonstrated a resting pressure less than the lower limit of normal (15mmHg). Mean LOS pressure in the groups was similar (Group A: 22mmHg, Group B: 23mmHg). This is comparable to the findings of Fouad et al[56] who reported similar LOS resting pressures in their study examining the manometric profile of GOR suffers with typical symptoms and those with extra oesophageal manifestations (such as cough and laryngitis). One of the explanations for the difference in LOS resting tone between Kastelik et al[4] and the current study could be that their cough group was comprised from a group of patients of which the majority also reported symptoms suggestive of GOR such as heartburn, dysphagia and regurgitation. As well as this, clinically, the patients making up Group A in the current study are very different given the secondary diagnoses indicated in chapter 2.

The results of the present study indicate that although UOS pressure is slightly higher in group A, no significant difference exists between the UOS resting tone of groups A and B. This is consistent with the findings of Vardar et al[5] who demonstrated no significant difference between the UOS resting tone when comparing a group of cough patients to healthy controls. However, unlike Vardar et al[5] the present study did not use HRM to measure residual UOS pressure. This is a limitation of the study since Vardar and colleagues demonstrated an association with pathologically high residual UOS pressure and cough compared to healthy controls. This measurement could have been valuable in establishing the prevalence of pathological residual UOS in GORD and cough – to ascertain whether this is a pathology exclusive to those with respiratory associated GOR.

Since the Chicago Classification[3] specifies that peristaltic abnormalities are indicated when ≥30% swallows are affected by ≥2cm break in peristaltic integrity, oesophageal

motility was sub optimal in both groups. Similarly to Ribolsi et al [54], the results of the current investigation indicate reduced motility in patients with an abnormal acid exposure, however, peristaltic dysfunction was significantly more prevalent in group A who showed a much lower percentage of effective peristaltic contractions despite demonstrating a lower acid exposure time than group B. This is similar to findings with conventional manometry in patients with cough in general and reflux-associated cough in particular.[75,45, 56, 4]

No difference was found between groups in the number of intact bread swallows. 5 solid swallows of bread were performed in 69% of group A and 100% of group B. Both groups showed an average of 3 intact swallows out of 5. The parallel motility demonstrated in this parameter could be explained by the fact that no standardised protocol or localised normative values exist for the evaluation of bread swallows. The bread swallows of participants in this study were deemed ineffective if there was a break in the 20mmHg peristaltic integrity ≤2cm, however, recent publications suggest that using the distal contractile integral (DCI), which integrates pressure, distance and time along the oesophagus, could be a better measure of oesophageal motility and more accurately highlight sub-optimal motility [3] [76]. Unfortunately, to date, although the Chicago classification (v.2) stipulates the upper limit of normal for the DCI to identify the excessive contractile vigour associated with conditions such as jackhammer oesophagus, there is not an agreed lower range.

As part of the study protocol agreed by the Association of Gastrointestinal Physiologists, each patient was asked to drink 5 2ml boluses of water in quick succession. In normal physiology, peristalsis is inhibited during this type of quick swallowing but is followed by a strong peristaltic clearance contraction after the 5th swallow as normal nerve function indicates that the oesophagus needs to clear the accumulated bolus[77]. An adequate clearance contraction was absent in 52% of Group A and 50% of Group B indicating a similar level of neuromuscular function between the groups.

No difference was found in the IRP values between the groups. The normal mean IRP values for the groups indicate normal oesophagogastric outflow.

Inspiratory LOS augmentation

As described, poor motility and an increased inspiratory GOPG were observed in group A. These observations potentially predispose this group to reflux that may be inadequately dispersed as a result of insufficient peristaltic contractions. The investigation demonstrated that LOS augmentation during inspiration as a result of the contraction of the crural diaphragm occurs simultaneously with the increase in intragastric pressure and decrease in intra oesophageal pressure. LOS augmentation appears to be a mechanism protecting the oesophagus from an excess of acid reflux in individuals with an elevated GOPG – as evidenced by the significantly higher inspiratory increase in LOS pressure in group A.

The significantly higher increase in LOS augmentation in group A could be explained by 2 further reasons. Firstly, Pandolfino et al [19] showed that a group of GORD patients had significantly less inspiratory augmentation of the LOS pressure compared to healthy controls. The inspiratory augmentation at the LOS could be higher in group A simply because poor inspiratory augmentation is a proven characteristic of the GORD sufferers who make up group B. Secondly, Mittal et al[72] demonstrated that the depth of inspiration in a group of healthy volunteers was shown to be directly related the augmentation of pressure at the level of the LOS. A significant portion of the participants in Group A exhibit secondary complaints/underlying conditions, many of which are diseases that elicit hyperinflation. In respiratory diseases associated with hyperinflation, in order to move the air into the alveoli, sufficient force must be exerted by the respiratory muscles in order to expand the lungs and the chest wall. In addition, respiratory muscles must overcome the resistance and inertia in the system so that air will flow into the airways[78]. Another likely explanation for the significantly higher LOS augmentation in group A therefore, is that the higher pressures are reflecting the increased inspiratory effort required in some of the group due to underlying respiratory disease. Increased inspiratory effort is associated with increased diaphragmatic contraction[79]

Bardhan et al[80] speculate that aerolized reflux could be a factor in respiratory related GOR, since this is the only plausible way to explain the presence of refluxate deep in the lungs as demonstrated by Ward et al[81]. It is unclear from the present study whether the

increase in augmentation of the LOS is linear to the change in the inspiratory GOPG. If LOS augmentation during inspiration does not escalate directly in line with the increase in inspiratory GOPG this could potentially promote aerolized reflux. Further research is needed to examine this theory.

Limitations of the investigation.

The control group was purposefully chosen as a group of patients with typical reflux symptoms and therefore a high likelihood of gastro-oesophageal reflux. This was due to the fact that several studies had previously been conducted and demonstrated that compared to healthy controls, those with chronic cough/respiratory symptoms had a higher level of oesophageal dysmotilty. The study hypothesis was that Group A (patients with respiratory symptoms) would demonstrate a higher prevalence of dysmotilty even when compared to a group in which dysmotility is a relatively common finding (Group B) and the results did indicate this, however, it would have been advantageous to the current study to have a third group of healthy controls. This was not possible due to problems with recruitment since reimbursement for time and travel could be offered.

It would have been beneficial to know what proportion of Group A also exhibited typical GORD symptoms and this is one of the major limitations of the study. The reason for this omission is due to the fact that the study was carried out retrospectively and it was not possible from the clinical notes available to know for certain whether Group A patients also demonstrated these symptoms. It was possible to exclude those with respiratory symptoms from Group B as this age and sex matched group were predominantly chosen from more recent studies (2013-2014) in which the study investigation data listed a more comprehensive and detailed list of presenting symptoms.

Unlike many other investigators of GOPGs, intraoesophageal inspiratory pressure in this study was not measured at an appointed location in the oesophageal body. Pauwels et al[65] elected to measure the intraoesophageal pressure of their subjects 3cm above the upper border of the LOS whilst Ayazi et al[59] chose 5cm. The decision not to adopt this method was determined on the basis that at rest, the oesophagus is closed – opening readily to accept food and liquids. The lumen of the oesophagus does not evenly close and is therefore is unlikely to encounter uniform pressure throughout; because of this,

the minimum observed pressure in the oesophageal body at peak inspiration was recorded in two consecutive respiratory cycles and averaged to produce a final figure.

In similar studies, authors have used an average of 10 respiratory cycles to generate intraoesophageal and intragastric pressures necessary to calculate the GOPG. In the current investigation, time constraints limited the number of respiratory cycles that could be measured to two; this could make the results less reliable.

Retrospective analysis meant that BMI measurements for the groups was not available. This could have an effect on the results since BMI has been shown to increase the GOPG. Linear regression analysis carried out by Vries et al[61] showed that each kilogram per square meter of BMI caused a 0.031-kPa (0.3mmHg) increase in inspiratory GEPG.

The permissive exclusion criteria adopted in the present study may also limit the reliability of the data. In other studies exploring oesophageal motility in patients with respiratory symptoms, those with known hiatus hernia have been excluded to avoid confounding with oesophageal dysmotility common in this group. As indicated in chapter 4, 30% of each group were deemed to have a hiatus hernia based on a clear separation between the LOS and the crural diaphragm on manometry. Although the comparable frequency in hiatus hernia between the groups was not deliberate, it goes some way to negating the bias that would be created by not excluding those with a hernia all together.

5 participants had previously undergone a fundoplication. Although these individuals were investigated because of a decline in their symptomatic resolution, it should be noted that laparoscopic fundoplication has been shown to decrease reflux on postoperative pH tracing in 97% of patients and 68% of patients that have undergone an 'open' fundoplication[82]. This has obvious implications for the pH data recorded in those individuals in that DeMeester score and percentage of time <pH 4 are highly likely to be normal. When viewing the results of the investigation, it should be taken in to consideration that 3 out of the 5 participants who had undergone fundoplication demonstrated reduced oesophageal motility and a higher than normal IRP value.

CHAPTER 6 - CONCLUSION

The current literature leaves little doubt that oesophageal function and oesophageal acid exposure both play a role in the pathogenesis of cough. This study appears to be the first to demonstrate both an increased inspiratory GOPG, and reduced oesophageal motility profile in those with unexplained respiratory symptoms compared to an age and sex matched control group of suspected GORD sufferers.

Several studies have highlighted the reduced oesophageal motility observed in GORD groups compared to healthy controls. From this, we can conclude that the oesophageal motility amongst GORD sufferers is frequently substandard. What has been demonstrated in the current study is that oesophageal motility in the respiratory symptom group is diminished further still. Consequently, it is possible that the current criteria by which we define what is 'abnormal' in terms of GOR is not suitable or may not be sufficiently sensitive to demonstrate an association with refluxed material and respiratory disease. Theoretically, as a result of an increased GOPG it would be possible for 'physiological' amounts of reflux, deemed to be within normal limits, to remain in the oesophagus as a result of inadequate peristalsis. Poorly cleared refluxate could be encouraged upwards towards the proximal oesophagus - eliciting respiratory symptoms by way of the mechanisms described in Chapter 2. This could also explain the poor symptom association and the lack of a substantial excess of GOR frequently reported.

It is also apparent that TLOSRs may pose a significant risk in respiratory disease. This study demonstrated that the contraction of the crural diaphragm serves as a barrier to reflux given that it augments the pressure of the LOS to be higher than the inspiratory GOPG in the majority of cases. However, since it is recognized that any protection from the crural diaphragm is lost when its contraction is inhibited during a TLOSR, those who have been shown to have a significantly higher inspiratory GOPG are particularly at risk of GOR during this time.

Further research is required to determine the effect of the findings of this investigation in a larger study population, applying stricter exclusion criteria in sub groups of respiratory disease and controls. Going forward, the main problem faced in exploring the theories offered here further is the lack of technology to detect potentially miniscule amounts of reflux in the pharynx and larynx. As described in Chapter 2, given that the pharynx and larynx are air-filled cavities, the baseline impedance is unstable, and pH sensors can dry out. An effective method of quantifying this type of reflux is paramount in understanding the relationship between oesophageal function and respiratory disease.

APPENDIX 1

Protocol for using High Resolution Oesophageal Manometry

- Patient should be informed of their tests well in advance, to allow any medication, which will affect the test results, to be discontinued (as per patient information leaflet).
- At CHH, patients are not usually starved overnight (to prevent problems with diabetes, and changes in LOS due to MMC). A light meal is allowed up to 4 hours before the test.
- If patient is suspected of having achalasia then longer fasting is advisable for patients' comfort.
- The equipment must be calibrated monthly. A record of the monthly calibration must be filed in the calibration log book as per the calibration log (attached).
- Click on the 'patient' heading at the top left-hand side of the screen – this will produce a drop down menu. Click 'new'.
- Enter patient details in to the relevant boxes and click 'okay'. After clicking 'okay' the patient information should be highlighted with a grey box.
- Click 'investigation' at the top left hand side of the screen. This will provide a drop down menu. Click 'Stationary Solar Gastro'.
- A box will appear in the middle of the screen requiring selection of the investigation protocol. Select '1: OM 36 Channel' and click 'OK'.
- After this, a list of possible investigations will appear on the left hand side of the screen. Click directly on the words '1 Esophageal manometry'
- After this, a box will appear requiring confirmation of the selected catheter. (K123632-00-0818/0882 HRM-C35). Check that the catheter corresponds with this reference number. Click 'Continue'.
- Using the icons at the top left hand side of the screen, click the 'display graphs' icon (4^{th} from left). This will show the pressure value for each of the 36 pressure sensors.
- Hold the catheter away from any surfaces so that none of the sensors are touching other objects.
- Click 'Zero all'. Ensure that each pressure value is reading 0mmHg.
- The test is explained to the patient in detail. This is very important to allow full co-operation during the test. Written patient consent is always obtained prior to the start of the procedure.
- Check for any anaesthetic sensitivity or if alcohol is inappropriate for religious reasons.
- Apply local anaesthesia to nose and throat (if required) and allow time to take effect.
- With patient in sitting position, with the head tilted forward, insert the catheter into the nares and gently advance the catheter.

- Ask patient to put their chin to their chest and start taking very small rapid sips of water through a straw. Gently assist catheter to follow natural movement through sphincter. Too much pressure could make the patient vomit!
- Continue intubation of the catheter until the visual display unit indicates the correct positioning of the catheter.
- Lay patient down on the coach for their comfort, the patient may remain in sitting position if needed (or if the patient requests to remain seated).
- Allow adequate time for patient and tracing to settle.
- Start recording by clicking the 'Start investigation' button at the top left hand side of the screen.
- A box asking to confirm catheter depth will appear. Type in the depth by referring to the markings on the catheter. Click 'OK'.
- Explain each step of procedure with patient to ensure compliance.
- Give the patient 5ml of room temperature water from a syringe. Mark on trace precisely when patient swallows, repeat this at least 10 times, waiting 30 seconds from the end of the last swallow wave before administering the next 5ml bolus. Mark any events, which may occur during test.
- After this, give the patient 5x2mls of water with 2 second intervals. The fifth swallow should be the last, and no swallowing should take place within the 30 seconds following the fifth swallow. Mark on trace precisely when patient swallows.
- The patient may then be given a buttered bread roll to eat in order to assess the function of the swallow using a solid bolus. Ask the patient to eat the roll as they normally would, marking on trace precisely when patient swallows the solid bolus for the first time.
- Save recording (simply clicking on the 'Stop recording' button located on the top right hand side of the screen will save it).
- Ask patient to blow air through nose into a tissue and gently but quickly remove the catheter.
- Clean catheter as per cleaning protocol

APPENDIX 2

Please **READ CAREFULLY** and complete the following form, which gives your permission to have upper GI physiology investigations performed:

You have been referred for upper GI physiology studies at Castle Hill Hospital, by the consultant or your GP who you contacted regarding your GI symptoms. You will have your studies carried out by a member of staff from the GI physiology team, on occasions a doctor or student may also be in attendance (to observe and learn about the procedure); if you would prefer not to have others present, please state below.

The diagnostic tests will assess your oesophageal function by utilising High Resolution Oesophageal Manometry and measure the extent of your acidic reflux by means of a 24hr pH (+/-) Impedance monitoring study.

You are free to ask any questions (before, during or after the investigation), and may withdraw your consent at any time during the procedure(s).

I am / I am not* (*delete as appropriate) willing for other people to be present (doctor or student from outside the department).

I am / I am not* (*delete as appropriate) willing for the data from my investigations to be used for teaching and/or research purposes.

I have / I have not* (*delete as appropriate) read and fully understood the 'High Resolution Oesophageal Manometry and pH Monitoring' booklet (April 2014).

I am / I am not* (*delete as appropriate) willing to have my test results and reports readily accessible and distributed to the referring consultant (or his/her secretary).

FULL NAME: DATE OF BIRTH:

SIGNED: DATE:

To be completed by staff member prior to procedure(s):

I have explained the procedure to the patient and have addressed any particular concerns of this patient

Signed: Date:

ABBREVIATIONS

HRM – high resolution manometry

LOS – lower oesophageal sphincter

UOS – upper oesophageal sphincter

GPOG – gastro oesophageal pressure gradient

GOR – Gastro oesophageal reflux

GORD – Gastro oesophageal reflux disease

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