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# Gastro-Oesophageal Reflux Disease: Studies in Physiology and Innovations in Surgical Management

Thesis submitted by

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Towards

Degree of Doctorate in Medicine

Trinity College, Dublin.

2007.

## *Author's Declaration*

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***Dedication:***

*This thesis is dedicated to my wife Kavitha and my children Akshaya and Kiran.*

## ***Summary***

The work detailed in this thesis combined studies in surgical audit with assessment of outcomes relating to dysmotility, evaluated an innovative approach to quality assurance in surgery, explored new understandings of linked physiological mechanisms in GORD, specifically LPR and gastric function, and finally compared the clinical and physiological outcomes of the surgical standard of care with the Endocinch endotherapy technique.

**Defining Existing Standard of Care (Chapter 3):** An 8 year experience of 378 Rosetti -Nissen fundoplications was performed. At a median follow-up of 6 months there was improved symptom scoring and QOL with an almost 90% patient satisfaction rate and physiological and clinical evidence of control of reflux.

**Outcomes and Surgical Innovation in Laparoscopic Fundoplication (Chapter 4) :** The hypothesis that combination of endoscopic and laparoscopic assessment of the surgical wrap, would be a valuable quality adjunct for this operation was analysed in a consecutive series of patients in comparison with the previous 100 cases. Although the need for adjustments based on endoscopic assessment were few, there was a significant decrease in the incidence of dysphagia and re-intervention.

**Demonstrating the lack of need to tailor the type of fundoplication where preoperative dysmotility exists (Chapter 5):** This question i.e. whether manometrically-determined dysmotility should be managed with a partial wrap such as a Toupet or Dor rather than a 360-degree fundoplication, has been controversial in recent years. The analysis of this Unit's experience clearly demonstrated that preoperative dysmotility is not a contraindication to total fundoplication, and that postoperative acid control is associated with improved oesophageal clearance and symptoms.

**Unravelling the Relationship between Laryngopharyngeal Reflux, Laryngeal Symptoms, and GORD (Chapter 6):** This study reported for the first time the incidence of LPR in patients with GORD, the association between LPR and GORD, and emphasises the lack of linear association with laryngeal symptoms.

**Assessment of 360-degree Fundoplication on Gastric Motility (Chapter 7)**
A total fundoplication normalises gastric dysmotility in addition to increasing lower oesophageal sphincter tone. As a consequence the incidence of gastroesophageal reflux and LPR significantly decreases.

**Comparing the Clinical and Physiological Benchmarks of Anti-reflux Surgery with Endotherapy (Chapter 8):** Laparoscopic fundoplication was markedly superior to TEP in all physiological end-points, with an 8-fold reduction in median acid score, over 90% of patients with normalised acid scores, a significant increase in lower oesophageal sphincter pressure, and an increase in amplitude of contractions.

**Conclusions:**

1. Rosetti-Nissen fundoplication is a simple, safe and effective treatment for GORD.

2. On table endoscopy improves patient outcome and is a useful adjunct to anti-reflux surgery.

3. Preoperative dysmotility is not a contraindication to total fundoplication, and postoperative acid control is associated with improved oesophageal clearance and symptoms.

4. LPR is common in GORD with or without laryngeal symptoms and is related to distal acid exposure.

5. Gastric dysmotility as documented by EGG studies is common in GORD and is normalised by anti-reflux surgery.

6. Endotherapy (Endocinch) is inferior to Nissen fundoplication in controlling reflux.

## ***Acknowledgements***

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## ***Publications from this Thesis***

**Rosetti Nissen Fundoplication: A simple, safe and effective treatment for GORD**
***The Surgeon (submitted)*** ***Chapter 3.***

**On-Table Endoscopy Following Laparoscopic Fundoplication**
*J Gastrointest Surg (in press)* ***Chapter 4.***

**Acid normalization and improved esophageal motility after Nissen Fundoplication: Equivalent outcomes in patients with normal and ineffective motility.**

*American Journal of Surgery, 2005; 190:445-450* ***Chapter 5.***

**Laryngopharyngeal Reflux (LPR) in patients with symptoms of Gastroesophageal Reflux Disease.**
***Diseases of the Esophagus,*** *2006;19(5): 377-381.* ***Chapter 6.***

**Evaluation of gastric function and control of migration of esophageal reflux after Nissen fundoplication.**
***J Clin Gastroenterol. 2006; 40 Suppl 4:S181.*** ***Chapter 7.***

**Comparison of Transesophageal Endoscopic Plication (TEP) with Laparoscopic Nissen Fundoplication (LNF) in the Treatment of Uncomplicated Reflux Disease**
***American Journal of Gastroenterology, 2006; 101: 431-436*** ***Chapter 8.***

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# Chapter 1:

# Background : Gastro-Oesophageal Reflux Disease (GORD)

## 1.1: Epidemiology

Epidemiologic studies of GORD date back to the late 1970s. Initial reports indicated a prevalence of 7-15% in the community.[1] Later studies using better instruments for detecting GORD[2] reported weekly GORD symptoms in 20% of the population and occasional GORD symptoms in about 40% of the population in the USA.[3] A recent meta-analysis of different studies has confirmed these figures.[4]

## 1.2: Clinical background

Almost everybody has some degree of reflux of gastric contents into the oesophagus. Physiologic gastro-oesophageal reflux (GOR) does not usually cause any symptoms and is not associated with physical damage to the oesophagus. On the other hand, some people suffer from pathologic reflux disease (GORD). By definition, all patients exposed to the risk of physical complications of GOR or those who experience clinically significant impairment of their quality of life due to GO reflux, have GORD. Some occasional pyrosis or heartburn may be experienced by many people. By convention, clinical GORD is diagnosed when a patient suffers two or more episodes of pyrosis, heartburn or other GORD symptoms in a week [7] or the symptoms seriously affect the quality of life.

Several factors are known to cause reflux, the most familiar are dietary indiscretions. Of the various foods that promote heartburn, many fall into a class of essential oil known as carminatives, nearly all of which lower Lower Oesophageal Sphincter pressure (LOSP). These include onions, garlic, peppermint, spearmint, cinnamon, dill, fennel, ginger, rosemary, caraway and cloves.[5] Onions are the most common

offenders. Because heartburn is delayed in onset, one cannot say that direct irritation of the oesophagus is responsible. Virtually every food that can cause an "upset stomach" is an inciting agent for heartburn - Tabasco sauce, hot peppers, Italian dressing, barbecue sauce, nutmeg, chocolate, smoky links, alcohol, histamine, fatty foods. It is significant that the "gas" producing foods - especially cucumbers and members of the cabbage family are on the list.

These and other substances known to provoke reflux are generally either stimulants or irritants. It would be more in keeping with the normal physiological pattern if the provocative agent stimulated an end organ than inhibited the sphincter. Nicotine and coffee are inciting agents. Pregnancy has a long term provocative effect now considered due to endogenous progesterone. Birth control preparations may have the same effect due to exogenous progesterone.

Known risk factors for GORD are summarized in Table 1. Among these, obesity and fatty or heavy meals appear to be the most important ones.

**Table 1.** Risk factors for GORD.

| | |
|---|---|
| Obesity | Emotional stress |
| Fatty meals | Rapid eating behavior |
| Heavy meals | Coffee, tea |
| Spicy food | Pregnancy |
| Cigarette smoking | Medication |
| Tight fitting garments | Reclining after eating |

### 1.3: Natural history and complications of GORD

GORD is a chronic and recurrent disease. It has been shown that more than 90% of cases of erosive GORD and more than 75% of cases of non-erosive GORD (nonerosive reflux disease, NERD) recur after discontinuation of effective medical therapy.[7]

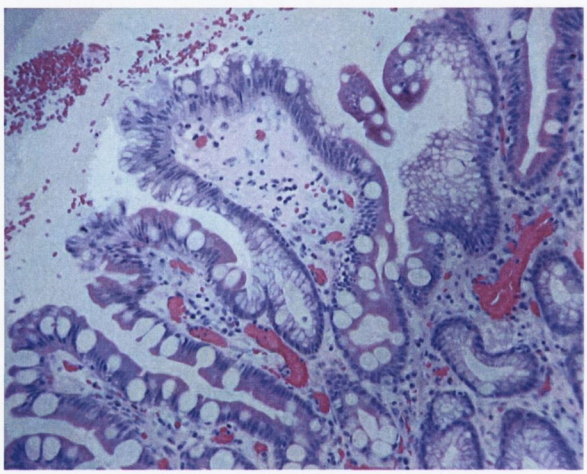


Fig 1. Lower oesophageal biopsy showing specialised intestinal metaplasia with goblet cells of Barrett's oesophagus

Current evidence also supports the central role of GORD in development of specialized intestinal metaplasia in the distal oesophagus (Barrett's oesophagus), which by itself increases the risk of distal oesophageal adenocarcinoma 30 to 100-folds.[8] A red velvetty mucosa lining more than 2 – 3 cm of the distal oesophagus instead of the usual pale esophageal mucosa extending to the gastro-oesophageal junction has traditionally been used to define Barrett's oesophagus.[9,10] More recently, it has been shown that the histological type of the metaplastic mucosa (fundal, oxynto-cardiac, or specialized intestinal) is more important than the length of the columnar-lined mucosa.[11-13] Only specialized intestinal metaplasia, containing goblet cells (Figure 1) is considered Barrett's oesophagus; the other histological types do not

appear to increase the risk of malignancy. Therefore, the diagnosis of Barrett's oesophagus can only be made after careful examination of adequate biopsy samples of apparently metaplastic mucosa from the distal oesophagus.[11-13] Hence the terms short- and long-segment Barrett's oesophagus (SSBE and LSBE) (Figure 2), referring to respective less and more than 2 cm of columnar-lined mucosa in the distal oesophagus respectively, have been coined.[14] However, the pathophysiologic differences between, and natural histories of SSBE and LSBE remain to be determined.[15,16] It is generally believed that SSBE and LSBE are different entities and that the chances of SSBE transforming to LSBE are minimal. Recent data indicate that the chance of developing specialized columnar gastric metaplasia increases significantly with longer duration of and more severe GORD symptoms.[9]

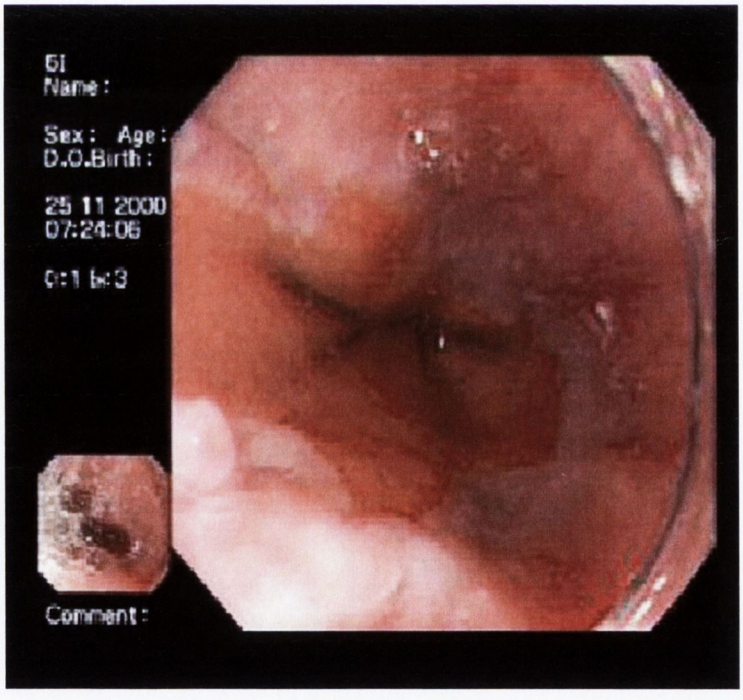



Fig 2:
Barrett's
Oesophagus

Specialized columnar metaplasia and its dysplastic changes have been reported in apparently normal gastroesophageal junctions without any evidence of visible Barrett's oesophagus.[15,16] Although this makes the issue a little more complicated,

looking for such changes in an apparently normal gastro-oesophageal junction is not recommended.

Other complications of GORD include erosive distal oesophagitis, oesophageal strictures and ulcers, and significant impairment of quality of life. [17-19] Some reports indicate that the quality of life in patients with severe GORD may be even worse than that in patients with chronic ischemic heart disease.[20,21] In practice, this impaired quality of life may be the most bothersome aspect of the patient's complaints and should be addressed carefully.

Thus, GORD should be considered a pathophysiologically heterogeneous group of diseases (erosive GORD, NERD, and Barrett's oesophagus) that, despite having relatively similar clinical manifestations, follow different natural courses and may respond differently to treatment. These are hot issues actively being investigated. It is generally accepted that there is no direct correlation between GORD symptoms, endoscopic, and histological findings in the mucosa of the distal oesophagus.

### 1.4: Underlying mechanisms

The underlying mechanism of GORD is not yet fully understood, but various factors contribute to the generation of GORD. The most important known mechanisms include the following:

**1.4.1.Transient lower oesophageal sphincter relaxation:** Transient lower oesophageal sphincter relaxation (tLOSR) is currently considered a major pathophysiologic cause of GORD,[22,23] especially in milder forms of endoscopic

oesophagitis. Lower oesophageal relaxation is a physiological action during swallowing. tLOSR has several characteristics: it is not associated with swallowing, it has a longer duration, and it is not associated with oesophageal peristalsis.[22] tLOSR is considered a physiological response to gastric fundal distension, to rid the stomach of excessive swallowed gas (as part of the belching reflex). Increased tLOSR frequency exposes the oesophagus to acid and other gastric and duodenal contents, which if not cleared normally, leads to GORD. Despite reports relating tLOSR to GORD,[24] it is well-established that most episodes of tLOSR are not associated with GORD symptoms and not all people with GORD have tLOSR.[25]

**1.4.2.Hiatus Hernia:**Usually, the lower oesophageal sphincter (LOS) is located at the

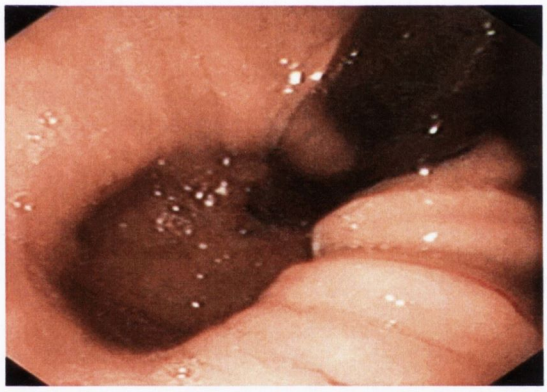


Fig. 3: Hiatal Hernia

level of the diaphragmatic opening (hiatus) through which the oesophagus traverses from the chest to the abdomen. Therefore, the diaphragmatic crura add to the contractile force of the LOS. In some people, the LOS is located in the chest instead of the level of the diaphragmatic hiatus, hence losing diaphragmatic crural support during contraction. Meanwhile, this abnormal location of the LOS gives rise to a pouch of stomach just beneath the LOS and above the diaphragm, which acts as a reservoir that can contain gastric contents to be regurgitated into the oesophageal lumen. This is called a sliding hiatal hernia (SHH), and contributes (Figure 3) to

development of GORD.[26] However, many people have SHH without experiencing GORD symptoms or its complications and vice versa.[26-28] A new concept, known as the 'acid pocket' [29], which exists even in the absence of a hiatal hernia, comprising of unbuffered highly acidic gastric juice at the gastroesophageal junction after a meal, is likely to contribute to the symptoms and consequences of GORD and high prevalence of disease at this site.

**1.4.3. Hypotensive LOS:** Hypotensive LOS, defined as a resting LOS pressure of less than 5 mmHg, is another contributing factor. It appears to be especially important in the more severe forms of erosive endoscopic oesophagitis, i.e. grades C and D (Los Angeles Classification) (Table 2). This is usually associated with hiatal hernias and the two (hypotensive LOS and hiatal hernia) act in concert to cause severe GORD. Newer experimental therapeutic options, such as baclofen, have this mechanism as their main target of action.

**Table 2.** Savary-Miller and Los Angeles Classifications of endoscopic GORD.

| |
|---|
| **Savary-Miller Classification** |
| **Grade 1:** One or more supravestibular reddish spots, with or without exudates. |
| **Grade 2:** Erosive and exudative lesions in the distal oesophagus that may be confluent but are not circumferential. |
| **Grade 3:** Circumferential erosions in the distal oesophagus covered by hemorrhagic and pseudomembranous exudates. |
| **Grade 4:** Presence of chronic complications such as deep ulcers, stenosis, or scarring with Barrett's metaplasia. |
| **Los Angeles Classification** |
| **Grade A:** One or more mucosal breaks ≤ 5 mm in length. |
| **Grade B:** At least one mucosal break > 5 mm long, but not continuous between the tops of adjacent mucosal folds. |
| **Grade C:** At least one mucosal break which is continuous between adjacent mucosal folds, but not circumferential (< 75% of periphery). |
| **Grade D:** Mucosal breaks that involve at least three-quarters of the luminal circumference. |
| **Note:** Ulcers, strictures, Barrett's metaplasia, and other findings are reported as an adjunct to each grade. |

**1.4.4. Oesophageal Clearance:** Impaired oesophageal acid clearance is another contributing factor.[30] Acid, regurgitated into the oesophagus, is usually cleared with oesophageal peristalsis and the bicarbonate secreted in the saliva. If either of these mechanisms is impaired, GORD supervenes.[30-32]

**1.4.5. Hypersensitivity:** Oesophageal hypersensitivity has also been reported among GORD patients.[33] Patients with oesophageal hypersensitivity may have no evidence of pathologic reflux on 24-hour pH monitoring or endoscopy but still suffer from significant GORD symptoms.[33,34] This is a very important aspect and should be considered especially in patients scheduled for antireflux surgery, as they may respond poorly to surgery.

**1.4.6. Bile Reflux:** Duodenogastroesophageal reflux (DGER) has attracted considerable recent attention. Bile and other duodenal contents may be present in the oesophagus of patients with GORD.[35,36] Different duodenal contents have different effects on the oesophageal mucosa. For instance, conjugated bile acids and pepsin are more injurious to the ioesophageal mucosa at acidic pH, while unconjugated bile acids and trypsin are more harmful at pH 5- 8.[23] Hydrochloric acid inhibits the damaging effects of trypsin and unconjugated bile acids, whereas conjugated bile acids decrease the damaging effect of pepsin at acidic pH.[23, 34] Therefore, alkaline reflux oesophagitis is caused by both unconjugated bile acids and trypsin at neutral pH.[23, 38-40] Recent studies of patients with and without complications of Barrett's oesophagus have found increased reflux of bile and acid into the lower oesophagus of both groups as compared with controls.[41] More importantly, reflux of acid paralleled DGER, and both were significantly higher in patients with complicated Barrett's oesophagus than in those with uncomplicated Barrett's oesophagus.[38] These studies

support earlier findings in animals that suggest a possible synergy between acid and DGER in the development of oesophagitis and Barrett's oesophagus. DGER in the absence of acid reflux is a rare event (7%) in patients without prior gastric surgery.[23, 39] DGER without excessive acid reflux can cause reflux symptoms but does not usually produce oesophagitis.[23,39] Therefore, reflux of duodenal contents and gastric acid put the patient at increased risk of oesophageal injury, especially complicated Barrett's oesophagus.[41] Initially, DGER was considered synonymous with alkaline reflux (vs acid reflux), but it is well-documented that the two terms are not synonymous, because other potentially harmful substances are present in bile.[23] Hence, the preferred term is "bile reflux".

**1.4.7. H Pylori:** *Helicobacter pylori* has been the focus of numerous investigations in the field of gastroenterology. There is unequivocal evidence that *H. pylori* has a pathogenic role in peptic ulcer disease, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma.[42-48] The literature on the relationship between *H. pylori* and GORD is controversial. Although *H. pylori* does not affect LOS pressure or tLOSR, its effect on oesophageal mucosal hypersensitivity is still not known.[49] Currently, it should be considered that *H. pylori* has no direct pathogenetic role in GORD, but it affects the clinical outcome in some instances. Therefore, there is no consensus to eradicate or not eradicate *H. pylori* in GORD and the issue is under intense investigation.

Despite all these proposed mechanisms, the exact pathophysiology of GORD is as yet poorly understood. Considering that GORD is a group of heterogeneous diseases with some common symptomatology, it is conceivable that various mechanisms could be

responsible for them, with no one explanation capable of explaining the whole range of diseases.

### 1.5: Symptomatology and Diagnosis

There are a variety of diagnostic modalities for GORD. These include symptom analysis, symptom score, 24-hour ambulatory pH monitoring, and upper gastrointestinal endoscopy. pH monitoring is the gold standard, especially when combined with careful symptom evaluation.

Major GORD symptoms include acid regurgitation and heartburn.[50,51] Heartburn may be defined differently by patients; therefore, it should be addressed carefully and through words that are comprehensible to the patient. By heartburn, we mean feeling a burning sensation just below or behind the sternum. Acid regurgitation, another major GORD symptom, refers to the feeling of a sour, bitter fluid running up to the mouth from the abdomen. Other symptoms and related conditions are shown in Table 4. Interestingly, more than 50% of patients with non-cardiac chest pain and more than 50% of patients with chronic cough, for whom no demonstrable etiology is found, actually suffer from GORD and may respond to prolonged and aggressive treatment for GORD.[50] Antireflux surgery has even been used for long-term control of symptoms in these patients. Although chest pain is a relatively common GORD symptom, patients presenting with chest pain should always be evaluated for cardiac causes of chest pain. Reports on the association of asthma and GORD are numerous, but the association is one of the most controversial.[52,53] Overall, it seems that in patients with severe asthma, GORD is relatively common and asthma symptoms may be better controlled by concomitant treatment of GORD, especially among children.[54]

Minor, extraesophageal, and atypical GORD symptoms such as nausea or waterbrash may be the only presenting symptoms of GORD and therefore should be specifically addressed by the evaluating physician. It should be kept in mind that these atypical or extraesophageal symptoms may be very difficult to control even in the absence of endoscopic oesophagitis (Table 3).

**Table 3.** Other symptoms or related conditions of GORD.

| | |
|---|---|
| Dysphagia | Chronic hoarseness |
| Chest pain | Bitter mouth and sore throat |
| Globus sensation | Halitosis |
| Water brash | Laryngitis |
| Chronic cough | Sinusitis |
| Aspiration pneumonitis | Hiccups |
| Sleep apnea | Asthma |
| Nausea | |

**1.5.1. 24-Hour pH Monitoring:** Twenty-four-hour pH monitoring is about 80–85% sensitive and specific for diagnosing GORD.[6] It is particularly indicated in patients who are candidates for anti-reflux surgery. The test is also useful to confirm acid control after surgery, although only a few specialist centres routinely do this.

There are several reasons for normal pH readings in a patient with reflux, including a hypersensitive oesophageal mucosa, bile reflux, oesophageal motor abnormalities,

and inadequacy of the scores and calculations.[55] Currently, this technique is reserved to make the diagnosis of GORD in patients whose diagnosis is controversial after careful history taking and endoscopy. A device similar to that used for 24-hour pH monitoring, the Bilitec 2000® (Medtronic A/B, Copenhagen, Denmark), has been developed to measure bile reflux and its applications are increasing. In this instance, the catheter is sensitive to electromagnetic wavelengths in the range of 470 nm (the range of bile) instead of pH.[56,57] It has been reported that this device will identify at least 70% of patients with bile reflux.

**1.5.2. Electrogastrography:** Electrogastrography (EGG) is a term applied to the non-invasive measurement of gastric myoelectrical activity in humans. The technique has been 'rediscovered' in the last two decades, mainly due to the development of computer technology [58,59]. The first recordings in 1922 involved placing two electrodes on the abdominal surface of an elderly female and connecting them to a sensitive string galvanometer. The recordings were crude and the raw data was difficult to analyse. The development of more modern technology and the personal computer, improved recording techniques, and automated analysis have contributed to the increased popularity in the use of the EGG. Abnormalities in EGG have been reported in gastroparesis, gastric surgery, motion sickness, nausea and other clinical disorders [60-62].

Information obtained from an EGG includes the frequency and regularity of the gastric myoelectrical activity; abnormal rhythms in gastric myoelectrical activity and EGG power/amplitude increase after a meal. EGG is an important research tool but its validity as a diagnostic tool and its clinical relevance have yet to be determined.
The electrical activity of the stomach dictates the rate and strength of smooth muscle

contraction, and consists of rhythmic waves of depolarisation and repolarisation of the smooth muscle cell. Myoelectrical activity plays a vital role in the control of gastric motor activity. It has long been known that the smooth muscle of the gastro-intestinal tract exhibits two kinds of electrical activity, the basal electrical rhythm (BER) or gastric slow wave, and the action potential or spike activity. The BER is a regularly recurring wave whose frequency varies in different parts of the gastro-intestinal tract.[63]The wave is initiated from the gastric pacemaker, which is located in the proximal part of the stomach at the greater curvature. Proximal to this site, in the upper third of the stomach and the oesophagus slow waves are not detected. The wave moves aborally towards the pylorus with increasing velocity. This electrical activity is constantly present and very stable, pre or post prandially, during sleep or exercise, whether contractions are present or not. This activity controls the direction of propagation and the velocity of the contraction.

The action potential or spike activity that is superimposed on the gastric slow wave, is directly associated with the initiation of a gastric contraction and therefore gastric motility. The association of abnormalities in gastric myoelectrical activity and gastric motility disorders and gastrointestinal symptoms has been well documented. [64-69].

Normal human gastric BER occur at three-cycles/ min. Its spontaneous depolarisation brings the muscle very close to excitation and to the threshold of contraction. When studied with extracellular electrodes, the depolarisation phase is recorded as "electrical control activity" or BER, and the contraction related activity as the "electrical response activity" or spike activity. Whether the stomach has a contraction depends on its physiological state. Although the pace setter potentials determine the velocity and frequency of gastric contractions, it does not initiate them. The most

likely time for a contraction to occur is during eating, when the stomach is distended, or there may be stimulation from the chemicals in the food in contact with gastric mucosa and release of hormones, digestive juices etc. The result is that the threshold for contraction is achieved and a mechanical event occurs, which can be demonstrated directly by implanted strain gauge transducers or indirectly by monitoring intraluminal pressure changes. The electrical equivalent of this event is an action potential or electrical response activity (ERA), which can be measured non-invasively by placing electrodes cutaneously on the abdomen. Every electrical depolarisation has an associated mechanical event, however whether we are eating quickly or slowly the inherent gastric contraction is three times per minute. It is these contractions that produce the mixing and segmenting waves which turn food into a chyme, that can be propelled through the pylorus and on into the duodenum and intestines (Fig. 4).

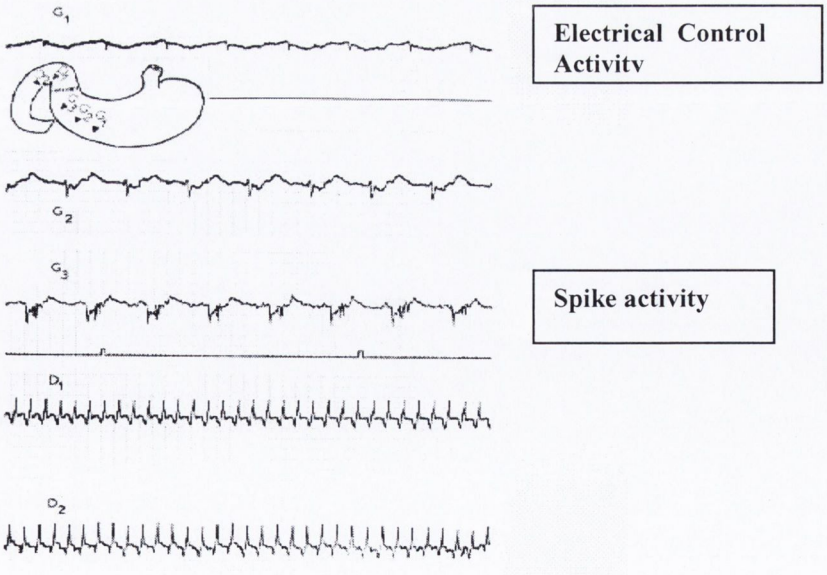



**Fig 4: Basal Electrical Rhythm showing superimposed spike activity.**

In the analysis of EGG, running spectral analysis has become the standard method of analysis [70-74]. In running spectral analysis, Fast Fourier Transform (FFT) analysis is applied to consecutive 256 second signal stretches, that have an overlap of approximately 75%. This results in a series of minute-by-minute frequency spectra that can be represented in pseudo-3-dimensional plot or in a greyscale plot, giving an overview of the changes in frequency and amplitude with time

**1.5.3. Endoscopy:** Generally recommended indications for upper gastrointestinal endoscopy (UGIE) are shown in Table 4. Signs of GORD on UGIE include distal oesophageal erosions(the most frequent), ulcers in the lower oesophagus, oesophageal stricture, and distal oesophageal gastric metaplasia (Barrett's oesophagus).[75] Currently, it is widely accepted that distal oesophageal redness without discrete mucosal breaks should not be considered evidence of endoscopic GORD. Endoscopic GORD can be diagnosed if definite mucosal breaks are observed in the distal oesophagus or if strictures, ulcers, and columnar metaplasia are noted. The two most widely used classification systems for endoscopic GORD (the Savary-Miller and the Los Angeles Classifications) are shown in Table 3. It is recommended that the endoscopist describes what he/she sees exactly and then decides about the degree of oesophagitis and notes which system he/she has used. Detailed descriptions should not be omitted in favor of recording the classification.

**Table 4.** Generally recommended indications for upper gastrointestinal endoscopy in GORD.

| |
|---|
| • Any suspicion of GORD complications or GORD-related malignancy |
| • Presence of alarming signs including significant weight loss, anemia, upper gastrointestinal bleeding or melena |
| • Recent change in character of symptoms |
| • Age of onset after 40 years |
| • Long-term GORD symptoms (more than 5 years) |
| • Family history of GORD-related cancer |
| • Suspicion of concomitant upper GI lesions |
| • Before antireflux surgery |
| • Equivocal diagnosis |
| • Patient reassurance |

Although endoscopic signs of GORD are quite specific, these signs can be seen in 30–50% of GORD cases at best. Most GORD patients do not have any endoscopically visible damage to their mucosa. These patients have non-erosive reflux disease (NERD).[76,77] Some data show that symptoms in NERD patients may be even more difficult to control than those in patients with erosive GORD.[77] Hence, it is generally a false belief that patients with GORD symptoms but normal endoscopy have a milder

form of disease. Longitudinal studies have shown that most NERD patients never develop endoscopically visible oesophageal mucosal damage, yet they have a recurrent and sometimes difficult-to-control condition. A significant portion of NERD patients present with extraesophageal symptoms and even a normal 24-hour ambulatory pH-metry. Therefore, it is widely believed that symptoms and endoscopic and pathologic findings are not directly correlated in GORD patients.[75] It is extremely important to bear in mind that not seeing endoscopic evidence of GORD does not rule out GORD.

Potent proton pump inhibitors (PPIs) such as omeprazole have been used for both diagnosis and treatment of GORD.[77,78] In the so-called omeprazole test (O-test), omeprazole at a dose of 20 – 40 mg/day is prescribed orally for 7 – 14 days. If the patient's symptoms are totally controlled, the test is interpreted as positive and GORD is the basis of the patient's symptoms. If used in conjunction with a detailed history and careful follow-up, the O-test is useful and cost-effective for diagnosis of GORD.[77,78]

Biopsies from the lower oesophagus are also helpful in diagnosing GORD. Pathologic findings suggestive of GORD are shown in Table 5. None of these findings are specific to GORD and a constellation of clinical and pathologic findings is needed to make the correct diagnosis. Taking biopsies from appropriate sites is very important for correct interpretation and yield of the pathology report.[75] Usually, biopsies are taken only if there is an ulcer, a stricture, columnar metaplasia, lumps, or other lesions raising the suspicion of more serious conditions such as dysplasia or malignancy. Some investigators have noted columnar metaplasia and even dysplasia in an apparently completely normal gastroesophageal junction, but routine biopsies of this

area are not generally recommended.[14] If the biopsy is taken merely to diagnose GORD and none of the above lesions are present, then it should be taken from about 3 cm above the Z-line, because minor changes suggestive of GORD are present lower than that even in people without GORD.

**Table 5.** Histologic findings suggestive of GORD on lower oesophageal biopsy.

| |
|---|
| • Proliferation of the basal cell layer |
| • Elongation of papillae |
| • Infiltration of neutrophils and eosinophils in lamina propria |
| • Dilated vascular channels in papillae of the lamina propria |
| • Distended, pale squamous ("balloon") cells |

Other, rarely used, methods to diagnose GORD include barium oesophagography, which is neither sensitive nor specific. It is mostly useful for high-grade oesophagitis and detection of some of the complications of GORD,[79] The Bernstein test (dripping 0.1 normal hydrochloric acid over the distal oesophagus at a rate of 6 – 8 mL/min and looking for reproduction of symptoms not reproduced with saline infusion), although sensitive, is cumbèrsome and has a low specificity.[80] The intraluminal impedance technique is a relatively new way to diagnose GORD but is still considered investigational and is not in general clinical use.[81] Transabdominal ultrasonography has been used to diagnose GORD among newborns, with varying results.

Overall, taking a detailed history with adequate attention to atypical and extraesophageal manifestations of GORD, functional studies, and endoscopy, are the best ways to make the diagnosis. Sometimes, it may be necessary to out-rule life-

threatening conditions (e.g. coronary artery disease) before securing the diagnosis of GORD.

### 1.6: Treatment

The goals of treating GORD are two-fold: 1) relieving the patient's symptoms and improving his/her quality of life, and 2) minimizing or eliminating the physical damage to the oesophagus caused by GORD, which can lead to potentially serious long-term consequences including Barrett's oesophagus and oesophageal adenocarcinoma. There are four categories of treatments for GORD: lifestyle modification and dietary changes, medical therapy, surgery, and endoscopic interventions.

**1.6.1. Lifestyle modification and dietary changes:** Risk factors for developing GORD are shown in Table 2. Correcting these risk factors, i.e. losing weight; avoiding weight gain; avoiding fatty, heavy, and high-calorie food; quitting smoking; avoiding reclining at least 2 to 3 hours after meals; avoiding activities involving bending forward after meals; engaging in regular exercise that does not increase intraabdominal pressure; and avoiding tight clothing may help in decreasing GOR episodes and symptoms. Also, elevating the head of the bed by 20 – 30° by placing blocks beneath the bed may help. These measures alone can improve GORD symptoms in up to 20% of cases at best, although if not observed, they can potentiate GORD symptoms. Therefore, they are used as an adjunct to other modalities. They should be used alone only in the mildest forms of disease.

**1.6.2. Medical therapy:** All acid-reducing agents have been used in treatment of GORD, albeit with variable success. Antacids that directly neutralize acid have been used at high doses. Although they are effective in alleviating acute GORD symptoms, they maintain a symptom-free state in only about 20% of cases and are therefore not suitable choices for long-term use.

Various $H_2$ blockers, which proved to be excellent for peptic ulcer treatment in the pre-*H. pylori* era, are effective in only about 50 – 60% of GORD cases, even at higher doses than usual. Prokinetic agents such as cisapride (Prepulsid®), which is no longer available because of concern about its cardiac side-effects, has the same efficacy as $H_2$ blockers.[82] Cisapride improves gastric emptying and increases LOS pressure. Metoclopramide is of limited use in GORD, and there is only evidence for some benefit in diabetic patients with GORD.[83,84] $H_2$ blockers may be started at the usual dosage used to treat peptic ulcer disease, but it is usually necessary to increase the dosage to control patients' symptoms.[84] Sucralfate, a coating agent, can be used in some circumstances, especially in postgastric surgery patients, but it has limited value in the overall management of GORD.

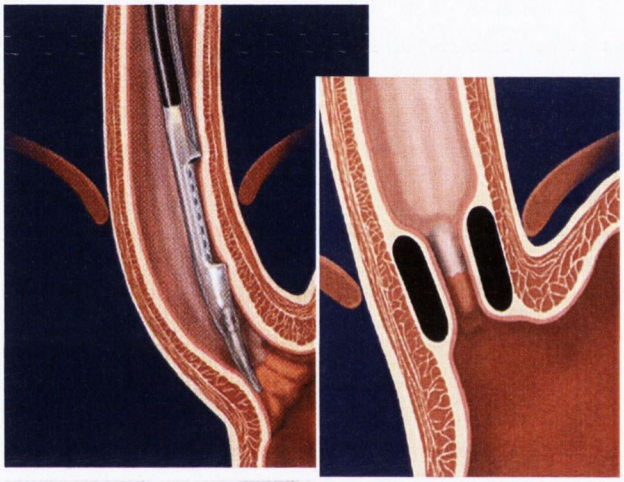
The proton pump inhibitors (PPIs), have proven to be the most effective medical treatments for GORD.[85,86] These drugs have revolutionized both GORD management and our clinical understanding of this disease. At adequate dosage, they control GORD symptoms in at least 85 – 90% of cases. They have been shown to be safe even at higher doses for extended periods of time (up to 11 years).[86] There are few problems with these drugs, but one is nocturnal acid break-through, defined as oesophageal pH less than 4 for more than an hour during the night [87] This may or may not be associated with symptoms that awaken the patient in the middle of the night.

Increasing the dosage of conventional PPIs has not controlled this phenomenon, because of the difference in mechanisms of acid secretion during the day and night (fed and unfed states). Adding an $H_2$ blocker at bedtime to the regimen of these patients may be useful for controlling these nocturnal symptoms.[85] This is the only instance that combining PPIs and $H_2$ blockers has been supported by scientific evidence. Newer studies propose that the newer generation of PPIs (e.g. esomeprazole, and pantoprazole) can overcome the problem of nocturnal acid break-through without the need for an $H_2$ blocker, but further studies are expected. Interestingly, PPIs also decrease DGER and its symptoms. This probably happens through decreased gastric secretions volume.[23]

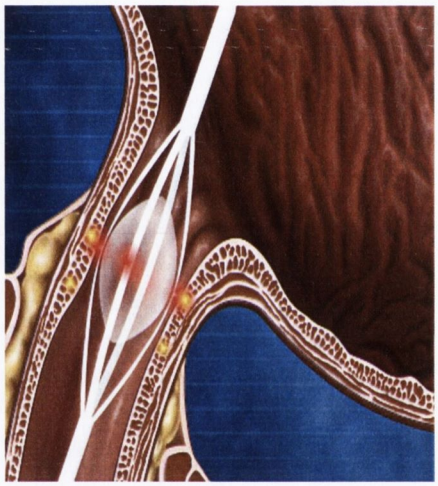
Acid-reducing agents do not directly affect the underlying mechanism of reflux, therefore, a great deal of research is under way to find an agent that adequately increases LOS pressure. One of the proposed medications in this newer category is baclofen, a gamma-aminobutyric acid type B (GABA-B) receptor agonist, which in animal and human studies has been shown to increase LOS pressure.[88] Despite this, the clinical benefit has been marginal and conflicting in studies to date and its routine use for this indication is not currently suggested.

**1.6.3. Endoscopic methods:** Over the past few years, endoscopic modalities to potentiate LOS contractility and resistance have been proposed as alternatives to surgery for GORD. Various endoscopic suturing devices have been developed and are being used in clinical trials.[89-92] Although interim results are encouraging, their role in long-term control of GORD symptoms and complications is largely unknown, therefore they are not yet recommended outside investigational protocols.

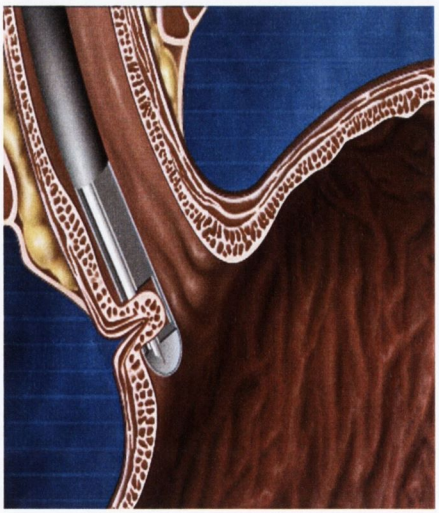
Other techniques developed for endoscopic treatment of GORD include the "Stretta procedure",[93,94] which delivers radio-frequency energy waves to create thermal lesions in the LOS, increasing its contractility. Effective acid control is achieved in only about 40% of patients. There are also methods in which biopolymers are injected into the LOS to potentiate its resistance (enteryx), although results are no better than Stretta for acid control. Both of these techniques have the major disadvantage of being non-reversible (Fig. 5).Gatekeeper system is potentially reversible.



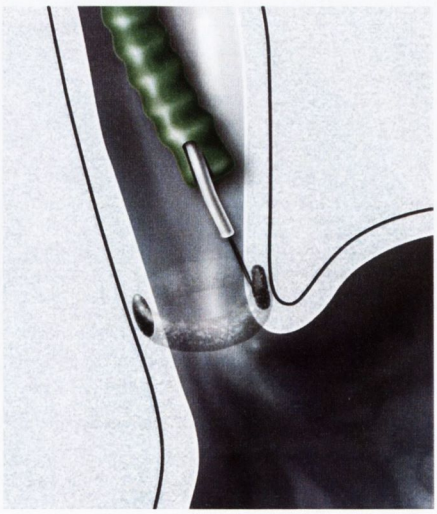
**Gatekeeper**



**Stretta**



**Endocinch**



**Enteryx**

Fig. 5: Endotherapies for GERD

## 1.7: Anti-Reflux Surgery

### History of Nissen Fundoplication

In 1955, Rudolph Nissen, of Basel, Switzerland, operated on a 49-year old woman with a long history of GORD without radiological evidence of hiatus hernia [95]. He used a technique that he had used nearly 20 years previously to minimize postoperative reflux after resection of peptic ulcer in the region of the cardia. This involved envelopment of the lower oesophagus with the gastric fundus by suture approximation of anterior and posterior fundal folds anterior to the oesophagus, within which a large intraesophageal bougie had been positioned. Subsequently in 1965 Nissen and Rosetti suggested that only the anterior wall of the stomach be wrapped around the lower oesophagus. In neither technique did Nissen recommend division of the short gastric vessels. The wrap originally formed by Nissen extended over 4-6cm. In a seminal paper only 20 years ago, in 1986, De Meester [96] and colleagues in a series of 100 cases established the fact that a short wrap of 2-3 cm achieved equivalent acid control but markedly reduced the problem of gas-bloat so prevalent after the original operation.

The first laparoscopic fundoplications were performed in 1991 [97,98] and this has become the standard of care in the surgical management of GORD.

### Mechanisms of action of antireflux operations

Antireflux operations have been devised to restructure and augment the lower oesophageal sphincter (LOS) mechanisms. The primary objectives are to tighten the oesophageal hiatus, lengthen the intra-abdominal oesophagus, and augment the LOS. Antireflux surgery seems to work equally well when reflux occurs in the presence of a

normal lower oesophageal sphincter pressure as it does when the sphincter is mechanically defective. Exactly how the procedures works is debated and the following list of possible mechanisms of action indicate the lack of consensus on the exact mechanics of a successful fundoplication.

1. The floppy valve principle of the abdominal oesophagus means that when the gastric luminal pressure rises the lower oesophagus is compressed by the fundal wrap.
2. There may be a reduction in the triggering of tLOSRs.
3. Exaggeration of the flap valve at the angle of His where the oesophagus joins the stomach.
4. Increase in the residual or resting pressure in the lower oesophageal sphincter pressure as measured during swallowing in postoperative manometric studies.
5. A reduction in the volume of the gastric fundus aiding gastric emptying.
6. Prevention of the shortening of the abdominal oesophagus during gastric distension.
7. The smooth muscle of the wrap may act in a manner similar to the smooth muscle of the normal LOS.

The absolute increase in lower oesophageal sphincter pressure is not important. As mentioned, over the past 25 years there has been a gradual reduction in the length of the Nissen wrap [99] together with an understanding of the need to use a floppy wrap. This has resulted in procedures which are as effective but better tolerated with fewer side effects of dysphagia and gas bloat.

### 1.8: Indications for Surgery and Surgical Methods

Before the advent of PPIs, surgery was considered the only effective long-term treatment for GORD. Surgery was a last resort used to treat patients with refractory symptoms. In recent times, with more extensive use of PPIs and the introduction of effective laparoscopic methods for antireflux operations, the debate has grown and the role of surgery has changed dramatically[100] . Currently, with potent PPIs available, there is a general consensus that patients who respond poorly to medical therapy will most probably not respond to antireflux surgery. Therefore, surgery is generally reserved for patients who respond fully to medical treatment but relapse upon discontinuation of therapy and require PPIs in the long-term.The subgroup of patients with persistant volume reflux inspite of heartburn control with PPIs benefit from surgery.Surgery may still be offered to selected patients with refractory symptoms, but they should be warned of the relatively high chances of not responding to surgery before they decide. Surgery has also been advocated for those who have extraesophageal symptoms of GORD, with variable outcomes. Overall, the best results are expected for patients with typical GORD symptoms on presentation (heartburn, and acid regurgitation), endoscopic findings suggestive of GORD before surgery, 24-hour pH monitoring cofirming reflux, and a good response to medical therapy.[89] There are reports indicating that the psychological status of the patient is also a determinant of the outcome of antireflux surgery. Hence, surgery should be advised with caution for patients with depression, serious anxiety, or other psychiatric conditions mandating psychiatric attention.

### 1.8.1. Total Fundoplication (Complete wrap - 360°):Nissen's

The component steps of the Nissen fundoplication[101] are mobilization of the gastro-oesophageal junction with division of the upper two to three short gastric vessels, crural repair with interrupted non-absorbable sutures, and a complete 3-5 cm fundal wrap with the sutures taking bites of the anterior wall of the abdominal oesophagus (Figure 6). There is no question about the efficacy of this operation in abolishing reflux, and a 360-degree fundoplication of this type assists in preserving intra-abdominal length and adds an external force to the LOS during gastric distention to prevent GORD.

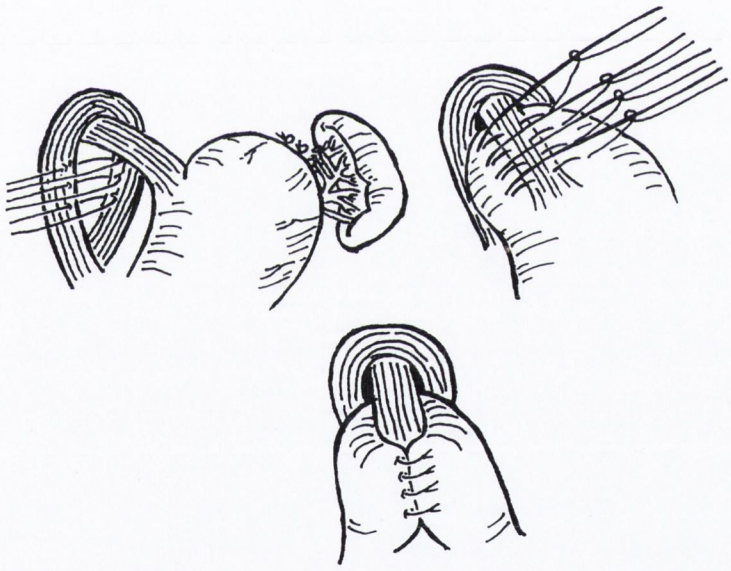


Fig 6:
Classic Nissen
Total
Fundoplication

The advantage of a supercompetent one-way valve abolishing "physiological reflux", resulting in excellent GORD control in approximately 90% of patients, also mediates often unpleasant sequelae such as gas-bloat, early satiety, inability to vomit and belch, abdominal distension, alterations in the swallowing pattern and upper abdominal pain

[102-105]. The aetiological role of diminished gastric volume and gastroparesis with delayed gastric emptying or loss of adaptive relaxation, following inadvertent vagotomy, in the production of these non-reflux related symptoms has not been evaluated.

### 1.8.2. Rosetti-Nissen fundoplication

Rosetti with Nissen modified the original Nissen operation so that the part of the stomach used to create the wrap around the oesophagus is the anterior wall of the fundus (fig. 7) [106].With both the Rosetti and the classic Nissen operations the hepatic branch of the vagus nerve is preserved, if at all possible, as this makes a useful natural limit to the lowermost part of the fundoplication and reduces the postoperative complication of 'slipped Nissen'. The logic behind the Rosetti modification is to allow adequate fundus to be involved in the wrap without the need for mobilisation of the greater curve and separation of of the short gastric vessels from the spleen.

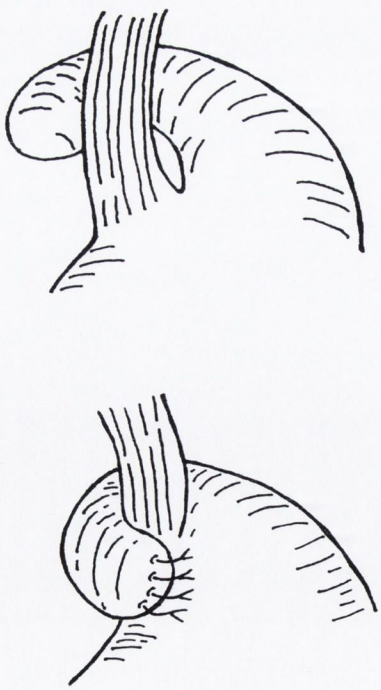


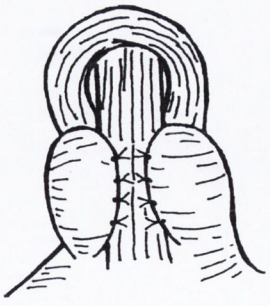
Fig 7:
Rosetti Nissen
Fundoplication

Apart from gas-bloat etc as outline above, technical problems resulting from faulty technique (tight wrap, wrap disruption, slipped wrap and para-oesophageal hernia), recurrent reflux, and ulcerative sequealae (gastric ulcer in the wrap, gastro bronchial fistula, gastrointestinal bleeding) may occur. In an attempt to overcome some of the problems including early dysphagia, the tendency has been to fashion increasingly loose and short complete wraps.

### 1.8.3. Partial Fundolication - Incomplete wraps (270-180°)

These approaches leave varying segments of the anterior or posterior wall of the oesophagus unbuttressed (240-270° wraps) to reduce supercompetence and allow erucatation [107,108]. The disadvantage of these operations lies in the reduction in objective reflux control rate in exchange for the lower incidence of expected dysphagia. In addition, the two rows of sutures placed longitudinally along the wall of the oesophagus which pull in opposite directions favouring disruption, especially in the presence of significant peri-oesophagitis where there is a tendency for sutures to cut out (Figure 8).[107]

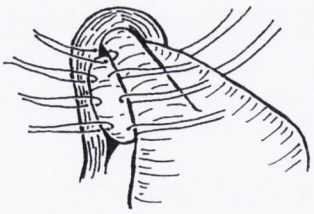
Fig 8: Incomplete Wrap



### 1.8.4. Toupet

The most physiological variation is the posterior 180-240° crurally fixed wrap first described by Toupet [109] and subsequently modified by Boutelier and Jonsell [110].

The peritoneum and phreno-oesophageal ligament are divided, the crura of the diaphragm are dissected and the cardia and the oesophagus fully mobilized. The right vagus is freed from the oesophagus, following which the fundus and upper portion of the posterior wall of the stomach are sutured to the right crus behind the oesophagus. A second row of sutures approximates the right border of the oesophagus to the fundus. Similar fixation is carried out on the left side. This step is facilitated by the insertion of the left crural sutures prior to the fixation of the right side (Figure 9) The fixation of the partial wrap to the crura of the diaphragm is important because, not only does it prevent herniation through the hiatus but, more importantly it is expected to abolish any drag on the oesophageal sutures.



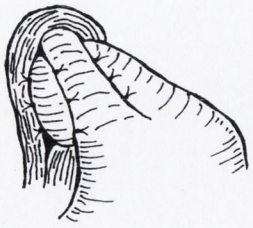


Fig 9:
Toupet crurally fixed
fundoplication

### 1.8.5. Dor

Another technique, first described by Dor *et. al.* in 1962 [111] and reported favourably by others [112], is the anterior 180° wrap. The mobilized fundus is brought in front of the oesophagus and maintained in this position by the placement of two lines of sutures between the oesophagus and the stomach, with the highest sutures anchored to the right crus of the diaphragm.

### 1.8.6 Hill's posterior gastropexy

This operation first reported by Hill in 1967[116] is less commonly used than fundoplication despite being more physiological. In experienced hands, the success rate of this procedure is high and is relatively free of untoward sequelae [117,118]. Its disadvantages include technical difficulty, the need for intraoperative manometry during the construction of the wrap and the risk of damage to the celiac axis and the pancreas. The principle of the Hill repair is simultaneous plication of the lower oesophagus and maintenance of an intra-abdominal length of oesophagus by fixation of the repair to the median arcuate ligament. After mobilization of the abdominal oesophagus and the proximal portion of the lesser curve of the stomach, interrupted sutures are passed through (in order) the anterior leaf of the lesser omentum at the lesser curve, the gastric seromuscular layer of the lesser curve and the posterior leaf of the lesser omentum. Then they catch the median arcuate ligament to which they are tied. The number of sutures required and the degree of infolding of the medial wall of the oesophagus is determined by intraoperative manometry, the objective being to create a high pressure zone of 45-55 mmHg. In essence this procedure creates a medially placed partial longitudinal fixed buttress of infolded lower oesophagus. This results in a long intra-abdominal segment gently curving to the right (Figure 11)

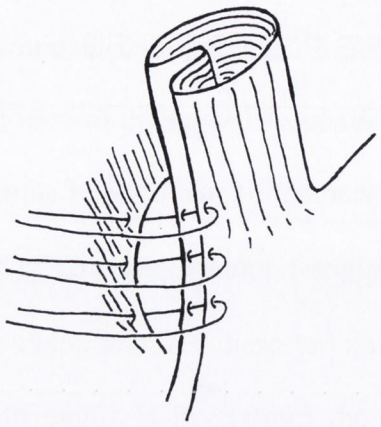


Fig. 11: Hill's posterior gastropexy

### 1.8.7. Belsey Mark IV

The favoured thoracic operation is the Belsey Mark IV [131], although this approach is less commonly employed by general surgeons. The Belsey procedure is a good operation with a long-term proven efficacy but is technically exacting. Its main disadvantage is the need for a thoracotomy approach which increases the magnitude of surgery and may result in chronic thoracotomoy pain .

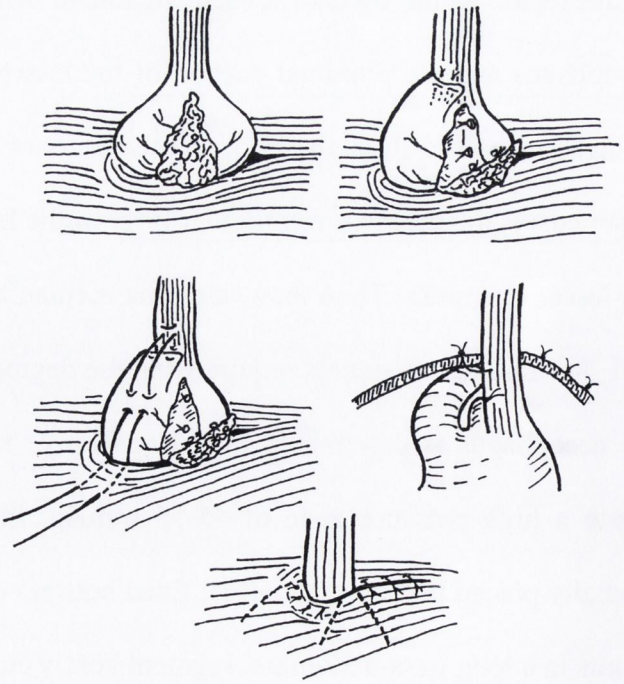


Fig 12 :
Belsey Mark IV operation

Following mobilization, the hernial sac is excised, the stomach mobilized further by division of the upper short gastric vessels, the right crus repaired posteriorly and the fundus of the stomach wrapped twice around the anterior three-quarters of the lower 3-5 com of the oesophagus by means of two rows of sutures, the second overlapping the first. In addition, the second layer of sutures is carried through the hiatus to the diaphragm and, when tied, results in reduction of the gastro-oesophageal junction below the diaphragm and firm fixation of the repair to this structure (Figure 12).

### 1.8.8. Other anti-reflux operations

In addition to the anatomical repair of Allison, there are several other anti-reflux procedures which have been described over the years. Some of these, such as the anterior gastropexy of Boerema[119], are of historical interest only. Others, such as fixation of the gastro-oesophageal junction by a sling of the liagmentum teres[120], have never been adequately evaluated. Vagotomy, antrectomy and Roux-en-Y diversion is a procedure is useful in selected cases of complicated reflux [122].

## 1.9: Surgery for complicated reflux

The important major complications of reflux disease are persistent oesophagitis, aspiration pneumonia, stricture formation, bleeding and Barrett's columnar cell metaplasia. Practice is again not standardized particularly with regard to the management of patients with reflux strictures. There is general agreement that dilatation alone constitutes inadequate therapy since the recurrence rate is high and average 40% [123], whereas dilatation combined with anti-reflux medical treatment is

effective in 70%. There have been few controlled clinical trials to outline the optimum subsequent management of these patients following relief of dysphagia and conflicting anecdotal statements based largely on uncontrolled clinical trials to outline the optimum subsequent management of these patients following relief of dysphagia and conflicting anecdotal statements based largely on uncontrolled and retrospective data remain. There are retrospective reports which indicate that the results of dilatation followed by surgical treatment are better than can be achieved by medical anti-reflux measures [124,125].

There is little doubt that major gastro-oesophageal reflux of acid continues and may indeed be enhanced subsequent to dilatation of reflux stricture [126]. In this study both the cumulative oesophageal exposure to acid and reflux event analysis showed that acid reflux was more pronounced and was associated with slower oesophageal clearance in patients with strictures when compared to patients without. Some 20-30% of patients in 11 reported series of dilatation followed by medical treatment required frequent dilatation and were considered fit enough for anti-reflux surgery. In one of the few controlled clinical trials comparing dilatation and medical therapy vs. dilatation and anti-reflux surgery, 56% of the medically treated group need more than one dilatation as opposed to 25% in the surgical group [127].

Thus it would seem prudent to suggest that these patients ought to be treated medically in the first instance and surgical treatment performed if the stricture recurs and the patient is fit for operation.

Oesophageal shortening is a major problem and, if substantial, precludes a simple

anti-reflux operation of any type. It results from long-standing severe oesophagitis with contracture and fibrosis of the of the oesophageal musculature, the peristaltic motility of which may be impaired. It is often accompanied by peptic stricture formation.

**1.9.1.Supradiaphragmatic wraps:**These have been performed for the surgical correction of reflux in patients with an acquired oesophageal shortening. The procedure is usually carried out through a left thoracotomy. Following dilatation of any strictures, the hiatus is dilated and the mobilized stomach is wrapped round the distal oesophagus without taking suture bites in the oesophagus and over a size 42 bougie. The upper border of the wrap is anchored to the oesophagus by interrupted non-absorbable sutures and the main portion of the wrap sutured to the dilated hiatus to prevent herniation of the abdominal contents into the chest. This operation, though favoured by some [128], has been reported to have a high morbidity with the development of gastric ulcers in the wrap, para-oesophageal colon hernia and outlet obstruction of the wrap following its herniation through the hiatus.

**1.9.2. Collis-Belsey and Collis Nissen procedures:** Gastroplasty was reported by Collis in 1961 as an anti-reflux method suitable for patients with oesophageal shortening and stricture formation [133]. Although it creates a "gastric neo-oesophagus" with a stable intra-abdominal segment, the long-term results of this procedure alone have been disappointing. This operation was subsequently modified with the addition of a Belsey procedure – the combined Collis-Belsey procedure [134]. Although this improved the overall results, a high incidence of continued or recurrent reflux was reported [135,136]. Total fundoplication gastroplasty, the combined Collis-Nissen

procedure, was therefore introduced to incorporate the anatomical stability of the Collis procedure and provide a more effective control of reflux [137]. In general the results of combined Collis-Nissen procedure for these patients are better than those obtained by the combined Collis-Belsey procedure [138,139]. This is also therefore the operation of choice in patients with one previous failed anti-reflux operation and oesophageal shortening, provided the dismantling of the original procedure is technically feasible and does not result in devascularization of the fundus. The gastroplasty can be performed by hand suturing or stapler guns. It should be of sufficient length to ensure 3-5cm gastric tube below the diaphragm. The resulting elongated gastric fundus is passed behind the neo-oesophagus and a loose 360° (around and F60 bougie) 2.0cm wrap performed. If the gastric walls are oedematous and inflamed in reoperations, the fundoplication sutures should be tied over Teflon pledgets (Figure 13).

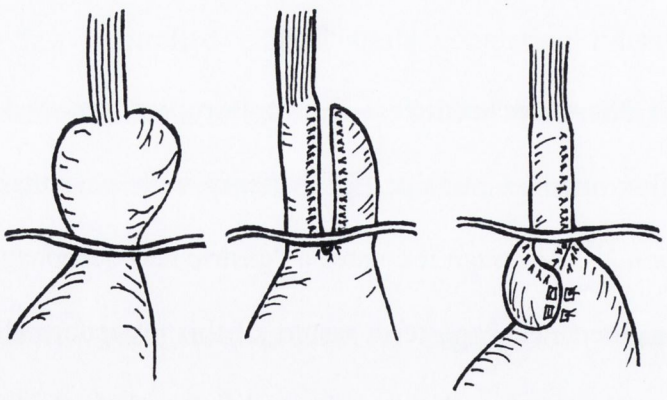


Fig 13:
Collis-Nissen
Operation

There is one problem concerning oesophageal lengthening by the Collis gastroplasty which has not been sufficiently addressed. This procedure effectively creates an "artificial Barrett's oesophagus" and fears have been raised regarding the risk of adenocarcinoma and several such cases have been reported although the aetiological relationship between the Collis gastroplasty and the development of the carcinoma remains unproven.

### 1.10: Re-operation for failed anti-reflux surgery

The common causes for failure of an anti-reflux operation are poor patient selection,technical errors due to inexperience, defects in the design of the procedure itself, oesophageal shortening from chronic oesophagitis and age of the patient. Infants and the elderly have high recurrence rates because of poor tensile strength of their tissues. All operations seem to have the same failure rate which increases with the duration of follow-up [129].

The interval from the most recent failed anti-reflux procedure to revisional surgery is variable but half of the symptomatic recurrences occur during the first 5 years. Aside from age, risk facts for recurrence include obesity, chronic obstructive airway disease and previous gastric surgery.

The symptoms of patients coming to revisional surgery are usually those of recurrent reflux: heartburn, regurgitation and dysphagia. Others present with weight loss,

evidence of aspiration, oesophageal spasm or obstruction, gastrointestinal bleeding or the gas-bloat syndrome.

The management of these patients is difficult, and requires careful assessment and case selection based on thorough investigation[130]. In addition to the usual tests for reflux disease, these patients require assessment of oesophageal motility and transit and, in some instances, gastric emptying studies. An additional gastric drainage operation, usually a pyloroplasty, maybe required in 10-20% of these patients.

The surgical approach depends on the nature of the previous surgery, the number of operative interventions and the degree of oesophageal shortening. Irrespective of the operation used the objectives include restoration of the gastro-oesophageal junction some 3-5 cm below the diaphragm, repair without tension, correction of any pathology attributed to the previous interventions and crural approximation using adequate bites of crural musculature and tendinous diaphragm.

Laproscopic redo surgery is being adopted more and more in high volume centres with large experience. Short term outcomes reported are comparable to standard antireflux procedures. A transthoracic or thoracoabdominal approach may be sometimes necessary after previous failed transthoracic procedure or multiple previous anti-reflux operations [131,132]

### 1.11: Conclusions

Familiarity with a particular anti-reflux operation is important to ensure consistent and good results. Despite this, patient selection based on certain factors such as the build of the patient, previous surgery etc., is necessary to optimise the results of surgical treatment. The majority of patients who are not adequately controlled by medical therapy might be well served by an open or laparoscopic loose short total fundoplication, or incomplete wrap. Finally, complicated, failed anti-reflux surgery, or reflux after previous gastric surgery pose management and technical problems and these patients should be treated in tertiary referral centres with the necessary expertise.

### 1.12: Objective of Thesis and Specific Aims

The primary objective of the thesis is to fully assess existing standards and outcomes of anti-reflux surgery in a single tertiary centre, to better understand the physiology of reflux control, and to explore mechanisms of surgical qualitative improvement in the management of GORD.

The specific aims are as follows:

1. To report on an 8-year audit of the standard practice of Rosetti-Nissen fundoplication (Chapter 3)
2. To investigate a novel innovation aimed at qualitative improvement in anti-reflux surgery, in particular the reduction of post-operative dysphagia (Chapters 4)
3. To evaluate whether pre-existing oesophageal dysmotility should influence the type of anti-reflux surgery undertaken (Chapter 5)
4. To study increasingly recognised extra-oesophageal manifestations of GORD, in particular the association between laryngopharyngeal reflux (LPR) and laryngeal symptoms, and the relationship of LPR to distal reflux (Chapter 6)
5. To study gastric motility non-invasively in patients undergoing anti-reflux surgery (Chapter 7)
6. To compare anti-reflux surgery with the Endotherapy, specifically the Endocinch (Chapter 8).

# Chapter 2:

# Material and Methods

## 2.1 Symptom Questionnaires:

Symptomatic outcome was assessed by completion of standardized reflux and quality-of-life questionnaires before surgery and again at least 6 months after surgery. Severity of GORD symptoms and dysphagia were assessed before surgery, when off medication, according to the self-completed modified DeMeester Scoring [140] (appendix A1). The patients independently completed the Quality of Life in Reflux and Dyspepsia (QOLRAD) [141] questionnaire before surgery and again at least 6 months after surgery (appendix A2) and also the GORD-Health-Related Quality of Life Questionnaire (appendix A3) [142]. Regurgitation was assessed on a scale of 1-3. Reflux Symptom Index [261] was used in the laryngopharyngeal reflux studies (Appendix A4).

**2.2 Oesophageal Manometry:** Stationary perfused oesophageal manometry was carried out using a 4 lumen oesophageal catheter (Mui, Ontario, Canada) with side holes at 5cm apart and orientated at 90 degrees from each other (Fig. 14).

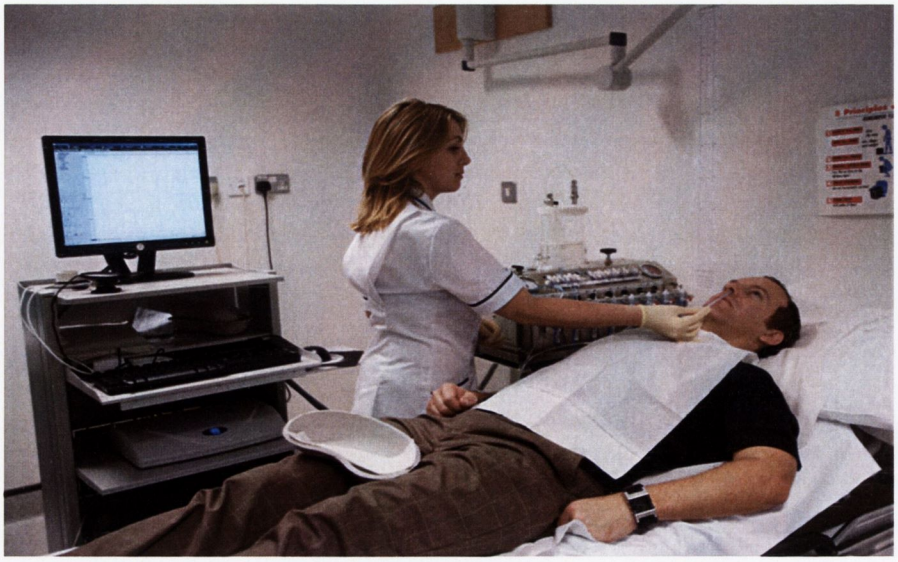


Fig 14: Oesophageal manometry set-up

The catheter was passed per nares and positioned in the stomach. It was then withdrawn by 1cm increments to document the lower oesophageal sphincter pressure (LOSP). LOSP was measured as end expiratory pressure at the point of respiratory

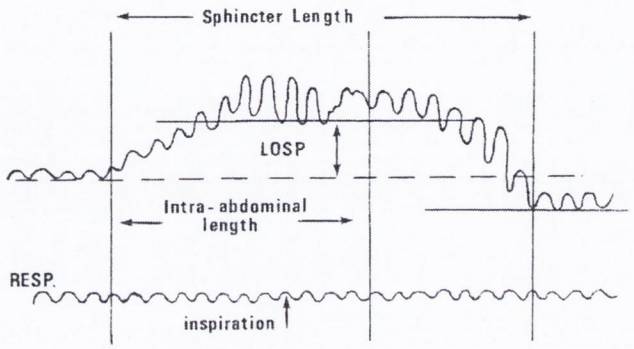



Fig 15: Manometric Lower Oesophageal Sphincter profile

reversal (Fig. 15). Three proximal sensors were then advanced to the oesophageal body and the fourth sensor was positioned within the LOS. Oesophageal body function was assessed by measuring the presence of peristalsis in the oesophageal body in response to 5ml boluses of water (Fig. 16).

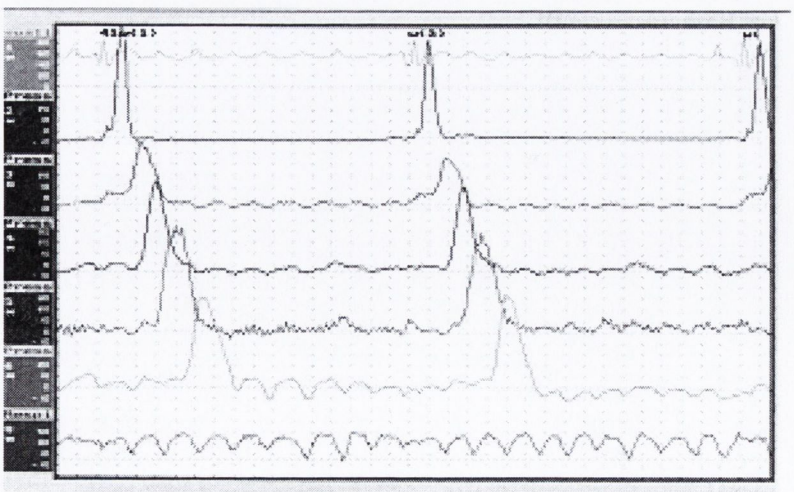


Fig 16: Four-Channel perfused manometry showing normal peristalsis

Abnormal motility was defined as evidence of hypocontraction in the distal oesophagus with at least 30% of wet swallows exhibiting any combination of the following abnormalities: (1) distal oesophageal peristaltic wave amplitude <30 mm Hg, (2) simultaneous contractions with amplitudes < 30 mm Hg, (3) failed peristalsis in which the peristaltic wave did not tranverse the entire length of the distal oesophagus, or (4) absent peristalsis [143]. The manometry catheter was then advanced to the proximal oesophagus and the pressure profile, length and position of the Upper Oesophageal Sphincter (UOS) was measured. The catheter was further advanced by 1 cm increments until the proximal side-hole was in the pharynx, the next side-hole was in the UOS and the other two side-holes were in the proximal oesophagus. Five ml boluses of water were then administered to observe pharyngeal and UOS contraction and peristaltic activity in the proximalo esophagus.

**2.3 Twenty-Four hour pH Monitoring:** For 24-hour pH monitoring, a thin pH catheter is passed into the lower oesophagus and connected to a portable digitrapper (Medtronic, Digitrapper 400). The device is worn around the waist for 24 hours and the patient is instructed to do his/her routines and just push specific buttons for events such as eating, reclining, and having symptoms. The beginning and the end of each event is recorded and correlated with the recorded pH. The data are then analyzed by specific computer software and several indices including a total score (DeMeester score) are calculated. Variations on the technique include dual channel pH monitoring which can allow pharyngeal pH changes, so called laryngopharyngeal reflux (LPR), in addition to the standard distal oesophageal pH (Fig 17).

Fig. 17: pH set-up on patient

All patients discontinued proton pump inhibitors for a minimum of 10 days and other anti-reflux medications for at least 48 hours prior to the study. Twenty-four hour pH monitoring was carried out by positioning an antimony pH probe 5cms above the proximal border of the LES and connecting it to a Mark III Digitrapper (Medtronic, Denmark). No restrictions were placed on diet but patients were advised to avoid citrus drinks and avoid snacking between main meals (Fig. 18).

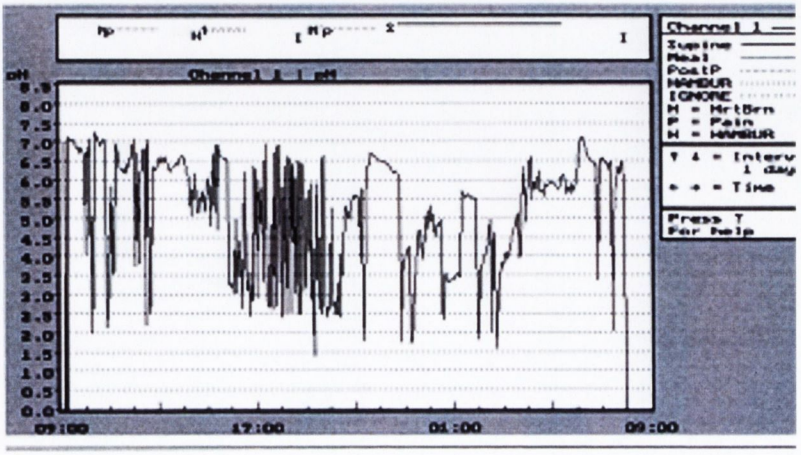



Fig. 18: 24 hour pH trace

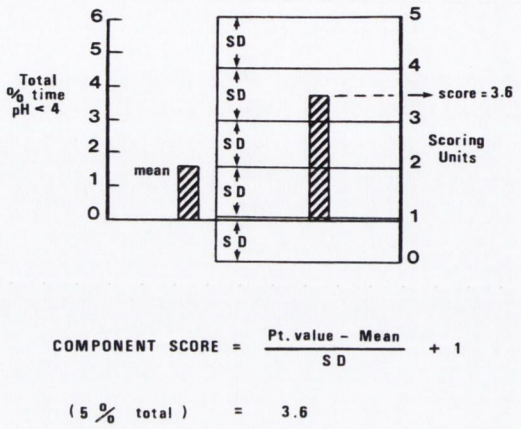



**Fig 19: Calculation of DeMeester Acid Score: 95th percentile = 14.75 for sum of 6 components**

**DeMeester's Acid Score:** Normal values obtained from 50 volunteers were used in the development of the DeMeester Scoring system [144]. The scoring system is based on the use of weighting factors of six components calculated from 24 hour pH monitoring, in the form of the standard deviation of the mean. The components include: total, upright and supine percentage time less than pH 4.0, numbers of episodes less than pH 4.0, number of episodes longer than 5 minutes and the longest episode (Fig 19). The 95th percentile for composite score for this normal data is 14.75, and has gained widespread acceptance.

**2.4 Multi-Channel Electrogastrography:** Patients referred for EGG were fasting for at least six hours, usually from midnight, having discontinued all drugs known to alter gastric myoelectrical activity (pro-kinetic or anti-emetic drugs) 48 h prior to investigation. The patient was encouraged to remain perfectly still for the duration of the study, approx. 2- 3 hr., and refrained from using Walkman, mobile phones etc. Recordings were made in a semi- recumbent position (30°-45°).

The abdominal surface of the recording sites were cleaned thoroughly by abrading the area with a skin prepping paste (Omni-prep, Medtronic, Copenhagen) to reduce skin impedance, and conduction was optimised by applying a conductive gel (Sigma, Medtronic, Copenhagen). Abdominal hair was removed by shaving Skin prior to abrasion. Alcohol and other drying organic solvents were not used on the skin. The electrodes were placed on the abdomen along the antral axis of the stomach. It was assumed that the lesser curvature of the stomach begins at the Xyphisternum and ends at the point where the midclavicular line meets the costal margin, i.e. greater curvature is located to the left of that line. Four active electrodes were placed along the antral axis of the stomach (Fig. 20).

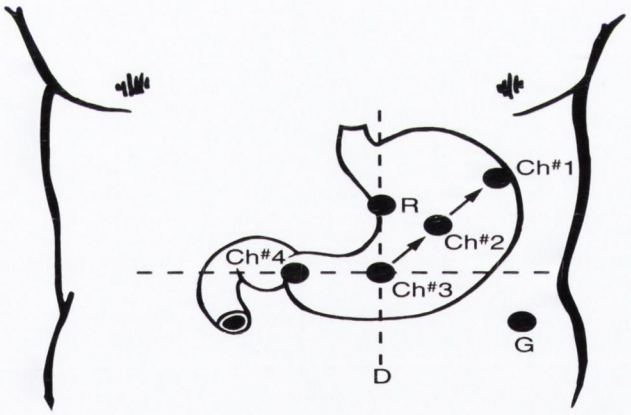



Fig. 20: Four Channel EGG

One electrode (Channel 3) was placed on the patient's ventral mid-line, midway between the xyphoid process and umbilicus, a second active electrode (Channel 2) was placed on the patients left side, 5cms distant and 45 degree's upward from Channel 3. The third active electrode (Channel 1) was placed another 5cms away and 45 degrees upwards from Channel 2. The fourth electrode (Channel 4) was placed

5cms away from Channel 3 to the patients right at the same level. The reference electrode was placed just below the xyphoid whilst the ground electrode was placed 10-15cms to the patients left lateral line. An impedance check was then performed to ensure that the resistance between the electrodes was less than 10k Ohms. A motion sensor was placed to the patients skin close to the active electrodes. After an appropriate baseline recording, a test meal/stimulant was given, and a further recording post prandially was measured. The test meal was warm with medium calorific value (340-480kCal), with low fat and high fibre content. Patients were studied for a minimum of 30 minutes pre-prandially and 45 minutes post-prandially (Fig. 21). The data was captured on-line in real time to a PC and analysed using Polygram Net software version 4.1 (Medtronic, Copenhagen).

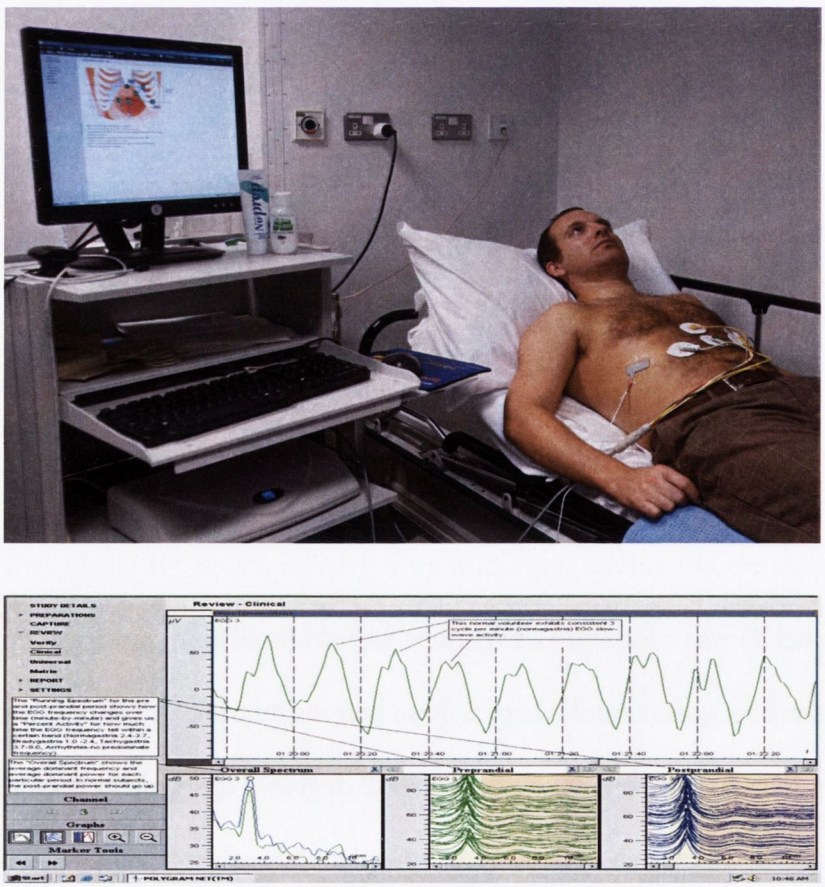



Fig 21: EGG set-up and sample tracings

**Interpretation of EGG:** Several parameters can be used in the interpretation of EGG recordings. However, the main parameters used by the majority of researchers are dominant electrical frequency (DF) and the power ratio. These parameters are documented both pre and post prandially. The dominant slow wave frequency (DF) is approximately 3cpm(contractions per minute) in normal healthy humans. It is defined as the frequency at which the EGG power spectrum has a peak power in the range 1-12cpm.It can be presented as a percentage of dominant frequencies recorded for a given range i.e. Bradygastria, Normogastria and Tachygastria [145,146]. Values for the normal range can vary between institution e.g. 2-4cpm (Table. 6).

| **Parameters** | **Normal Values** |
|---|---|
| **Dominant Frequency** | |
| Number of cycles per minute | Gastric rhythm = 3cpm |
| **% Dominant Frequency** | |
| Bradygastric range | 0.5- 2cpm |
| Normal range | 2 - 4cpm, BER >70%(post prandially) |
| Tachygastric range | 4 - 10cpm. |
| Duoden-Resp | >10cpm. |
| **Power Ratio** | |
| Post-prandial to fasting power ratio | PR >1 |

Table 6: Parameters used to analyse an EGG recording

The postprandial to fasting power ratio (PR) is reported as the absolute value of power of the dominant frequency. This value can be influenced by many factors, e.g., skin resistance, position of the electrodes from the stomach wall etc. It is defined as the

ratio of power of the post-prandial to fasting dominant frequency peak. Meal ingestion results in an increase in EGG amplitude. [147,148]. Several investigators have suggested that an increase in power is associated with changes in the intensity of spike activity and antral contraction amplitude; [149-151] others consider the increase in power as a reflection of the distended stomach[152-154]. Care in the interpretation of increased amplitude of the EGG must be taken, as it may be related to both gastric contraction and to changes in the position of the stomach. The power of a normal frequency range usually increases two-fold, and so a ratio of less than one is unusual in normal subjects and may indicate an abnormal gastric response to meal ingestion.

The Dominant frequency instability coefficient (%) is a measure of how much the dominant frequency changes over the period of investigation. It is defined as the coefficient of variation of dominant frequency (standard deviation/mean DF x 100%)

Abnormal rhythms include low frequency range (bradygastria), or high frequency range (tachygastria). Frequencies greater than 10cpm are thought to originate from respiration. Very low frequencies (<1cpm) are probably artefactual and are unlikely to originate from the stomach.

Numerous studies have been performed to validate the EGG [155-157] and it is now generally agreed that:

1) Dominant EGG frequency accurately reflects the frequency of the gastric slow waves, determining the maximum frequency of gastric contractions:

2) Relative changes of EGG amplitude or power are correlated with gastric contractions:

3) Gastric dysrhythmias are associated with gastric dysmotility.

## 2.5 **Statistics**

Non-parametric data were analysed using Fisher's exact test for 2 by 2 contingency tables and the Mann-Whitney U-test. For parametric data, an unpaired t test was used for comparison of differences between means in 2 groups. Statistical significance was ascribed to a p value of less than 0.05. All data are reported as medians and inter-quartile ranges unless otherwise stated.

# Chapter 3:

# Audit of Existing Surgical Standards in Anti-Reflux Therapy

### 3.1 Introduction:

Rudolph Nissen performed the first fundoplication [158] approximately 50 years ago. The efforts in recent years, both before and since the introduction of laparoscopic fundoplication[159] in the early 1990s, has focused on maximising effectiveness of fundoplication and minimising side-effects, in particular dysphagia. Despite numerous reports in the literature and several clinical trials, areas that remain controversial include the type of wrap, complete or partial [160], and the need to divide the short gastric vessels [161], close the hiatus (i.e. hiatoplasty) and the calibration of the wrap by an oesophageal bougie [162] . Laparoscopic Nissen fundoplication, first reported in 1991[97], is now well proven with respect to control of reflux, quality of life, short hospital stay, and cost savings, but the complication of dysphagia remains [99,163,164]. Perceived poorer outcome in a minority of patients after surgery is frequently based on symptoms other than dysphagia, often without reference to whether these post-operative symptoms are new or different.

This study was a prospective audit of a Units's 8 year experience of Rosetti -Nissen fundoplication using a predominantly laparoscopic technique, selective hiatal repair, no bougie and a standardised protocol of pre and postoperative functional endoscopic and symptom assessment. The goal was to evaluate symptomatic and physiological outcomes in a large cohort with good follow-up.

### 3.2 Methods:

A prospective database (Microsoft Excel) on patients with reflux disease was established in this Unit in 1997. The data include clinical features, endoscopic and pathologic grade of oesophagitis, quality of life, pH studies and manometry, and

surgical details and complications. In the period from 1997 to 2004, 378 patients underwent antireflux surgery. All patients had documented data on endoscopy, quality of life, surgical details and complications pre-operatively and at 6 months post-operatively. Seventy-seven percent of patients had pre-operative physiology studies, and 57% had post-operative pH studies. Motility studies were completed on 73% pre-operatively and 56% post-operatively. Repeat physiological testing was at 6 months.

**Operation and indications:** The Laparoscopic procedure used was Rossetti-Nissen fundoplication in all cases [165]. In brief, after dividing the phrenoesophageal ligament, the diaphragmatic crura are dissected, a Penrose drain is passed behind the esophagus and anterior to the posterior vagus, and a generous posterior window is created. The fundus is mobilized and freed posteriorly, but the short gastric vessels and the gastrosplenic omentum are left undisturbed. A judgement is made by the operating surgeon as to the need for hiatal repair, and if required one or two sutures are used to close posteriorly the diaphragmatic crura. Thereafter, a fold of the anterior fundus is brought behind the esophagus, and a loose $360^0$ wrap is created with 2 to 3 interrupted non-absorbable sutures (0 Ethibond, Ethicon, Dublin) over a length of 2 cm. No bougie is used, and the "floppiness" of the wrap is deemed satisfactory by both surgeons prior to closure. Postoperatively, free fluids are permitted on day 1, and a soft diet from day 2, and most patients are discharged on the second or third postoperative day.

### 3.3 Results:

There were 260 male and 118 female patients. The median age was 42 y (range 16-77). All patients had been receiving acid-suppression therapy, either PPI's and/or histamine-2 receptor antagonists for at least 6 months before surgery. All patients

underwent Rosetti-Nissen Fundoplication; 270 laparoscopically and 108 via an open procedure. One-hundred and seventy patients had no oesophagitis pre-operatively, 86 had grade A, 59 had grade B, 45 had grade C, and 18 had grade D oesophagitis by the LA classification. Of patients with grade D oesophagitis, there were 7 with ulcers and 11 had strictures. There were 78 patients with Barrett's oesophagus confirmed by biopsy; the outcome of 58 of these have been reported previously[166].

**Hiatal Hernia:** Fifty-nine percent (222/378) of patients had hiatal hernia pre-operatively, 21% of these were >5 cms long.

**Symptoms:** Preoperative median symptom scores while off medication were grade 0 dysphagia ( 68%), grade 3 regurgitation (73%) and grade 3 heartburn (86.7%). At a median follow-up of 6 months, symptom scoring showed significant improvement for dysphagia, regurgitation and heartburn (Table 7). Eighty-two percent (311/378) had no symptoms or had minor symptoms not interfering with quality of life or requiring medication. Eighty-nine percent of patients (336/378) considered the outcome to be excellent or good. Out of a total of 60 patients complaining of heartburn post-operatively, 9 had the same heartburn score and 51 had improved heartburn score. Thirty-eight patients (10%) developed significant recurring symptoms at the time of questioning and all were back on regular PPI medication. Despite recurrent symptoms in these 38 patients 28 considered surgery to have been successful in controlling regurgitation and believed they had a good outcome.

| | Pre-Op | Post-Op p | |
|---|---|---|---|
| Dysphagia | 0 (0-3) | 0 (0-3) | <0.01 |
| Regurgitation | 3 (0-3) | 0 (0-3) | < 0.001 |
| Heartburn Frequency | 3 (0-3) | 0 (0-3) | < 0.001 |

**Table 7 : Median Symptoms Scores pre surgery and at median 6 months post surgery.**

One hundred and seventeen patients had pre-operative dysphagia, in 78 cases (67%) this symptom resolved, 39 persisted, 3 of whom worsened post-operatively. Seventy-five percent of patients (283/378) had no early dysphagia i.e within the first 3 months postoperatively. Ninety-five patients (25%) had some element of postoperative dysphagia, in most cases [71 (75%)] describing a transient sensation of food sticking, ie grade 1 dysphagia. Sixteen (17%) of patients with dysphagia had grade 2 dysphagia, without stricture, characterized by food sticking and cleared by liquids. There was no intervention in 9 of these at 6 m after surgery. Eight patients with dysphagia (8%) had grade 3 symptoms, 6 of whom had pre-existing strictures (Table 8).

Thirty-six patients had a dilatation within 6 months post-operatively, eighteen of these patients (50%) had grade D esophagitis of which 11 were with strictures before surgery. Of the total of 95 patients with any dysphagia, 91 reported the outcome of their surgery to be excellent or good. Two of remaining four patients had reoperation without improvement in QOL, one of the wraps were found to be undone at endoscopy. The other two patients had dilatations at three and four months respectively. All of these four patients were back on medication with Visick scores 3-4.

| | |
|---|---|
| No dysphagia (%) | 283 (75) |
| Grade 1 dysphagia (%) | 71 (19) |
| Grade 2 dysphagia (%) | 16 (4) |
| Grade 3 dysphagia (%) | 8 (2) |

**Table 8: Post-operative Early Dysphagia ( within 3 months)**

**Quality of Life:** The principal parameters ie emotional distress, sleep disturbance, food and drink problems, physical and social functioning, and vitality, had all significantly improved at a median of 6 months after surgery compared with pre-operative values (Table 9). The 38 patients with recurrent symptoms had QOL scores <10 in each QOL category, which was significantly less ($p<0.01$) than the scores for the entire group.

| | Pre-op | Post-op | p |
|---|---|---|---|
| Emotional Distress | 16 (6-42) | 42 (7-42) | < 0.001 |
| Sleep Disturbance | 14 (5-35) | 35 (5-35) | < 0.001 |
| Food/Drink Problems | 13 (6-42) | 42 (6-42) | < 0.001 |
| Physical/ Social Functioning | 15 (5-35) | 35 (8-35) | < 0.001 |
| Vitality | 7 (3-21) | 21 (4-21) | < 0.001 |

**Table 9 : Median QOL Scores at median 6 months after surgery**

**pH Monitoring: :** A total of 290 (77%) patients presented for pH studies pre-operatively and 215 (57%) post-operatively, although all patients were invited for postoperative studies. There was a significant decrease in DeMeester acid scores, from a median of 41 pre-operatively to 3.5 at 6 months after surgery (Table 10). All other reflux parameters showed a similar trend. Fourteen patients had heartburn and abnormal pH profile post-operatively. Thirty-one (14%) were either symptomatic with normal or abnormal pH profiles, or asymptomatic with abnormal pH profiles after

surgery. There were 23 (11 %) positive post-operative pH studies. A further 8 (4%) patients were symptomatic for heartburn with normal pH profile.

**Oesophageal Motility:** Two-hundred and seventy-seven patients had manometry pre-operatively and 213 post-operatively at a median of 6 months (Table 10). Seventy-seven (28%) patients had dysmotility before surgery; 29 of these reverted to normal motility and 5 patients who had normal pre-operative motility, developed ineffective motility post-operatively. Distal oesophageal amplitudes were significantly increased (Table 4) after surgery. A comparison of pH & motility parameters between patients with dysmotility and normal motility showed no significant differences.

| | Preop | Postop | p |
|---|---|---|---|
| Manometry data | | | |
| LOSP (mmHg) | 6.0 (3-30) | 15 (7-35) | <0.001 |
| Amplitude (mmHg) | 45 (30-277) | 59 (38-170) | <0.01 |
| Dysmotility (%) | 28 | 11 | <0.01 |
| | | | |
| pH data | | | |
| Acid Score | 41(7-246) | 3.4 (0.2-102) | <0.001 |
| % Total | 11 (6-74) | 0.6 (0-25) | <0.001 |
| % Upright | 12 (7-68) | 0.9 (0-23) | <0.001 |
| % Supine | 7.7(0-94) | 0 (0-60) | <0.001 |
| % Postprandial | 16 (0-73) | 0.6 (0-20) | <0.001 |
| | | | |
| Acid Control (%) | 192/215(89%) | | |

**Table 10: Manometry & pH Data pre and at median 6 months after surgery.**

### 3.4 Discussion

This study shows improved symptom scoring and QOL after Rosetti- Nissen fundoplication with an 89% patient satisfaction rate, consistent with the best results in the literature. The mix of open and laparoscopic techniques reflects the gradual introduction over this time period of the laparoscopic approach. Twenty-five percent of patients had early dysphagia. The occasional transient sensation of food sticking occurred in 18% of the total group and represents 75% of the dysphagia problems, whether this represents a complication or is an anticipated sequalae of total fundoplication is a moot point. In this regard, of the 95 patients reporting any grade of dysphagia, 91 reported the outcome of surgery to be excellent or good. Thirty-eight patients (10%) had recurring heartburn and 28 were back on medication at 6 months post-op. Thirty-one patients (14%) of 215 who had functional studies post-operatively either complained of heartburn with or without evidence of acid reflux on pH studies or no heartburn with abnormal pH profile. Of these patients, 14 (45 %) showed persistent reflux and symptoms, 9 (29%) were asymptomatic with abnormal pH and 8 (4%) patients were symptomatic with normal pH profile.

Symptoms alone can be notoriously unreliable in GORD, as evidenced by the wide variety of symptoms reported with normal and abnormal acid exposure. Patients with suspected oesophageal disorders complain of odynophagia, pharyngeal pain, nausea, belching, retrosternal pain, acid regurgitation, retrosternal burning and heartburn with almost equal frequency irrespective of pH profile status [167]. A wide variety of post-operative symptoms after fundoplication have been reported, including heartburn, regurgitation and chest pain. Ten to 20% of patients complain of postoperative side effects such as dysphagia, bloating, and excessive flatulence [168,169] . However, there is

poor correlation with post-operative symptoms and abnormal distal esophageal acid exposure. Many patients are on inappropriate maintenance therapy: Lord[170] showed absence of GORD in the majority of patients taking acid suppression medication after Nissen's fundoplication.

Multifactorial analysis of factors that determine the outcome of antireflux surgery have been attempted by many groups [171,172]. Among the factors identified as prognostic for success are case volume and expert centres. Patient-related factors have included erosive versus non-erosive disease, gender, and upright compared to combined upright and supine pH profile [173]. There has been vigorous debate as to whether the laparoscopic technique has similar long-term outcome compared to open procedure. Open and laparoscopic fundoplications were not directly compared in this series, but the outcomes were similar, consistent with that of no significant differences in postoperative results[174] in 6 randomized controlled trials regarding recurrence, dysphagia, bloating and re-operation rates at 3-24 months.

Anti-reflux interventional procedures are still evolving. Indications for intervention, technique and outcome assessment are not fully standardised. In our experience the procedure of Rosetti-Nissen fundoplication, with noo esophageal bougie, no division of short gastric vessels is a simple and effective procedure giving 89% patient satisfaction and significant improvement in QOL parameters and physiologic measurements. This establishes the quality standard within this Unit, and further studies aim to simplify the technique, improve a physiological understanding of symptoms and outcomes, and to minimise sequelae, particularly dysphagia.

# Chapter 4:

# Quality Initiative in Anti-reflux Surgery: Combined Endoscopic and Laparoscopic Approach

## 4.1 Introduction:

Since the first fundoplication by Rudolph Nissen in 1956 [95] the magnitude of the operative insult, the complication of gas-bloat relating to a long fundoplication, and the problem of persistent dysphagia resulted in poor acceptance among many, in particular medical gastroenterologists. De Meester modified the open technique, and in a seminal paper in 1986 reported three modifications that were associated with excellent long-term control of reflux and a reduction of persistent dysphagia from 21% to 3%: complete division of the short gastric vessels, use of a large oesophageal bougie (60Ch), and a short wrap, reduced from 4cm to 1-2cm [96]. This latter understanding helped simplify the laparoscopic approach, first reported in 1991[97,163], and , despite the widespread availability of proton pump inhibitors, the years succeeding these reports has seen an enormous increase in anti-reflux surgery. The laparoscopic approach is well proven with respect to control of reflux, quality of life, short hospital stay, and cost savings, but the complication of dysphagia remains, and further technical improvements in the laparoscopic approach largely aim to minimise this risk[99,164,175,176].

The principle of the short wrap is widely accepted, but other technical elements remain controversial. Much of the focus in the literature has been on partial versus total wraps, division of short gastric vessels, and calibration of the wrap by an oesophageal bougie, and all remain unproven by Grade A evidence [176]. In this tertiary Unit, the standard approach has been the Rosetti modification of the Nissen fundoplication, with no division of the short gastric vessels, no bougie, and selective hiatal repair, as outlined in the previous Section and in published work [166].

In this study the addition of on-table endoscopic assessment of the wrap, noting positioning, looseness, and angulation, was introduced as a simple quality assessment tool, and this study reports the impact of this assessment on outcomes, with a particular focus on the complication of postoperative dysphagia.

### 4.2 Patients and Methods:

**Study population and Design:** This study reports on 153 consecutive patients, from 2001 to the December 2004. On-table endoscopy was introduced in late 2003, and the study was designed as a simple adjunct to an established audited technique performed by two surgeons experienced in laparoscopic upper gastrointestinal surgery, both of whom had performed over 100 fundoplications each. The patients were divided into two groups: Group 1 underwent no on-table endosocopy, and Group 2 had endoscopy on completion of what appeared laparoscopically to be a satisfactory result. Patients were followed up symptomatically at one month and at 6 months, and by physiological assessment at 6 months.

**Operation and indications:** Laparoscopic Rosetti Nissen Fundoplication was the technique employed in all cases[177], and is described fully in the previous Chapter. Of note, no bougie is used, and the "floppiness" of the wrap is deemed satisfactory prior to closure by both senior surgeons. In the study group, an endoscopy was performed on patients at the completion of the procedure, giving a combination of simultaneous endoscopic and laparoscopic views of the wrap. Postoperatively, free fluids are permitted on day 1, and a soft diet from day 2, and most patients are discharged on the second or third postoperative day.

**Oesophageal Function studies:** These were performed as described previously on all patients preoperatively. At 6 months postoperatively patients were invited to have the test repeated.

### 4.3 Results

Demographics, including endoscopic grading, and preoperative symptom scores is shown in Table 11. There was no difference between groups, and the majority of patients in each group had severe heartburn and regurgitation. A dysphagia grade of 2 or 3 was present preoperatively in 15 patients (15%) in Group 1 and 3 patients (6%) in Group 2, and a grade of 1 was reported in 12% and 19% in groups 1 and 2 respectively. All patients were on proton pump inhibitors at the time of surgery, and over 90 per cent of patients in each group were on treatment for over 12 months. .

In Group 1, 15 patients (15%) had Grade 3 or 4 esophagitis, compared with 10 (19%) in Group 2, and 26 (26%) in Group 1 had B, C or D esophagitis, compared with 20 (43%) in Group 2. Barretts esophagus was present in 21% and 23% respectively.

| | Group 1 (n=100) | Group 2 (n=53) |
|---|---|---|
| Male / female | 71/29 | 37/16 |
| LA Classification | | |
| 0 | 32 | 11(21) |
| A | 42 | 10(20) |
| B | 13 | 12(23) |
| C | 9 | 5(8) |
| D | 4 | 3(5) |
| | | |
| Barretts | 21 | 12(23) |
| 1 | 74 | 31(58) |
| 2 | 11 | 12(23) |
| 3 | 11 | 6(11) |
| 4 | 4 | 4(7) |
| | | |
| Dysphagia score | | |
| 0 | 73 | 40(75) |
| 1 | 12 | 10(20) |
| 2 | 10 | 2(3) |
| 3 | 5 | 1(2) |
| | | |
| Regurgitation Score | | |
| 0 | 4 | 0 |
| 1 | 8 | 8(15) |
| 2 | 26 | 9(17) |
| 3 | 62 | 36(68) |
| | | |
| Heartburn Score | | |
| 0 | 2 | 2(3) |
| 1 | 1 | 2(3) |
| 2 | 4 | 5(9) |
| 3 | 93 | 44(85) |
| | | |
| * Group 1: n = number and percent. Group 2: n (%) | | |

**Table 11:DEMOGRAPHICS AND PRE-OPERATIVE SCORES**

**Surgery and Intra-operative Modifications**

Hiatal closure was performed in 62 patients (62%) in Group 1 and 34 (64%) in Group 2. In Group 2, 5 patients had modifications of the wrap performed based on endoscopic assessment, in 3 cases because of angulation at the cardia, and in 2 cases where the J-manouvere showed that the stack of coils were not parallel, suggested a rotated or angulated fundoplication.

**Postoperative Dysphagia**

The reported prevalence of early (within 1 month) and late (at 6 month assessment) dysphagia, and the need for endoscopic or surgical reintervention is shown in Table 12.

| | | Group 1 (n=100) | Group 2 (n=53) |
|---|---|---|---|
| | | | |
| Early Dysphagia | 0 | 69 | 41(77) |
| | 1 | 16 | 10(19) |
| | 2 | 5 | 1(2) |
| | 3 | 10 | 1(2) |
| | | | |
| Late Dysphagia | 0 | 73 | 48(91) |
| | 1 | 20 | 4(7) |
| | 2 | 4 | 1(2) |
| | 3 | 3 | 0 |
| | | | |
| Reintervention | None | 87 | 50(95) |
| | Dilatation | 11 | 3(5) |
| | Re-operation | 2 | 0 |
| | | | |
| Group 1: n = number and percent. Group 2: n (%) | | | |

**Table 12: Postoperative Dysphagia and Reinterventions**

An occasional transient sensation of dysphagia (grade 1) was reported by 15% in Group 1 and 19% in Group 2. There was significant ($p < 0.0001$) differences in both groups in episodes of dysphagia requiring liquids to clear, 5% vs 1% in groups 1 and 2 repectively, and in severe symptomatic dysphagia, 10% vs 1 per cent. At 6 months follow-up, just one patient in group 2 had occasional dysphagia for solids, compared with 7 in group 1, 3 of whom had troubling symptoms ($p < 0.001$).

In group 1 eleven patients (11%) underwent endoscopy and dilatation, 8 on one occasion and 3 more than once, and 2 underwent re-operaration, where in both cases excessive fibrosis and scarring of the wrap to a repaired hiatus was evident.

**Symptomatic outcome:**

At a minimum follow-up of 6 months, 88% of patients in group 1 and 95% in group 2 had no symptoms or had minor symptoms not interfering with quality of life or requiring medication. Ninety three per cent compared with 100% in groups 1 and 2 respectively considered the outcome to be excellent or good. Ten percent of patients in Group 1 reported Grade 2 or 3 heartburn, compared with none in group 2.

**Manometry and pH studies (Table 13):**

The median preoperative acid reflux score was similar in groups 1 and 2. Postoperatively 58 in group 1 and 30 in group 2 agreed to undergo repeat studies, and these cohorts included all patients who had dysphagia or recurrent symptoms. Postoperatively there was a significant reduction in the DeMeester score in both groups, from 37(18-146) to 2.5(0.2-55) in group 1, and 42(19-196) to 4.2 (0.3-8.8) in group 2 ($p < 0.001$ pre vs post ; $p =$ ns, Group 1 vs 2). All other reflux parameters

showed a similar trend and there was no significant difference between the two groups. Acid control, however, defined as a DeMeester score less than 15, was achieved in all patients tested (n=30) in group 2 compared with 85% (50/58) of patients in group 1.

Lower oesophageal sphincter pressure increased significantly in both groups, as well as the amplitude of contractions. Oesophageal dysmotility, present in 31% of group 1 patients and 36% of group 2 patients preoperatively, was still evident in 15 and 17% respectively at 6 months follow-up.

| | Group 1 | | Group 2 | |
|---|---|---|---|---|
| Manometry | Pre | Post | Pre | Post |
| LOSP (mm Hg) | 6(5-15) | 14 (5-40) ** | 6(3-8) | 13(7-23) ** |
| Amplitude | 54 (30-277) | 71 (35-153) * | 59(10-131) | 73(16-155) * |
| (mm Hg) | | | | |
| Dysmotility | 31% | 15% | 36% | 17% |
| PH Data | | | | |
| Acid Score | 37(18-146) | 2.5(0.3-55) *** | 42(19-196) | 4.2(0.3-8.8) *** |
| % Total | 11(3-42) | 0.4(0-15.5) *** | 13(4-59) | 0.7(0-4.5) *** |
| % Upright | 13(2.5-44) | 0.7(0-12) *** | 15(1.7-53) | 1.2(0-3.9) *** |
| % Supine | 6.4(0.1-65) | 0(0-16.7) | 8.7(0-67) | 0(0-2.4) |
| % Post Prandial | 17(4.2-63) | 0.5(0-24.9) *** | 22.5(2.5-95) | 0.7(0-16) *** |
| Acid Control | | 50/58 (85%) | | 30/30 (100%) |
| | | | | |
| ( pre vs post *** $p<0.001$, ** $p<0.01$, * $p<0.05$) | | | | |

**Table 13: Manometry & pH Data**

## 4.4 Discussion

In both the open and laparoscopic era this Unit has favoured the Rosetti modification of the Nissen fundoplication. This technique as originally described uses an anterior fold of fundus for the right limb of the fundoplication, rather than the posterior wall of the fully mobilised fundus as per the Nissen approach[176,178]. The procedure does not require division of the short gastric vessels, utilises selective hiatal repair, and no sutures are inserted in the esophagus as the risk of wrap migration is low. Although Rosetti originally utilised a small (24Ch to 30Ch) bougie in the stomach from the beginning of the operation, and many surgeons use very large bougies, up to 60Ch, the use of a bougie was abandoned in this Unit in 1997 after a mid oesophageal perforation from a 56Ch bougie required a thoracotomy and repair. The patient survived without major sequelae, but since then the Unit protocol does not require bougie calibration, and has involved both principal surgeons either working in combination on these cases or auditing the key technical steps and intra-operative outcome of each fundoplication. The outcomes from the control group in this study and from other reports[179] is consistent with respect to control of reflux with benchmarks from the open and laparoscopic literature, and the focus in the Unit has increasingly been on attempting to eliminate the problem of early and persistent dysphagia, and re-operation. In this report, in a sequential prospective analysis of the value of the adjunct of on-table endoscopy at the completion of fundoplication compared with the 100 previous cases without endoscopy performed by an experienced team, a significant qualitative improvement for these primary goals was achieved.

There are several qualitative assessments achievable through on-table endoscopy. First, the endoscope must pass easily into the stomach, without obstruction or angulation at the level of the wrap, or at the cardia. Either event requires refashioning of the wrap, and this was observed in three cases in this series. Second, retroversion of the endoscope in the stomach, the J manouvere, allows for visualisation of the swirl pattern of folds, the so-called "stacked coils" appearance, which should be in precise alignment along the long axis of the endoscope [180,181]. If the alignment is incorrect, it may infer oblique angulation across the cardia, and should be corrected. In this latter scenario, redundant gastric fundus may be observed above the fundoplication. Finally, the location of the wrap relative to the squamocolumnar junction, normally located below the lower esophageal sphincter, can be determined. Although no formal scoring system was utilised in this study, it may be possible, using an 11 point criteria for the endoscopic appraisal of the gastroesopageal valve, recently described by Jobe et al [182] in relation to postoperative assessment, to develop a modified assessment tool for intraoperative assessment.

The study of dysphagia is relatively complex, for several reasons [162,164,176]. First, the symptom may be present in many patients prior to surgery, reported to some degree in 26% of patients in this report, more commonly associated with oesophagitis and acquired dysmotility. Second, published reports may also be imprecise with respect to the definition of dysphagia, the grading of symptoms, and the timing of study, and studies frequently use different systems of dysphagia assessment. Early postoperative dysphagia is common and almost invariably temporary, with no identifiable cause, perhaps relating to oedema, stretching or hypomotility. Identifiable causes include a tight fundoplication, a slipped fundoplication, hiatal stenosis or paraoesophageal

herniation [162]. In this study, where early Dysphagia was defined to be within the first three months after surgery, some element of dysphagia was reported in 43/153(28%) of patients, with Grade 2 or 3 dysphagia reported in 17 patients.

Long-term dysphagia, most commonly assessed beyond three months, and in this study at six months, is reported in between 5 and 30 per cent of cases [162,176,181]. In addition to persistence of identifiable mechanical factors that commonly are evident early after surgery, and occasional persistence of severe oesophagitis or stricturing, fundoplication may also predispose to dysphagia by increasing lower oesophageal sphincter pressure, both resting and residual pressure on swallowing, impairing lower oesophageal sphincter pressure on swallowing, delaying oesophageal emptying, promoting retrograde competence in the presence of gastric distension, and inhibiting transient LOS relaxation [181,183]. In one report, patients with pre-existing normal LOS pressures had a higher incidence of postoperative dysphagia than patients with reduced sphincter pressure [184]. In this study, grade 2 or 3 dysphagia was evident in 8/153 (5%) of patients, consistent with the lower end of the reported series. If grade 1 is included, this rises to 32/153 (21%), but whether the occasional transient sensation of food sticking justifiably comes under the umbrella of dysphagia as a complication rather than an occasional sequelae of a fundoplication is a moot point.

In this sequential prospective study, we have shown that the addition of on-table endoscopy post fundoplication has significantly impacted on the problem of dysphagia, and the need for re-intervention. Early dysphagia, grade 3 in 10% of the control group, and in 2% of the study group, was markedly reduced, and the need for endoscopy and dilatation, required in 11 patients in the control group, with early re-

operation in 2, was reduced to no re-operation and 3 endoscopies and dilatation in the study group. Persistent dysphagia of grade 2 or 3 was reduced from 7 to 2 per cent. In terms of symptom control, quality of life and physiologic assessment of acid reflux and manometry, there was little difference between the groups. In both groups, a significant decrease was evident in acid reflux, an increase in lower oesophageal sphincter pressure, an increase in oesophageal pressure amplitude, and in many cases pre-existing oesophageal dysmotility was reversed. The association of symptom control with control of acid reflux attests to the benefit of the fundoplicaton, as symptom control does not always correlate with physiologic control with non-surgical approaches [140,162]. Moreover, effective acid control was observed in all patients who underwent on-table endoscopy, compared with 85% in the cohort that did not.

The report also highlights the efficacy of the laparoscopic Rosetti Nissen fundoplication. Given its simplicity, with no requirement for short gastric division or bougie, the overall study suggests that this is an effective anti-reflux operation and challenges tenets from the open era which are associated with an approximately 0.5-1% risk of oesophageal perforation and a longer operating time. In this regard, there is no evidence from randomised trials supporting the routine division of short gastric vessels [182]. The only randomised study [162] evaluating a bougie appeared to show a reduction in dysphagia from 31 to 17%, and of severe dysphagia from 14% to 5%, but paradoxically more patients (9.9%) in the bougie group underwent dilitation compared with the non-bougie group (7.8%). This study, particularly with the added refinement of on-table endoscopy, raises questions posed by others as to its routine value [186].

There are elements of the study open to critical comment. First, it is not a randomised trial, and even though each surgeon had performed over 100 procedures prior to this analysis and were comfortably beyond the learning curve [186], it is possible that qualitative improvement with experience is a continuous process. Second, since only the group 2 cohort represent the study group, bias in technical elements within this study cohort is possible. Finally, the rate of re-intervention in the study group was low, reflecting in large part the reduced incidence of dysphagia, but the confidence gained from completely satisfactory on-table endoscopy may increase the threshold for endoscopic dilatation in this group and further skew the differences in a non-randomised study. Notwithstanding these issues, the data supports on-table endoscopy as a futher qualitative improvement to a successful technique, and the subjective experience of this initiative, as well as the objective evaluation, is compelling enough for neither surgeon to be enthusiastic about further evaluation within a randomised trial.

In conclusion, in a prospective sequential study of the addition of on-table endoscopy to laparoscopic Rosetti-Nissen fundoplication, a significant reduction in early and late dysphagia, and endoscopic and operative re-intervention was observed. Technical adjustments were made in 5 patients (9%), but the data suggests that endoscopic knowledge of lack of tightness, angulation and redundant fundus may have clearly defined benefits, and the study supports this approach as a qualitative improvement in laparoscopic antireflux surgery.

# Chapter 5:

# Assessment of the Suitability of a 360-degree Fundoplication in Patients with Pre-existing Manometric Evidence of Oesophageal Dysmotility

## 5.1 Introduction:

Medical management remains the standard initial therapy for symptomatic gastroesophageal reflux disease (GORD) [185,186]. Control of reflux symptoms with medical therapy is not always corroborated by physiologic evidence of control of acid reflux, and symptoms can be completely absent in the presence of high acid exposure [187,188]. In contrast, Nissen fundoplication provides control of reflux in addition to excellent long-lasting relief of symptoms, and the advent of the laparoscopic era has shifted the paradigm towards early consideration of anti-reflux surgery in patients with severe reflux [189]. A by-product of successful surgery may be an improvement in reflux-acquired motility disturbances of the oesophagus [190]. The choice of surgery in the presence of reflux-associated dysmotility is controversial, whether to perform the 360-degree wrap of a total (Nissen) fundoplication and theoretically increase the risk of post-operative dysphagia, or to perform a partial wrap with reduced risk of dysphagia but a higher likelihood of treatment failure [191,192].

The policy in this Unit has been to perform a total fundoplication on all patients with reflux-acquired dysmotilty. The report herein highlights the lessons learned from this experience.

## 5.2 Patients and Methods:

**Study population and Design:** In the period 1996 – 2003, 315 patients underwent anti-reflux surgery. This study reports on 98 patients, 38 with dysmotility, the entire cohort who presented during this period, and 60 patients with normal motility, selected based on the fulfilment of having had all the tests including clinical assessment, quality of life studies and repeat physiological testing at 6 months

postoperatively. The patients were divided into two groups based on their pre-operative oesophageal manometry. Group 1 had normal motility and group 2 had dysmotility, defined as evidence of hypocontraction in the distal oesophagus with at least 30% of wet swallows exhibiting any combination of the following abnormalities: (1) distal oesophageal peristaltic wave amplitude <30 mm Hg, (2) simultaneous contractions with amplitudes < 30 mm Hg, (3) failed peristalsis in which the peristaltic wave did not tranverse the entire length of the distal oesophagus, or (4) absent peristalsis [143].

**Operation :** The Rosetti Nissen Fundoplication was the technique employed in all cases.

**Symptom assessment:** Symptomatic outcome was assessed by completion of standardized reflux and quality of life questionnaires. Severity of GORD symptoms and dysphagia were assessed pre-operatively, when off medication, according to the self-completed modified DeMeester Scoring System [140]. The QOLRAD [141] quality of life questionnaire was completed independently by the patients pre-operatively and at or after 6 months post surgery.

**Oesophageal Function studies:** pH studies and manometry were performed as described in previous Chapters.

## 5.3 Results

There were 66 male patients and 32 female patients. Male to female ratio was similar for the normal and dysmotility groups. The median age was 45(range 16-74) and the median weight was 73.2 kg at operation. The duration of reflux symptoms ranged from 0.5 to 5 years, with a median of 3 years. All patients were on acid suppression therapy, either proton pump inhibitors (PPIs) and/or histamine- 2 receptor antagonists (H2RA) for at least 6 months prior to surgery. All patients underwent a Rosetti-Nissen Fundoplication, 75 laparoscopically.

In the normal motility group, 34 patients had no oesophagitis, 15 had Grade A, 6 had Grade B and 5 had Grade C oesophagitis. In the dysmotility group, 16 had no oesophagitis, 9 had Grade A, 2 Grade B, 7 Grade C, and 4 had Grade D oesophagitis with strictures.

**Symptomatic outcome:**

At a median follow-up of 6 months, 88% (53/60) in the normal motility group versus 89% (34/38) in the dysmotility group had no symptoms or had minor symptoms not interfering with quality of life or requiring medication. Eighty-nine per cent (53/60) versus 92% (35/38) of patients considered the outcome to be excellent or good. Eleven patients (7 in normal group, 4 in the dysmotility group) had developed significant recurrent symptoms at the time of questioning (= heartburn score 2 or 3) and all were back on regular proton pump inhibitor medication (Table 14).

| | Normal Motility (n=60) | | Dysmotility (n=38) | | |
|---|---|---|---|---|---|
| Symptoms | Pre-OP | Post-Op | Pre-Op | Post-Op | p |
| Dysphagia | 0(0-2) | 0(0-2) | 1(0-3) | 0(0-3) | ns |
| Regurgitation | 3(1-3) | 0(0-2) | 3(0-3) | 0(0-3) | ns |
| Heartburn Frequency | 3(1-3) | 0(0-3) | 3(0-3) | 0(0-3) | ns |

**Table 14: Median Symptom Scores**

Eight of these 11 post-operative 24-hour pH studies had abnormal post-operative DeMeester scores (5 from the normal motility group and 3 from the dysmotility group). Despite recurrent symptoms in these eight patients, 3 from the normal motility group and 2 from the dysmotlity group considered that surgery had been successful in controlling regurgitation and felt that they had a good outcome.

| | Normal Motility (n=60) | Dysmotility (n=38) |
|---|---|---|
| Recurrent Symptoms | 7 (12%) | 4 (11%) |
| Recurrent Symptoms plus abnormal pH | 5 (8%) | 3 (9%) |
| | | |
| No Dysphagia | 43 (72%) | 26 (68%) |
| Grade 1 Dysphagia | 12 (20%) | 7 (18%) |
| Grade 2 Dysphagia | 5 (8%) | 2 (5%) |
| Grade 3 Dysphagia | 0 | 3 (9%) |
| | | |
| Difficulty Burping | 9 (15%) | 3 (9%) |
| Difficulty Vomiting | 6 (10%) | 7 (18%) |

**Table 15: Post-operative symptoms.**

Seventy percent (69/98) had no dysphagia during this six month period i.e Grade 0 [( normal in 72%, vs dysmotility in 68%) ]. Nineteen patients (19%) reported a transient sensation of food sticking ie Grade 1 dysphagia (20% vs 18%). Seven percent (7/98) of patients had grade 2 dysphagia characterized by food cleared by liquids (8% vs 5%). All three patients with Grade 3 dysphagia were from the dysmotility group. In the normal motility group, 2 of 60 (3%) of patients overall and 2 of 17 (12%) with an episode of dysphagia required intervention with dilitation or re-operation, and in the dysmotility group, 3 of 38 (8%) overall and 3 of 12 (25%) with dysphagia required dilatation ( p =ns). All 3 patients had Grade D oesophagitis with strictures preoperatively. Of the 29 patients reporting any dysphagia whatsoever, 28 reported the outcome of their surgery as excellent or good.

**Quality of Life**

The baseline QOLRAD scores were not significantly different between the normal motility and the dysmotility group (Table 16). The principal parameters, emotional distress, sleep disturbances, food/drink problems, physical/social functioning, and vitality all significantly improved at 6 months postoperatively compared with pre-operative values. Eleven patients with recurrent symptoms all had QOLRAD scores less than 10 in each QOL category, which was significantly less than the scores for the entire groups.

| | Normal Motility (n=60) | | Dysmotility (n=38) | |
|---|---|---|---|---|
| QOLRAD | Pre-Op | Post-Op | Pre-OP | Post-Op |
| Emotional Distress | 16.5 (6-34) | 42 (13-42)*** | 13.5 (6-42) | 42 (6-24) *** |
| Sleep Disturbance | 14 ((5-35) | 35 (10-35)*** | 11.5 (5-35) | 35 (5-35) *** |
| Food/Drink Problems | 13.5 (6-23) | 41 (16-42)*** | 12 (6-42) | 40 (6-24) *** |
| Physical/Social Functioning | 14 (5-33) | 35 (13-35)*** | 14.5 (5-35) | 31.1 (5-35) *** |
| Vitality | 7 (3-14) | 21 (7-21) *** | 6.5 (3-21) | 21 (3-21) *** |

**Table 16: Quality of Life ( *** p < 0.001)**

**Manometry and pH studies (Table 17):**

The median preoperative acid reflux score was significantly higher in the dysmotility group compared with the normal motility group ($p< 0.001$). Postoperatively there was a significant reduction in the DeMeester score in both groups, from 36(7-186) to 2.5(0.2-128) in the normal motility group, and 53(22-197) to 4.2 (0.3-102) in the dysmotility group ($p <0.001$ pre vs post; p = ns, Group 1 vs 2). All other reflux parameters showed a similar trend and there were no significant differences between the two groups. Lower oesophageal sphincter pressure increased significantly from 6(5-15) mmHg pre- to 15(5-40) mmHg post-surgery in the normal motility group and 6(5-45) to 12.5 (5-22) in the dysmotility group ( $p <0.001$). Thirteen patients had a DeMeester score above normal (>15.0) after their surgery, 8 of whom were from the normal motility group and 5 from the dysmotility group [median (range) 31.7(19-128) versus 27.7 (19.9-55.4)].

Distal oesophageal amplitudes were significantly increased after surgery in both groups. Twenty patients (54%) in the dysmotility group reverted to normal motility after surgery. Of note, 4 patients in Group 1 developed ineffective motility post-operatively. The statistically significant difference between the amplitudes in each group pre-operatively was maintained post-operatively in spite of increased amplitudes in Group 2 and lack of abnormal motility in 54% of patients in this group.

| | Normal Motility (n=60) | | Dysmotility (n=38) | |
|---|---|---|---|---|
| Manometry | Pre | Post | Pre | Post |
| LOSP mmHg | 6(5-15) | 15(5-40) ** | 6(5-45) | 12.5(5-22) ** |
| Amplitude mmHg | 50(30-227) * | 69(35-153) | 23(10-25) | 36(10-94) * |
| Dysmotility | 0% | 6% | 100% | 46% |

| | Normal Motility (n=60) | | Dysmotility (n=38) | |
|---|---|---|---|---|
| pH Data | Pre | Post | Pre | Post |
| Acid Score | 36(7-186) | 2.5(0.2-128)*** | 53(22-197) | 4.2(0.3-102)** |
| % Total | 10(6-49) | 0.4(0-29) *** | 13(7-65) | 0.8(0-24) *** |
| % Upright | 13(7-61) | 0.7(0-18) *** | 15(7.5-68) | 1.2(0-26) *** |
| % Supine | 6.4(0-84) | 0(0-62) | 8.7(0-72) | 0(0-55) |
| % Post Prandial | 17(0-73) | 0.5(0-24) *** | 22.5(2.5-95) | 0.7(0-16) *** |
| Acid Control | | 52/60 (87% ) | | 33/38 (87%) |

**Table 17: Manometry & pH Data**
*** p<0.05, ** p< 0.01 , *** p<0.001**

## 5.4 Discussion

This study supports the view that a total 360-degree fundoplication is appropriate even in presence of manometrically-confirmed pre-existing GORD-induced dysmotility. Many surgeons favour partial fundoplication in this scenario out of concern that a compete wrap will result in high dysphagia rates, and that dysmotility may not be reversible [193].This study indicates that the attainment of effective symptom and acid control and quality of life by a 360-degree wrap is achieved in patients in patients with reflux-acquired oesophageal dysmotility, that the majority of patients had a normal motility pattern postoperatively, and that the overall incidence of any type of dysphagia is not increased.

The majority of recent studies on antireflux surgery have concentrated on operative technique [194]. Gotley [140] reviewed 200 consecutive cases of laparoscopic Nissen and showed excellent short-term symptomatic and pH results but did not focus on oesophageal body motility. Reliance on symptoms alone may not be sufficient to measure outcome as evidenced by persistence of acid reflux [195,196] in the absence of symptoms. Munitiz et al [197] reviewed 93 patients who had open Nissen fundoplication and compared outcome based on pre-operative motility. The study reported that in a cohort of 41 patients with pre-operative ineffective motility who were followed for a median of 6.5 years, 37 had excellent clinical results, 2 patients developed severe dysphagia, and 2 developed late dysphagia due to a stricture relating to failed surgery. Eighteen of 26 patients in the dysmotility group who had a hypokinetic motor pattern recovered normal motility. The conclusion from this study regarding the acceptability of a total fundoplication in patients with ineffective motility was the same as the study reported herein, but some differences were evident: pathological GORD, measured at

1 year in the study of Munitiz et al, was evident in 20% of patients in the dysmotility group and 12% in the normal group, compared with 13% in the normal and dysmotility groups in this current study. Post-operative oesophageal amplitude increased in the ineffective motility group but was unchanged in the normal group in the study of Munitiz et al, contrasting with an improvement in both the normal and dysmotility groups in this study. This assessment in our study is consistent with a recent study by Scheffer et al which reported an increase in amplitude following surgery in patients with reflux and normal motility [198]. This study has shown that an improvement in motility at 3 months post-surgery is also likely to persist in the longer term, and supports our choice of 6month as a reasonable timepoint for functional assessment. The suggestion is that an increase in oesophageal peristaltic amplitude after Nissen fundoplication represents a compensatory mechanism to overcome the increased resistance at the gastroesophageal junction

Few studies have combined quality of life parameters with function studies to measure outcome after Nissen fundoplication. Studies [199] on the endoscopic treatment of GORD have reported improved QOLRAD measures in spite of incomplete acid control. This study shows that the quality of life outcome is related to acid control. We have moreover demonstrated that QOLRAD is significantly improved after surgery and the improvement is equally significant in patients with pre-operative normal motility or dysmotility. Patients with recurrent symptoms were more likely to have poorer quality of life outcomes in our study. We believe that the QOLRAD is a useful measure of outcome when combined with the other symptom scores and physiological indices.

This study supports the view that it is not necessary to tailor antireflux surgery according to preoperative manometry findings. We also suggest that acid control and increased oesophageal amplitude are indicators of good outcome. Patients are often reluctant to undergo repeat pH and manometry, especially if they are feeling well, but we suggest that these tests are valuable tools in post-operative evaluation, we were able to complete these tests in 100 percent of patients with dysmotility and it is increasingly becoming the standard for all our patients who have undergone anti-reflux surgery. In summary, this study has shown that pre-operative dysmotility does not have a higher rate of post-operative dysphagia or symptoms. Recurrent symptoms interfering with quality of life are more likely to be associated with incomplete acid control. Good outcome with improved quality of life after Rosetti Nissen fundoplication is equally achieved in patients with oesophageal dysmotility as in patients with normal motility, this relates to acid control and improved oesophageal clearance.

# Chapter 6:

# Laryngopharyngeal Reflux (LPR) in GORD, and Relationship to Laryngeal Symptoms and Implications in Surgical Management

## 6.1 Introduction

Few studies have simultaneously documented distal acid exposure, measured at the conventional oesophageal site, with LPR, mainly due to the difficulty of accurate placement of the pH probe during 24 hour monitoring. Oesophageal length can vary between 17-27 cm[200] and the use of a dual channel pH probe with a fixed distance between the sensors will result in the proximal sensor being sited at variable distances in relation to the upper oesophageal sphincter (UOS): it may be above or below the UOS, if the distal sensor is placed at a conventional 5 cms from the proximal border of the lower oesophageal sphincter (LOS). Some investigators have used two pH catheters to get over this difficulty [201] but this approach is often poorly tolerated by the patient and the added bulk of the second catheter may affect oesophageal motility.

Recent research has suggested that LPR may occur even when distal gastroesophageal reflux is within normal limits [202]. This has led to speculation that the patterns, mechanisms and manifestations of LPR are different to GORD. The aims of our study were (1) to document LPR in GORD and (2) to assess the value of fixed distance dual channel pH monitoring in identifying LPR in patients with GORD.

## 6.2 Patients and Methods

All patients referred to the GI Function Laboratory during a 12 month period, with symptoms of GORD, were included in the study. GORD symptom questionnaires, oesophageal manometry and dual channel 24 hour pH monitoring were completed in all patients. In addition, an ENT questionnaire was added as part of the prospective database after the start of the study and a sub-group of consecutive patients completed this also (appendix 6).

**24 hour pH Monitoring:** All patients discontinued proton pump inhibitors for a minimum of 10 days and other anti-reflux medications for at least 48 hours prior to the study. Twenty four hour pH monitoring was carried out by positioning a dual channel antimony pH probe with sensors spaced 21 cms apart, with the distal sensor at 5cms above the proximal border of the LOS and connected to a Mark III Digitrapper (Medtronic, Denmark). Distance (D) between the proximal borders of the LOS and UOS was calculated from data obtained at manometry. The position of the pH probe in relation to the proximal border of the upper oesophageal sphincter was then calculated as (26-D) cms where 26 represents the spacing between the pH sensors plus 5 cms. Only studies with the proximal pH sensor positioned at or above the proximal border of the UOS were included. The total percentage of time and the fractions of time in the upright and supine positions with pH < 4.0, and the number of reflux events were determined for the oesophageal sensor. A pH drop below 5.0, with onset to nadir in <20s, recorded by the proximal sensor and accompanied by a simultaneous pH drop in oesophageal pH below 4.0, was deemed to be a positive LPR event [203,204]. A diagnosis of a positive LPR study required at least three of these events, excluding meal periods. Each patient was instructed to continue with normal activity with the exception of avoidance of highly acidic or carbonated food.

### 6.3 Results:

A total of 276 patients were included in the study. The male to female ratio was 3:2 and the median age was 49 yrs (range 16-74).

**pH Studies:** All 276 patients completed dual channel pH monitoring. The median (range) distance of the proximal pH sensor above the proximal border of the UOS was 2 cm (0-4 cm). One-hundred and fifteen (42%) patients were positive for LPR on 24h pH monitoring and 105 (91.3%) of these studies corresponded with a distal acid score which exceeded a normal threshold of 15.0 (DeMeester Score). Further analysis of the data using a threshold value of pH 4.0 reduced the +ve LPR results to 21% (57/276). Distal percentage oesophageal acid exposure and numbers of reflux events was significantly greater in patients with +ve LPR (Table 18). Ten patients (9%) had laryngeal reflux and normal distal oesophageal acid exposure.

| | **LPR +ve (n=115)** | **LPR –ve (n=161)** | **p** |
|---|---|---|---|
| DeMeester Acid Score | 57 +/- 4.6 (4-295) | 33.2+/-2.7 (0-205) | <0.001 |
| Upright % pH <4.0 | 14.7+/-1.0 (1.5-64) | 8.6 +/-0.7 (0-49) | <0.001 |
| Supine % pH < 4.0 | 13.3+/-1.8 (0-100) | 7.6+/-1.0 (0-66) | <0.001 |
| Number of Events | 177+/-9.5 (27-672) | 117+/-7.6 (0-677) | <0.001 |
| GERD-HRQOL Score | 21.5+/-1.2 (0-49) | 19.3+/-0.9 (0-50) | ns |
| Regurgitation Score | 1.3 +/-0.1 (0-3) | 1.1 +/-0.1 (0-3) | ns |
| Abnormal Esophageal Acid Exposure (%) | 91 | 62 | <0.001 |

**Table 18: Distal Oesophageal acid exposure & GORD symptoms in patients with and without documented LPR. Mean +/- SEM (range).**

**Manometry:** All patients had manometry performed (Table 19). There was a significant difference between LOS pressures; patients with -ve LPR having higher LOS pressures. Distal oesophageal amplitude and length were equivalent for both groups. The incidence of oesophageal dysmotility was also similar for both groups;

ineffective oesophageal motility being the most common diagnosis. UOS pressures were also measured and there were no significant differences between patients with +ve and –ve LPR for this parameter.

| | +ve LPR (n=115) | -ve LPR (n=161) | p |
|---|---|---|---|
| LOSP (mmHg) | 7.0+/-0.4 (3-22) | 9.8+/- 0.4 (3-30) | 0.03 |
| UOSP (mm Hg) | 43.6+/-2.4 (23-160) | 45.7+/-2.2 (19-170) | ns |
| Distal Amplitude (mm Hg) | 61+/-3.1 (7-180) | 64+/-3.0 (5-223) | ns |
| Dysmotility (%) | 28/115 (24%) | 36/161 (22.4%) | ns |
| Oesophageal Length (cm) | 20+/-0.1 (17-25) | 20+/-0.1 (16-24) | ns |

**Table 19: Manometry Data & LPR diagnosed by pHmetry. Mean+/- SEM (range)**

**Symptoms:** All patients completed the GORD-HRQOL questionnaire and regurgitation score. There were no significant differences between patients with positive and negative LPR on 24h pH (Table 20) for these two parameters. A sub-group of 120 consecutive patients completed the RSI questionnaire for LPR in addition to GORD-HLQOL questionnaire, regurgitation score, dual-channel pH and manometry studies. Sixty-three patients (53%) had positive laryngeal symptom score (RSI>13) but only 22 (35%) were positive for LPR on pH monitoring (Table 20). Of the remaining 57 patients with negative laryngeal symptom scores, 31 (54%) were positive for LPR on pH monitoring. Laryngeal signs and symptoms were equally prevalent irrespective of +ve LPR and included: hoarseness and +ve LPR versus –ve LPR (23% vs 24%), throat clearing (29% vs 32%), excess mucus (23% vs 36%), breathing difficulties (19% vs 26%), annoying cough (21% vs 24%) and globus (29% vs 35%). There were no significant differences between laryngeal scores and incidence of LPR (Table 21).

| | Symptomatic | Asymptomatic |
|---|---|---|
| | RSI >13 (n=63) | RSI < 13 (n=57) |
| LPR +ve | 65.9+/-14.4 (4-295) | 61.7+/-9.1 (8-259) |
| (n) | (22) | (31) |
| LPR –ve | 30.5 +/-6.7 (1-205) | 28.6+/-5.5 (4-161) |
| (n) | (41) | (26) |
| p value | <0.001 | <0.002 |

**Table 20: DeMeester Acid Score & Laryngeal Symptoms (RSI) Mean +/- SEM (range).**

| | +ve LPR | -ve LPR | p |
|---|---|---|---|
| | (n=53) | (n=67) | |
| Hoarseness or a problem with your voice | 0(0-5) | 0(0-5) | ns |
| Clearing your throat | 0(0-5) | 2(0-5) | ns |
| Excess throat mucus or postnasal drip | 0(0-5) | 1(0-5) | ns |
| Difficulty swallowing food, liquids or pills | 0(0-5) | 0(0-5) | ns |
| Coughing after eating or lying down | 0(0-5) | 0(0-5) | ns |
| Breathing difficulties or choking episodes | 0(0-5) | 0(0-5) | ns |
| Troublesome or annoying cough | 0(0-5) | 0(0-5) | ns |
| Sensation of something sticking or lump in your throat | 0(0-5) | 2(0-5) | ns |
| Heartburn, chest pain, or stomach acid. | 3.5(0-5) | 4.0(0-5) | ns |

**Table 21: Comparison of Laryngeal symptom scores (Reflux Symptom Index) for LPR positive and LPR negative on 24 h pHmetry. Median (range).**

## 6.4 Discussion:

Chronic laryngitis and intractible sore throats are associated with acid reflux in as many as 60% of patients[205]. GORD is the third leading cause of chronic cough [206], after sinus problems and asthma, accounting for 20% of cases. Globus sensation may be caused by GORD in 25-50% of cases[207]. In symptomatic patients, laryngoscopic evaluation often suggests reflux by identifying signs of possible inflammation including erythema, edema, ulceration, vocal cord nodules, granuloma, or leukoplakia, and carcinoma [208]. The majority of LPR studies have concentrated on the cause and effect relationship between laryngeal symptoms and signs and GORD. However, few studies have looked at the incidence of LPR in the GORD population. This study identifies a high incidence of LPR (42%), using a pharyngeal pH threshold of 5.0 , reducing to 21% at threshold of pH 4.0, in patients with GORD. The majority of patients with +ve LPR (91.3%) in our study showed abnormal reflux into the distal oesophagus. The RSI questionnaire for LPR failed to show any correlation with LPR identified in GORD patients. There was no significant difference in LPR incidence between patients with laryngeal symptoms and those who did not have layngeal symptoms (Table 20). This sub-group also showed a significantly higher acid exposure in patients with +LPR on pH study.

Although acid reflux is a common aetiological factor, the signs and symptoms of disease vary considerably between GORD and LPR. This study revealed that increased oesophageal reflux does not necessarily correspond with an increased incidence of laryngeal symptoms. Recent research has shown that in acidic refluxate, pepsin and conjugated bile acids are the most injurious agents affecting laryngeal tissue [209,210]. Animal studies show that upper airway tissue is profoundly sensitive to

gastric contents; reflux events with a frequency of as little as a few times per week, may cause significant pathology [211].

Initial hopes that monitoring proximal oesophageal or hypopharyngeal acid reflux events might predict reflux related laryngeal signs have been tempered by the findings that reflux in the upper oesophagus and even hypopharyngeal areas may be prevalent in as much as 20% of asymptomatic normal volunteers [212]. There is no consensus on the range of normal for the number of pharyngeal acidification events or the fraction of time in a 24h period that is compatible with physiological reflux [213]. Hypo-pharyngeal pH monitoring has poor sensitivity and specificity for GORD; only 54% of patients with suspected laryngeal signs of GORD having abnormal oesophageal acid exposure, irrespective of the location of the pH probe [214]. This low accuracy rate may be due to either overdiagnosis of GORD as the cause of laryngeal pathology or poor analysis technique [215,216].

In this study the incidence of distal esophageal reflux in LPR positive patients with GORD was 91% for LPR positive, and 62% for LPR negative. Oelschlager[217] investigated typical symptoms of LPR and their predictability for the presence of LPR, documented as more than one episode of pharyngeal reflux with pH below 4.0, each corresponding with to a simultaneous episode of distal esophageal reflux. The incidence of distal oesophageal relux for patients with suspected reflux-induced airway disease was 76% for LPR positive and 51% for LPR negative. A limitation of this study was that the oesophageal pH sensor was placed at a median 12 cm (range 2-20) above the LOS and it was therefore difficult to conclude whether individual patients had normal amounts of oesophageal acid exposure. We acknowledge a criticism of our study that the proximal pH probe was not consistently placed at a

fixed distance from the UOS. To limit variation and error due to this we only included studies where the proximal pH probe was at or above the UOS.

In summary, this study attempted to examine the theories that LPR and GORD are distinct diseases and to document the incidence of LPR as diagnosed by dual probe 24 hour pH monitoring. We conclude that simultaneous oesophageal and laryngeal reflux can easily be documented with a fixed distance dual sensor pH probe. There is a high incidence of LPR in the GORD population but this may not translate into laryngeal disease, perhaps because the composition of the refluxate in GORD may not be always injurious to the hypo pharynx. Moreover, the diagnosis of LPR in the absence of symptoms and signs of laryngeal disease may not be diagnostically useful. It is also a plausible interpretation of our findings that LPR and moderate GORD are distinct, and further studies are required to investigate the role of the composition of the refluxate in LPR.

# Chapter 7:

# Evaluation of Gastric Function in GORD, and Impact of Laparoscopic Fundoplication

## 7.1 Introduction:

The impact of gastric motility on both gastroesophageal reflux disease (GORD) and anti-reflux surgery is unclear. These may both be important areas of study in understanding the range of effects of anti-reflux surgery, particularly since subgroups of patients with GORD are known to have delayed gastric emptying [218]. There is a proven association between gastric dysrythmia and gastric emptying [219]. Gastric motility can be documented by the technique of electrogastrography (EGG). EGG is evaluated in terms of changes in gastric wave amplitude and frequency after a standard meal. Deviations from the normal frequency of 3 cycles per minute are referred to as brady- or tachyarrhythmia. While not a direct measure of gastric emptying, EGG focuses on the underlying myoelectrical activity.

The aims of this prospective study were to investigate the role of gastric motility in GORD and after anti-reflux surgery, and its influence, if any, on proximal migration of oesophageal reflux. EGG was assessed before and after a standard meal. In addition, oesophageal manometry and dual channel 24 hour pH monitoring, was measured pre and post Laparoscopic Rosetti Nissen Fundoplication.

## 7.2 Methods:

The study group consisted of 27 symptomatic patients, with documented gastroesophageal reflux on 24 hour pH monitoring. All patients had detailed history, symptom questionnaire, manometry & pH and EGG studies before surgery and at approximately 6 months post-operatively.

**Symptom scoring:** Symptomatic outcome was assessed by completion of standardized reflux and quality-of-life questionnaires before surgery and again at least 6 months after surgery (Appendix 1-4).

**Multi-Channel Electrogastrography:** Patients referred for EGG were fasting for at least six hours, usually from midnight, having discontinued all drugs known to alter gastric myoelectrical activity (pro-kinetic or anti-emetic drugs) 48 h prior to investigation. The patient was encouraged to remain perfectly still for the duration of the study, approx. 2- 3 hr., and refrained from using Walkman, mobile phones etc. Recordings were made in a semi- recumbent position (30°-45°). This procedure is outlined in Materials and Methods (chapter 2).

**24 hour pH Monitoring:** All patients discontinued proton pump inhibitors for a minimum of 10 days and other anti-reflux medications for at least 48 hours prior to the study. Twenty four hour pH monitoring was carried out by positioning a dual channel antimony pH probe with sensors spaced 21 cms apart, with the distal sensor at 5cms above the proximal border of the LES and connected to a Mark III Digitrapper (Medtronic, Denmark). This procedure is previously described in Materila and Methods (chapter 2).

**Oesophageal Manometry:** Stationary perfused oesophageal manometry was carried out using a 4-lumen oesophageal catheter (Mui, Ontario, Canada) with side holes at 5cm apart and orientated at 90 degrees from each other. The catheter was passed per nares and positioned in the stomach. It was then withdrawn by 1cm increments to

document the lower oesophageal sphincter pressure (LOSP). LOSP was measured as end expiratory pressure at the point of respiratory reversal. Three proximal sensors were then advanced to the oesophageal body and the fourth sensor was positioned within the LOS. Oesophageal body function was assessed by measuring the presence of peristalsis in the oesophageal body in response to 5ml boluses of water as previously described (chapter 2).

### 7.3 Results:

Twenty-seven patients were eligible for inclusion in the study. Three patients had previous endotherapy and a further 12 patients had Barrett's oesophagus. All patients completed manometry, 24 hour pH, LPR and EGG investigations before and after laparoscopic Rosetti Nissen fundoplication. Post-operative assessment was at a mean of 215 days. Mean age was 44.5 years.

**Symptoms:** Preoperative median symptom scores while off medication were grade 0 dysphagia ( 68%), grade 3 regurgitation (73%) and grade 3 heartburn (86.7%). At a median follow-up of 6 months, symptom scoring showed significant improvement for dysphagia, regurgitation and heartburn (Table 22). Eighty-two percent had no symptoms or had minor symptoms not interfering with quality of life or requiring medication. Seven patients had developed significant recurring symptoms at the time of questioning and all were back on regular PPI medication. Post-operative symptoms were more likely to occur in patients with persistent gastric dysmotility and reflux.

| | Pre-Op | Post-Op | p |
|---|---|---|---|
| Dysphagia | 1 (0-3) | 0 (0-3) | <0.001 |
| Regurgitation | 3 (0-3) | 0 (0-3) | <0.001 |
| Heartburn Frequency | 3 (0-3) | 1 (0-3) | <0.001 |

**Table 22 : Median Symptoms Scores pre surgery and at median 6 months post surgery.**

**Gastric Function (EGG):** Seventy-four percent (20/27) of patients had some degree of pre-operative gastric dysrythmia (Fig: 22).

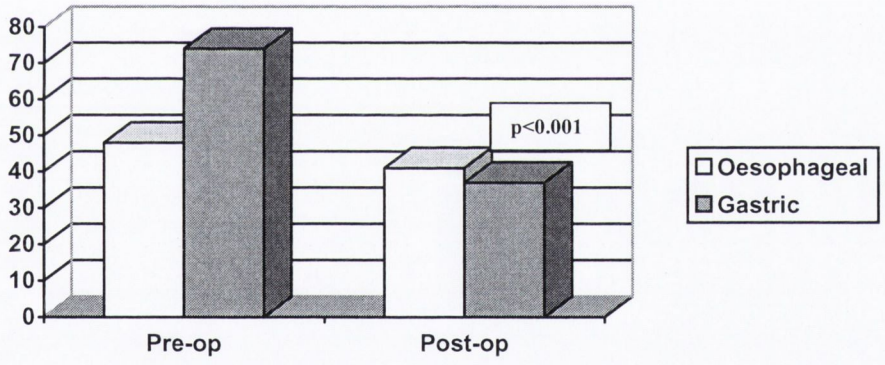



Fig. 22: Oesophageal & Gastric dysmotility

After surgery, 37% (10/27) of patients had abnormal percentages of basal electrical rythym (>70% range 2-4 cyles per minute). Comparing pre and post-operative values, (Fig. 23) bradygastria was significantly reduced from 25-5% ($p<0.001$), normagastria was significantly increased from 62-77% and tachygastria reduced from 9-5% (ns). Dominant frequency remained within the normal range but was significantly

increased ($p<0.01$) from 2.3 –3.0. Power ratio reduced from 2.1 to 1.8 (ns), but was consistent with an increase in force of contraction of gastric motility after meals, both before and after surgery. Sixteen patients who had preoperative gastric dysmotility had normal EGG post-operatively.

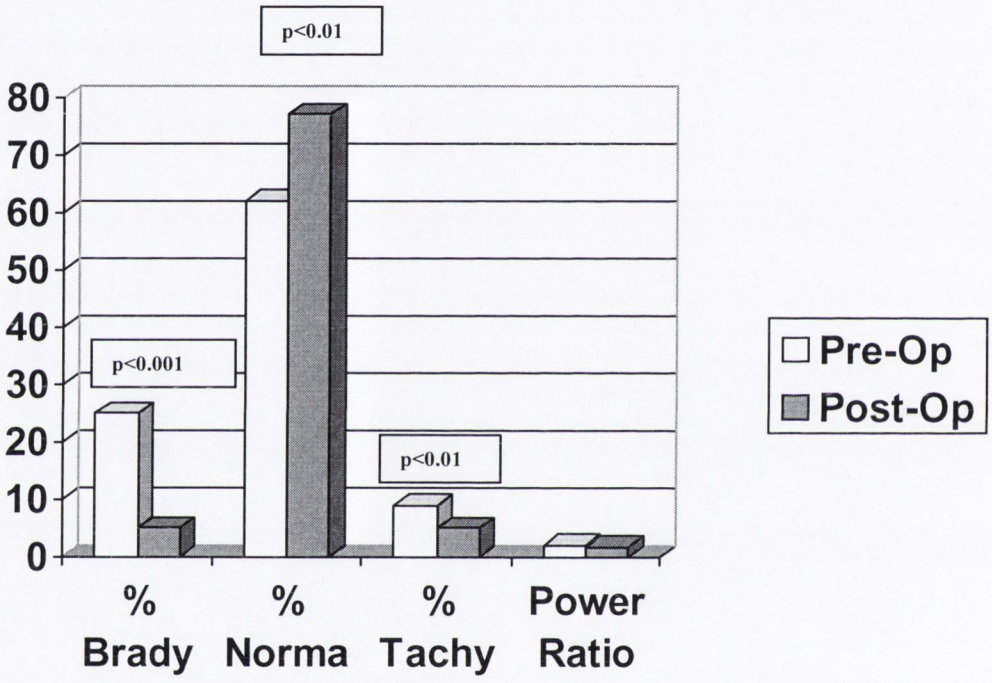



Fig.23 : Electrogastrography findings

**Oesophageal Manometry:** Lower oesophageal sphincter pressure and distal amplitude of oesophageal contraction were significantly increased after surgery. Ineffective oesophageal motility was present in 13 patients pre-operatively, two of whom reverted to normal motility post-operatively. There was no correlation between gastric and oesophageal dysmotility (Fig. 22).

| | Pre op | Post op | p |
|---|---|---|---|
| Manometry data | | | |
| LESP (mmHg) | 6.0 (3-20) | 15 (7-20) | <0.001 |
| Amplitude (mmHg) | 45 (30-89) | 59 (38-123) | <0.01 |
| Esophageal Dysmotility (%) | 48 | 41 | ns |
| Gastric Dysmotility (%) | 74 | 37 | <0.001 |
| pH data | | | |
| Acid Score | 69(17-180) | 10.9 (1-131) | <0.001 |
| % Total | 11 (6-74) | 4.1 (0-43) | <0.001 |
| % Upright | 12 (7-68) | 4.8 (0-32) | <0.001 |
| % Supine | 7.7(0-94) | 0.3 (0-60) | <0.01 |
| % Postprandial | 24 (6-72) | 2.6 (0-34) | <0.001 |
| LPR (%) | 18/27(67%) | 9/27(33%) | <0.01 |
| | | | |
| Acid Control(%) | | 21/27 (78%) | |

**Table 23: Manometry & pH Data preop and at median 6 months after surgery.**

**24 hour pH Monitoring:** DeMeester acid score reduced significantly from a pre-operative value of 63.4 to 14.1 (0.001). There was also a significant reduction in post-prandial reflux, from 29.9 to 2.6 % ($p < 0.001$) that was associated with an improvement in normagastria from a pre-operative value of 26% to a post-operative value of 76% (Table 23). Five patients had persistent post-operative reflux.

LPR was identified in 18 patients (67%) pre-operatively. This was significantly reduced ($p< 0.001$) to 9 positive LPR post-operatively. Five of these nine patients had abnormal post-operative DeMeester acid scores.

### 7.4 Discussion:

Gastric myoelectrical activity is responsible for controlling maximal frequency and aboral propagation of distal gastric contractions. An abnormal cutaneous EGG is more than 30% post-prandial gastric dysrhythmia and/or when meal ingestion fails to elicit an increase in signal amplitude [220]. This study showed that gastric dysrhythmia was present pre-operatively in GORD patients. Post-operatively, there was a significant improvement in normal EGG activity.

There is a paucity of studies focusing on gastric motility in anti-reflux surgery for GORD. Fundoplication is thought to alter the reservoir function of the fundus leading to reduced capacity and increased gastric tone [221]. This results in redistribution of gastric contents from fundus to antrum leading to enhancement of gastric emptying. A recent study showed increased presence of normal 3 cpm activity as a predominant effect of laparoscopic fundoplication on gastric myoelectric activity [222]. This finding supports the present study and suggests that extra-esophageal factors, including gastric dysmotility, may be of importance in the pathophysiology of GORD. The high incidence of pre-operative gastric dysmotility and significant improvement after surgery parallels the trend that delayed gastric emptying improves after surgery [223,224]. There was also a corresponding post-operative reduction in post-prandial gastro-esophageal reflux; supporting the theory that fundoplication interferes with the transient oesophageal sphincter relaxation mechanism (tLOSRs).

Suppression of gastric acid secretion with therapeutic doses of gastric acid suppressants is associated with delayed gastric emptying and increased antral motility [225]. Omeprazole eliminates the temporal relationship between intragastric pH and

characteristics of the migrating motor complex, and induces a delay in gastric emptying for both liquids and solids [226]. PPI usage may be implicated in the high incidence of gastric dysmotility identified in this study; all patients were on PPI medication for at least 6 months before their preoperative studies. Delayed gastric emptying is present in 10-33% of GORD patients [227] ,one suggested mechanism for reflux in this subgroup is that slowed gastric emptying may be associated with a progressive dilatation of the proximal stomach, which, in turn, shortens the length of the lower oesophageal sphincter until it becomes incompetent. More subtle postprandial abnormalities may contribute to gastric distension and tLOSRs. A study on proximal gastric tone, measured with an electronic barostat in GORD patients, showed that an exaggerated postprandial relaxation of the fundus, with retention of food, triggered tLOSRs[228]. GORD is characterised by increased numbers of reflux episodes which could be due to higher rates of tLOSRs, higher volumes of reflux during tLOSRs or reflux due to non-tLOSRs mechanisms. Iwakiri [230] investigated the hypothesis that the rate of acid reflux during tLOSRs in healthy subjects at the proximal margin of the LOS is similar to that of reflux patients. He found that the incidence of acid reflux 7 cm above the LOS during tLOSRs in GORD patients was significantly higher than controls but there was no difference 2 cm above the LOS. He concluded that reflux disease is not a disorder of tLOSRs but relates more to the proximal extent of the refluxate. There is evidence that reflux episodes occurring after meals, particularly during the early postprandial period, are more likely to reach higher proximal extent [229]. The additional association with gastric dysmotility provides some evidence that gastric motility may influence oesophageal clearance and patterns of reflux during tLOSRs, leading to proximal migration of reflux, and in some cases breaching the upper oesophageal sphincter causing LPR.

EGG is considered as an adjunct to gastric emptying measurements in correlating symptoms to gastric dysmotility [231,232]. A minority of patients develop new symptoms after fundoplication, most of which are attributed to anatomical and functional alterations at the gastroesophageal junction induced by the fundoplication. Fundoplication influences the function of the proximal stomach, the pattern of EGG, and gastric emptying. Delayed gastric emptying post-operatively is associated with postprandial distention, early satiety, dysphagia and gas bloat syndrome. At six months after surgery, we found that 5 patients had persistent post-operative acid reflux, 3 of whom were symptomatic and had abnormal EGG. Only two of 22 patients with normal post-operative pH and EGG had post-operative symptoms. Of 7 patients who were symptomatic post-operatively, 5 had abnormal post-operative EGG.

In summary abnormal gastric function promotes reflux of gastric contents into the oesophageal body in GORD. Rosetti Nissen fundoplication improves gastric dysmotility in addition to increasing lower oesophageal sphincter tone. We conclude that surgical control of reflux with a floppy Rosetti Nissen involves gastric motility, which in turn has consequences for proximal migration of oesophageal reflux. Control of acid reflux by surgery also appears to reduce the incidence of pharyngeal reflux. Further studies are required, however, to conclusively link gastric dysmotility with the occurrence of LPR.

# Chapter 8:

# Evaluation of Clinical and Physiological Outcomes after Endotherapy and Comparison with Fundoplication

## 8.1 Introduction

GORD was recognised as a clinical entity in the mid 1930's[233], the pathogenesis of which is complex and includes incompetence of the LOS. Today it is the commonest disorder of the gastro-intestinal tract [234 -236]. The aim of the management of GORD is to improve symptomatology, quality of life, and to prevent long-term complications. The dramatic increase in the incidence of adenocarcinoma of the oesophagus during the past 10 years are thought to result from several modifiable and interrelated risk factors, including chronic gastro-esophageal reflux disease[237]. This suggests that present management policies for GORD are inadequate and there is a need to find other more direct methods of repairing LOS function. The mainstay of medical therapy is the use of proton pump inhibitors (PPI's) [238-240] which effectively suppress gastric acid production but do not impact on an incompetent LOS. Patients for whom this therapy is inadequate become candidates for surgical therapy, and the Nissen fundoplication, first described by Rudolf Nissen in 1956[158], and the laparoscopic modification described by Dellemangne et al 1991[97], has become the standard surgical approach.

Fundoplication restores the competence of the LOS and very effectively controls GORD. Recently a variety of trans-endoscopic techniques have been developed which aim to directly correct impaired LOS function. The first of these was the transesophageal endoscopic plication (TEP) technique, which was originally described by Dr. Paul Swain[241] and later developed by BARD. We report herein a prospective non-randomised contemporaneous comparison of TEP compared with laparoscopic Rosetti Nissen fundolication (LNF) techniques.

## 8.2 Patients and Methods

Twenty-four patients were enrolled in the LNF and twenty-seven in the TEP group. All patients had persistent GORD symptoms that were dependent on continuous treatment with PPIs for their relief. In many instances patients were also experiencing breakthrough symptoms while on PPIs. Twenty-four hour oesophageal pH monitoring demonstrated pH < 4 for more than 4% of the time after discontinuing PPIs for 10 days, and antacids for 48 hours before the test. Patients agreed to be followed up for at least 12 months post procedure and also agreed to have repeat endoscopy and 24 hour oesophageal pH studies post procedure. The following groups were excluded: Age less than 18 years; dysphagia; body mass index (BMI) > 40; previous gastric or thoracic surgery; hiatus hernia > 2 cms length; oesophageal stricture; Barrett's oesophagus; patients on immunosuppressant drugs; patients with severe co-morbid illness or contra-indications for general surgery.

### *Patient Assessment*

The procedures were explained to all patients, and written and informed consent was obtained. Hospital ethics approval was also obtained for the study.

**Symptom scoring:** Severity of GORD symptoms were assessed when on and off medication, according to a validated symptom scoring scale[140]. A similar detailed history of all symptoms was obtained at 6 month and at a median duration of 12 months [10-18 months] post procedure.

**Endoscopy:** Upper gastrointestinal endoscopy was carried out pre- and at a mean duration of 3 months [2-4 months] post-procedure. Initial endoscopy established the

degree of oesophagitis present and the presence and size of any hiatus hernia. Post-procedure endoscopy also assessed the integrity of the plications.

**24 hour esophageal pH Monitoring, Manometry and Qualit of Life Assessment** were performed as described in the Methods Section (chapter 2).

**Assessment of complications:** The complication rate for dysphagia, difficult to vomit and belch were assessed by a modified version of the assessment described elsewhere[140]. Twenty-four hour oesophageal pH and esophageal manometry pre-and mean duration of 3-month [2-5months] post-procedure were analysed by the same physiologist.

**Dysphagia**

1. Can feel food sticking on occasion
2. Can feel food sticking and requires liquid to clear
3. Unable to swallow solid foods

**Vomiting**

1. Some difficulty in Vomiting
2. Unable to vomit

**Belching**

1. Some difficulty in belching
2. Unable to belch

**Transoesophageal endoscopic plication (TEP):** The TEP system included an overtube, suturing capsule attached to the endoscope, knot pusher and suture cutter. A minimum of two plications were placed in linear fashion 1cm and 2cm below the Z-line along the lesser curve. After sedating the patient (with midazolam and pethidine)

an oro-esophageal overtube (15.6mm inner diameter, 19.7 mm outer diameter, 30 cm long) was placed. The system was advanced through the over tube to a point 2 cm distal to the Z-line. The gastric mucosa was sucked into a suction chamber and the stitch was applied. The whole instrument was then drawn out to the surface, reloaded and re-inserted to deliver the second stitch adjacent to the first after rotating the endoscope to give 1 cm distance from the first stitch. The two stitches were knotted together to create the first plication. Similarly a second plication was applied 1 cm distal to the Z-line and linear to the first plication.

### 8.3 Results

Patient characteristics in both the LNF and TEP groups were comparable (Table 2). Mean duration of post-procedure follow up was 12 months in both the groups, (10-18 months in LNF and 11-14 months in TEP group). The mean procedure time was 65 (55-95) minutes for LNF, compared with 44 (25-90) minutes for the TEP procedure. The mean duration of stay was 3.5 days (2-7 days) for the LNF group, compared with 5.6 hours (4-24 hours) for TEP patients.

| | Lap Nissen | Endocinch |
|---|---|---|
| No. of patients | 24 | 27 |
| Age | 36yrs(17-68) | 39yrs(22-62) |
| M/F ratio | 16:8 | 15:12 |
| BMI | 25(17-33) | 26(21-34) |
| Hiatus Hernia | 6(3>5cms) | 6(<5cms) |
| Barretts | 0 | 0 |
| Mean follow-up | 12 months (10-18) | 12 months(11-14) |
| Mean procedure time | 65 minutes(55-95) | 44 minutes(25-90) |
| Mean duration of hospital stay | 3.5days | 5.6 hours |

**Table 24: Comparison of patient characteristics between Lap Rosetti Nissen Fudoplication and Endocinch**

**Symptoms:** There was significant improvement in the heartburn symptom score (frequency x severity) in both groups (LNF $p < 0.0001$ and TEP $p < 0.0001$) post procedure, which was maintained for at least a mean duration of 12 months, and was significantly better in the LNF group ($p=0.0383$) (Fig 24). The regurgitation frequency also significantly improved in both groups (LNF $p < 0.0001$ and TEP $p < 0.0001$), which was also maintained for at least 12 months ($p=0.208$) (Fig 25).

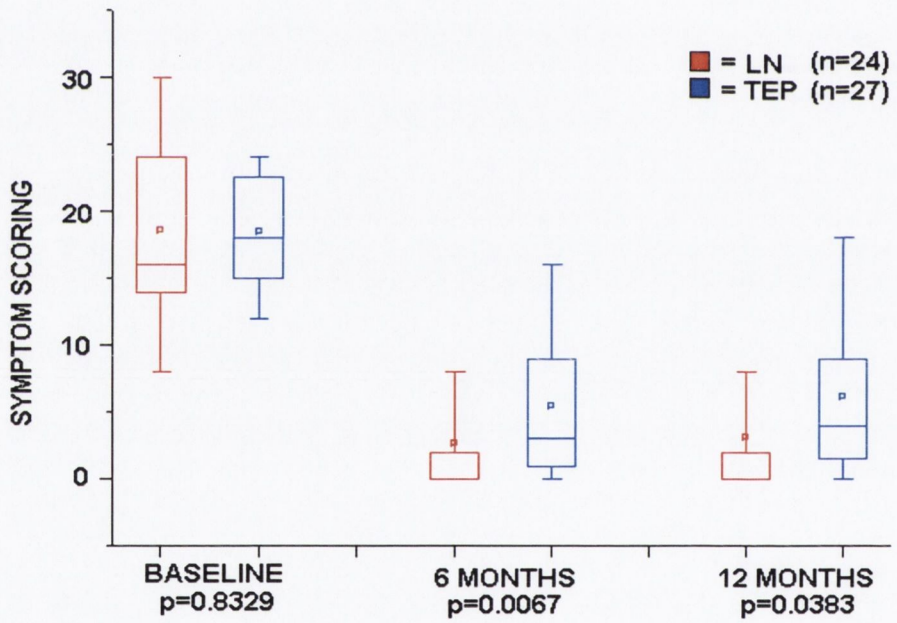



***Figure 24: Comparison (LNF Group vs TEP Group). Pre, 6 and 12 months post procedure symptom scoring of the patients data set where a maximum score is 30 and a minimum score 0.This is a box plot, where the horizontal lines of the box denote the inter-quartile range. The error bars denote the 5th and 95th percentile. The square symbol denotes the mean.***

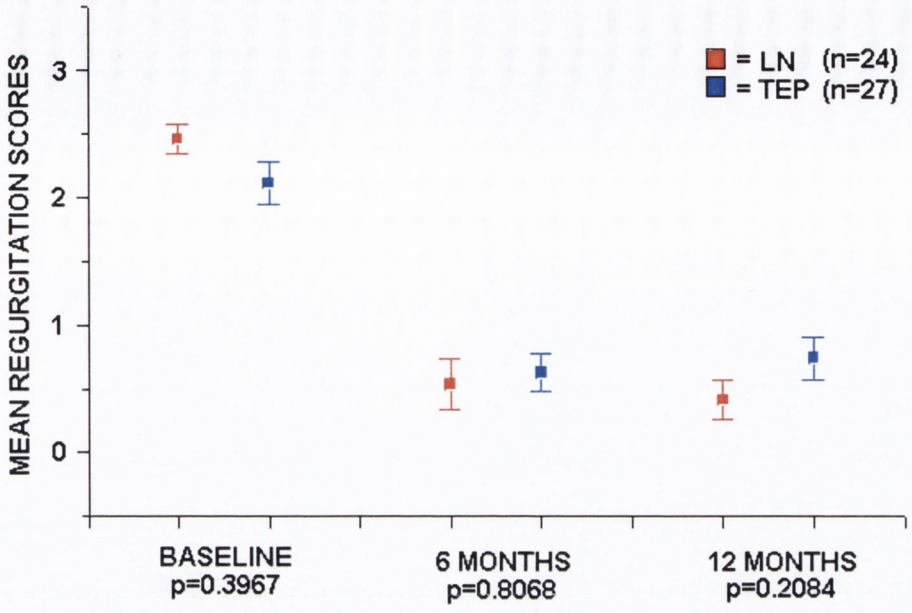



***Figure 25: Comparison (LNF Group vs TEP Group). Pre, 6 and 12 month post procedure mean of regurgitation scoring where maximum score is 3 and minimum score is 0.The square symbol denotes the mean and the error bars denote the standard error of the mean.***

**Endoscopic assessment:** All subjects underwent a repeat endoscopy at mean duration of 3 months [2-4 months] post procedure. In the TEP group, plications were found to be in position as recorded at the time of the procedure in 22 patients; in 3 patients one of the two plications had vanished and in 2 patients both plications had gone. There was no evidence of worsening of the degree of oesophagitis in any of these patients.

**Function Studies (Table 25):** Oesophageal pH values for both groups were compared pre and at a mean duration of 3 months [2-5 months] post procedure. Mean DeMeester acid score showed a significant improvement post procedure in both the groups (LNF $p=0.0003$ and TEP $p<0.05$) but was significantly better in the LNF group ($p=0.0007$) (Fig 26). 91% of patients in the LNF group achieved normal pH as compared to 48% in the TEP group. Both procedures were also effective in the reduction of the percentage of oesophageal pH values < 4 in the upright position

(LNF p< 0.0001 and TEP p=0.0047) and in the number of reflux episodes occurring in 24 hours (LNF p<0.0001 and TEP p=0.0007) and this effect was significantly better in the LNF group (Table 25). The manometric studies revealed no significant difference in pre and post procedure LOS pressures in the TEP group but were significantly improved in the LNF group in addition to the amplitude of contractions.

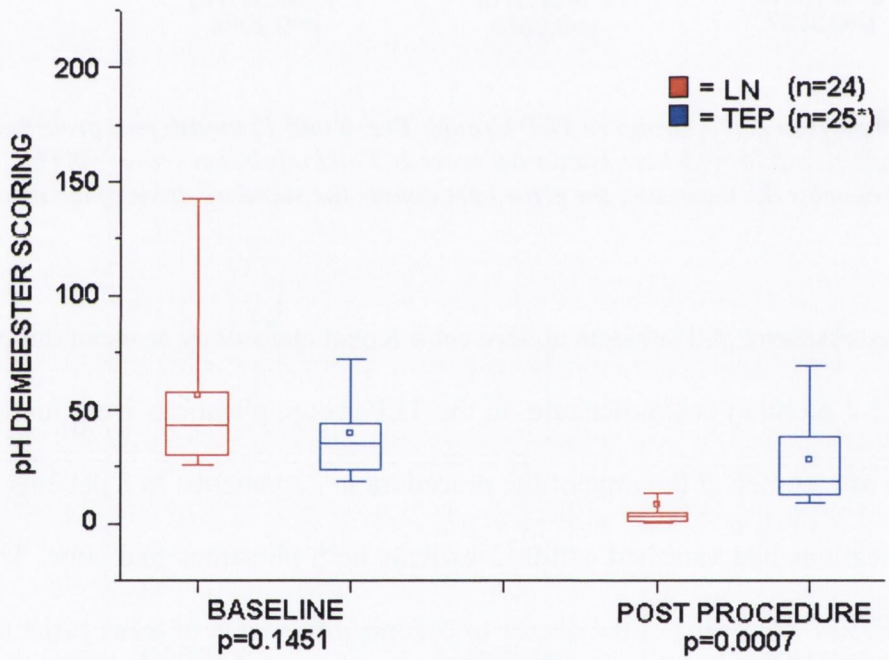



***Figure 26: Comparison (LNF Group vs TEP Group) of the pre-and post-procedure pH DeMeester scoring of each group of patients. This is a box plot, where the horizontal lines of the box denote the inter-quartile range. The error bars denote the 5th and 95th percentile.***
**** 2 patients in TEP Group failed to attend for follow up pH.***

| | **TEP n =25*** (Mean+/- SEM) | | | **LNF n= 24** (Mean+/- SEM) | | | **TEP vs LNF** |
|---|---|---|---|---|---|---|---|
| | **Pre** | **Post** | **p** | **Pre** | **Post** | **p** | **p** |
| **% Upright** | **12.7+/- 1.1** | **9.9+/- 1.2** | *** | **16.7+/- 2.1** | **1.2+/- 0.4** | *** | *** |
| **% Supine** | **5.5+/- 1.3** | **6.6+/- 1.8** | **ns** | **13+/- 4.7** | **0.3+/- 0.2** | *** | *** |
| **No Episodes** | **177 +/- 14.2** | **123+/- 11.4** | *** | **162+/- 17** | **37+/- 8** | *** | *** |
| **% Total** | **10.2+/- 0.9** | **8.5+/- 1.1** | **ns** | **15.5+/- 2.3** | **0.9+/-0.3** | *** | *** |
| **Acid Score** | **38.9+/- 3.4** | **32.5+/- 4.0** | **ns** | **56.6+/- 8.9** | **8.8+/- 4.3** | *** | *** |
| **LOSP** | **9.3+/- 1.8** | **9.7+/- 0.9** | **ns** | **6.4+/- 1.2** | **16.0+/-1.3** | *** | *** |
| **Amplitude** | **66.3+/-7.2** | **69.8+/- 7.2** | **ns** | **55.6+/- 6.7** | **73.4+/-7.3** | ** | **ns** |

**Table 25:** ***Pre and three month post procedure means of the 24 hour oesophageal pH values, LOS pressure and amplitude with standard error of means.***

****p<0.05*** ****p<0.01*** *****p<0.001***

**Consumption of Proton Pump Inhibitors (Fig. 27) :** Pre-procedure all patients were by definition taking PPIs. The requirement for PPIs was reduced to 13% (n=3/24) in the LNF and to 37% (n=10/27) in the TEP group at 12-month post procedure.

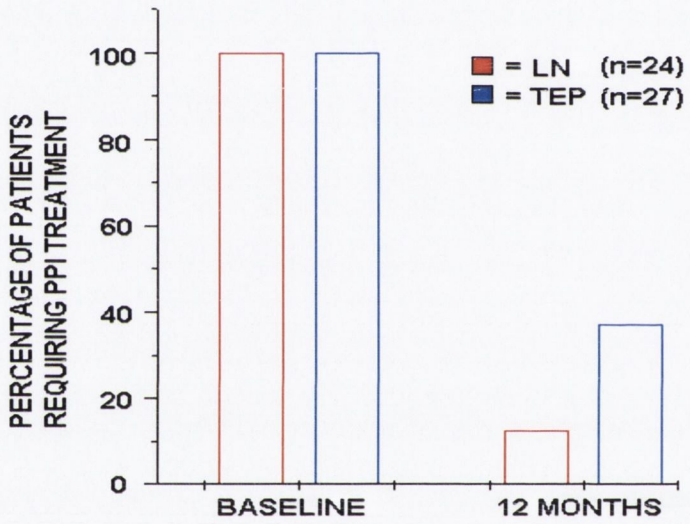



**Figure 27: Comparison (LNF vs TEP Group) of the pre- and post-procedure requirement for PPIs of each group of patients.This is a bar chart with the bar representing that percentage of patients requiring PPIs, where a requirement for PPIs is defined as greater than 4 doses per month.**

**Quality of Life Assessment(Fig. 28) :** There was a significant improvement in all five quality of life parameters at 12 month post procedure as compared to baseline in both the groups, but no significant difference between the two groups (p=0.1070) .

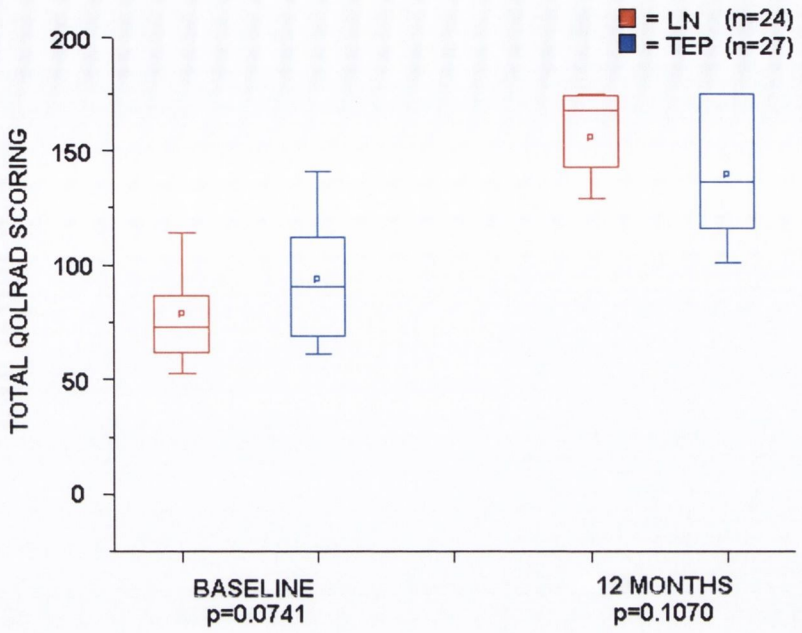



Figure 28: Comparison (LNF Group vs TEP Group) of the pre-and post-procedure combined totals of the 5 parameters of Quality of Life assessment where a maximum score is 175 and a minimum score is 0. This is a box plot, where the horizontal lines of the box denote the inter-quartile range. The error bars denote the 5$^{th}$ and 95$^{th}$ percentile. The square symbol denotes the mean.

**Complications at one year follow up:** There were no complications in the TEP group at one-year follow up. However the early postoperative transient complications included sore throat, vomiting, abdominal pain, chest soreness, and bloating and mild dysphagia. All the above complaints resolved spontaneously within 72 hours. Three patients had significant bleeds. Two patients received one unit of blood each. Both were retained for overnight observation. One patient had a gastric mucosal tear, which required no further attention. In the LNF group 4 patients had new onset moderate dysphagia and 2 had severe dysphagia requiring dilatation; 25%(n=6) had difficulty in vomiting (4% had some difficulty and 21% were unable to vomit), and 41% (n=10) also had difficulty in belching (33% had some difficulty and 8% were unable to belch).

## 8.4 Discussion

This study describes a non-randomized comparison of two separate populations of GORD patients who were treated by either laparoscopic fundolication (LNF) or an endoplication (TEP) technique. They were managed and followed up in the same hospital over the same time span and their progress was monitored using the same assessment methods. Both operations had zero mortality. The short-term complications following the TEP technique were minimal, consistent with previous reports[211].

Both treatments produced significant improvement in heartburn severity and quality of life (based on heartburn severity), and both interventions at one year of follow up significantly reduced the number of patients dependent on PPIs for control of their symptoms. The results were better following the LNF than the TEP technique, but the LNF does present some specific risks of complications, in particular dysphagia, and the often-unpleasant sequelae of an inability to vomit and belch, problems not observed after the TEP technique.

The study underscores the fact that the relationship between symptomatic and quality of life improvement on the one hand and the physiological control of acid reflux and restoring of lower oesophageal sphincter pressure on the other is not linear. Endoscopic plication had a relatively modest albeit significant impact on acid reflux. Notwithstanding this, the symptom score, regurgitation score and overall quality of life outcome data were satisfactory, and not significantly different from patients treated surgically. The TEP procedure however resulted in no significant improvement in the gastro-esophageal sphincter pressure in this study, at variance with one previous report[241]

. The laparoscopic fundoplication was markedly superior to TEP in all physiological end-points, with an 8-fold reduction in median acid score, over 90% of patients with normalised acid scores, a significant increase in lower oesophageal sphincter pressure, and an increase in amplitude of contractions.

Why does TEP, with relatively modest physiological improvements on 24h pH analysis, and none on manometric assessment, result in significant clinical improvement in GORD? Perhaps the significant improvement in the percent of upright reflux, and the number of reflux episodes, has considerable clinical relevance. Although the lower oesophageal sphincter pressure is unchanged, it is possible that the plications placed by the TEP method may form a plateau which allows the LOS to function better and to reduce both the volume and frequency of acid reflux events which occur during the periods of transient lower oesophageal sphincter relaxations (tLOSRs), or to alter the character of these transient relaxations [211,243]. Further refinements may increase the sphincter effect. In this study 2 plications 1 cm and 2 cm below the gastro-oesophageal junction along the lesser curve were placed; further analysis of the number and sites of plications may merit investigation. Finally, at a follow-up period of just one year, and with patients with severe GORD excluded from study, it remains possible that some placebo impact is evident, and longer-term study is required.

This is not a randomised trial, and patients with strictures, large hiatal herniae, and Barrett's oesophagus were excluded, and therefore the results must be interperetated with caution. The well-documented clinical and physiological effects of fundoplication were evident, and on the negative side the small but defined risk of

complications, in particular dysphagia. Intuitively clinical control should be matched by physiological control of acid reflux, and, although controversial[244], reducing the risk of adenocarcinoma in patients with complicated reflux appear to require effective physiological control[168]. This study shows that TEP can be performed safely as a day-case, achieves the desired clinical outcomes in the majority of patients, but falls short of the benchmarks defined by fundoplication in controlling acid reflux and augmenting lower oesophageal sphincter pressure. The objectives of TEP and other endotherapies is sound, and this study is supportive of further rigorous prospective evaluation, with a particular requirement for longer term follow-up, and a technical need to improve lower oesophageal sphincter function.

# Chapter 9:

# Significance

GORD is increasing in prevalence and is now the most commonly reported upper gastrointestinal disease. It has various clinical presentations, the most typical and common being heartburn and acid regurgitation. There is also an increasing awareness of extraoesophageal and atypical symptoms associated with GORD. Sever reflux may cause important complications including a significant decrease in quality of life, erosive oesophagitis, oesophageal ulcers and strictures, and Barrett's metaplasia, and the relationship of chrnoic and severe GORD to adencarcinoma of the oesophagus is becoming increasingly well recognised.

The pathophysiology of GORD is not well understood, but tLOSR, hypotensive LOS, hiatal hernia, hypersensitive oesophagus, and DGER are among the most widely accepted mechanisms. Current knowledge indicates that probably different pathophysiologic mechanisms are responsible for different subgroups of disease (i.e. erosive GORD, NERD, and Barrett's oesophagus). GORD, regardless of presence or absence of oesophageal erosions, is a chronic and recurrent disease that seriously affects quality of life, mandating long-term medical attention. The nonerosive form should be taken as seriously as the erosive form and be treated appropriately and aggressively. Various methods for treatment are available including lifestyle modifications, $H_2$ blockers or PPIs, and surgical and endoscopic treatments. It is generally recommended to start with general measures plus $H_2$ blockers or PPIs until the patient's symptoms are controlled and then maintain them on the lowest effective dose, either continuously or intermittently.

In the past, surgery, was usually reserved for patients who responded adequately to medical therapy but suffered frequent relapses and were either reluctant to take their medication (long-term) or were too young to receive potent acid- reducing agents for an undefined period of time. The advent since the early 1990s of laparoscopic approaches to reflux and resulted in a greater awareness and acceptance of anti-reflux surgery as an acceptable option in the management of many patients with significant GORD.

The work detailed in this thesis combined studies in surgical audit with assessment of outcomes relating to dysmotility, evaluated of an innovative approach to quality assurance in surgery, explored new understandings of linked physiological mechanisms in GORD, specifically LPR and gastric function, and finally compared the clinical and physiological outcomes of the surgical standard of care with one of the endotherapies.

**9.1 Defining Existing Standard of Care (Chapter 3):** An 8 year experience of 378 Rossetti -Nissen fundoplications was performed. This included a period of evolving dominance of the laparoscopic approach, and the nuances from this Unit of selective hiatal repair, no bougie and a standardised protocol of pre and postoperative functional endoscopic and symptom assessment. At a median follow-up of 6 months there was improved symptom scoring and QOL with an almost 90% patient satisfaction rate and physiological and clinical evidence of control of reflux. This study defines the Unit standard, it is consistent with outcomes from large reported series in the literature, and it represents the largest report of anti-reflux surgery from Ireland.

**9.2 Improving Outcomes → Surgical Innovation in Laparoscopic Fundoplication (Chapter 4) :** The idea to test the hypotheisis that simple endoscopy at the end of the laparoscopic fundoplication, and thus combining endoscopic and laparoscopic assessment of the wrap, would be a valuable quality adjunct for this operation was analysed in a consecutive series of patients in comparison with the previous 100 cases. Although the need for adjustments based on endoscopic assessment were few, there was a significant decrease in the incdience of dysphagia and re-intervention. Part of the benefit must result from knowing that the required perfect assessment postitively influences the postoperative management of patients with any symptoms. This work, in press in the *Journal of Gastrointestinal Surgery*, will represent the first publication of this quality initiative.

**9.3 Demonstrating the lack of need to tailor the type of fundoplication where preoperative dysmotility exists (Chapter 5):** This question i.e. whether manometrically-determined dysmotility should be managed with a partial wrap such as a Toupet or Dor rather than a 360-degree fundoplication, has been quite a controversial in recent years. This analsysis of this Unit's experience clearly demonstrated that preoperative dysmotility is not a contraindication to total fundoplication, and that postoperative acid control is associated with improved oesophageal clearance and symptoms. This study has been published in the *American Journal of Surgery*[247] , and represents for this Unit a further quality assurance of the existing standard of care in this scenario.

**9.4 Unravelling the Relationship between Laryngopharyngeal Reflux, Laryngeal Symptoms, and GORD (Chapter 6):** This study reported for the first time the incidence of LPR in patients with GORD, the association between LPR and GORD, and emphasises the lack of linear association with laryngeal symptoms. The paper has been published in *Diseases of the Esophagus* [248].

**9.5 Assessment of 360-degree Fundoplication on Gastric Motility (Chapter 7)**

A total fundoplication normalises gastric dysmotility in addition to increasing lower oesophageal sphincter tone. As a consequence the incidence of gastroesophageal reflux and LPR significantly decreases. This is the first study to show that surgical control of reflux with a floppy Rosetti- Nissen fundoplication involves gastric motility that in turn has consequences for proximal migration of oesophageal reflux, and it adds to a better understanding of the altered gastrc physiology in GORD and its improvement with surgery [249]

**9.6 Comparing the Clinical and Phsiological Benchmarks of Anti-reflux Surgery with Endotherapy (Chapter 8):** Laparoscopic fundoplication was markedly superior to TEP in all physiological end-points, with an 8-fold reduction in median acid score, over 90% of patients with normalised acid scores, a significant increase in lower oesophageal sphincter pressure, and an increase in amplitude of contractions. The clinical benefits of TEP were of interest, as it clearly showed that physiological control with normalisation of the De Meester score is not required for many GORD patients to achieve symptom control, albeit in short-term follow-up. This work has been published in the *American Journal of Gastroenterology*[250].

## 9.7 Conclusions:

1. Rosetti-Nissen fundoplication is a simple, safe and effective treatment for GORD

2. On table endoscopy improves patient outcome and is a useful adjunct to anti-reflux surgery.

3. Preoperative dysmotility is not a contraindication to total fundoplication, and postoperative acid control is associated with improved oesophageal clearance and symptoms.

4. LPR is common in GORD with or without laryngeal symptoms and is related to distal acid exposure.

5. Gastric dysmotility as documented by EGG studies is common in GORD and is normalised by anti-reflux surgery.

6. Endotherapy (Endocinch) is inferior to Nissen fundoplication in controlling reflux.

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## Appendix:

## Symptom Scores

**A1: Modified DeMeester Scoring [140]:** For heartburn, 0 = no episodes; 1 = occasional (<3 times/wk) and brief episodes that are controlled by antacids; 2 = frequent (3 to 5 times/wk) episodes; and 3 = daily episodes. For regurgitation, 0 = no episodes; 1 = mild and occasional episodes that are mostly postprandial and not predictable; 2 = moderate and frequent episodes ( 3 to 5/wk) that are predictable by posture; and 3 = severe and daily episodes that interfere with work and social activities. Dysphagia was graded from 0 to 3, with 0 = no symptoms; 1 = occasional transient sensation of food sticking; 2 = episodes of dysphagia requiring liquids to clear; and 3 = severe dysphagia requiring medical attention or dilation or a bolus obstruction requiring liquids to clear.

Score guideline sheet:

Modified DeMeester Symptom Score (Gotley BR J Surg.)

TOTAL = 9

Heartburn:

0. None
1. Occasional brief episodes; controlled by antacids.
2. Frequent episodes (>2/week); moderate discomfort; Requires H2 receptor antagonists.
3. Daily pain; nocturnal attacks interfering with sleep; interference with work, social activities.

Regurgitation

0. None
1. Occasional episodes, mostly postprandial, and not predictable.
2. Frequent episodes (>2/week); predictable by posture.
3. Daily episodes interfering with work/ social activity / ; nocturnal Episodes; aspiration.

Dysphagia

0. None
1. Occasional transient sensation of food sticking
2. Episodes of dysphagia requiring liquids to clear.
3. Progressive dysphagia for solids requiring medical attention; Need for dilation; bolus obstruction requiring hospital admission.

**A2: Quality of Life in Reflux and Dyspepsia (QOLRAD) [141] questionnaire**: The patients independently completed the Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire before surgery and again at least 6 months after surgery. The QOLRAD consists of 25 questions graded from 1-7 with a score of 7 indicating absence of symptoms. The questions are asked in a random fashion with groups of answers subsequently added together to produce 6 quality of life scores, ie emotional distress, sleep disturbance, food and drink problems, physical and social functioning, and vitality. The need to resume medical treatment for acid symptoms was also documented.

Patients ranked the outcome of surgery using modified Visick [121] grading (1 to 4) and were also asked to score the outcome as excellent, good, fair, or poor.
Excellent was defined as complete recovery, good as major improvement with only minor problems, fair as major improvement but still with significant problems or adverse effects, and poor as minor or no improvements or deterioration.

QOLRAD forms photocopies to follow:

| | Pre -Surgery | | | Post - Surgery | |
|---|---|---|---|---|---|
| | **Pre-proced** | **12mths PP** | | **Post proceed** | **12mths PP** |
| | | | | | |
| **Emotional Distress** | | | **Emotional Distress** | | |
| 12.Discourage/distress | | | 12.Discourage/distress | | |
| 14. Frustrated/ impatient | | | 14. Frustrated/ impatient | | |
| 15. Anxious or upset | | | 15. Anxious or upset | | |
| 17. Worries or fear | | | 17. Worries or fear | | |
| 19. Irrritable | | | 19. Irrritable | | |
| 22. Exact cause unknown | | | 22. Exact cause unknown | | |
| | | | | | |
| **Sleep Disturbance** | | | **Sleep Disturbance** | | |
| 8. Night sleep | | | 8. Night sleep | | |
| 10. Tired lack of sleep | | | 10. Tired lack of sleep | | |
| 11. Wake up at night | | | 11. Wake up at night | | |
| 18. Fresh and rested | | | 18. Fresh and rested | | |
| 21. Trouble getting sleep | | | 21. Trouble getting sleep | | |
| | | | | | |
| **Food drink problems** | | | **Food drink problems** | | |
| 3.Eating & Drinking | | | 3.Eating & Drinking | | |
| 5. Eat less than usual | | | 5. Eat less than usual | | |
| 9. Unable eat food/snack | | | 9. Unable eat food/snack | | |
| 13. Food unappealing | | | 13. Food unappealing | | |
| 16. No tolerate food/snack | | | 16. No tolerate food/snack | | |
| 20. Avoid certain food/drnk | | | 20. Avoid certain food/drnk | | |
| | | | | | |
| **Physical /social functioning** | | | **Physical /social functioning** | | |
| 2. Avoid bend over | | | 2. Avoid bend over | | |
| 6. Doing things with family | | | 6. Doing things with family | | |
| 23. Difficulty socialising | | | 23. Difficulty socialising | | |
| 24. Unable to do social activ | | | 24. Unable to do social activ | | |
| 25. Unable to do phys. activ | | | 25. Unable to do phys. activ | | |
| | | | | | |
| **Vitality** | | | **Vitality** | | |
| 1. Feeling tired or worn out | | | 1. Feeling tired or worn out | | |
| 4. Generally unwell | | | 4. Generally unwell | | |
| 7. Lack of energy | | | 7. Lack of energy | | |
| | | | | | |

## A2: Summary Sheet

GI FUNCTION UNIT, ST. JAMES HOSPITIAL, DUBLIN 8

PATIENT MRN: Patient Name: Date:

SURGERY: DATE OF PROCEDURE: NO. MTHS POST OP:

MEDICATION: DATE OF BIRTH:

HEIGHT: WT. BEFORE SURGERY: WT. NOW:

PLEASE FILL IN THIS FORM AS YOU ARE FEELING TODAY, WHILST OFF MEDICATION

1. How often during the past week have you been FEELING TIRED OR WORN OUT BECAUSE OF HEARTBURN OR ACID REGURGITATION?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

2. How often during the past week did you AVOID BENDING OVER BECAUSE OF HEARTBURN OR ACID REGURGITATION?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

3. During the past week how much HEARTBURN OR ACID REGURGITATION HAVE YOU HAD BECAUSE OF EATING OR DRINKING?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | A great deal | A great deal |
| ❑ | A lot | A lot |
| ❑ | A moderate amount | A moderate amount |
| ❑ | Some | Some |
| ❑ | A little | A little |
| ❑ | Hardly any | Hardly any |
| ❑ | None at all | None at all |

4. How often during the past week have you FELT GENERALLY UNWELL BECAUSE OF HEARTBURN OR ACID REGURGITATION?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

1(10)

5. How often during the past week was it NECESSARY TO EAT LESS THAN USUAL BECAUSE OF HEARTBURN OR ACID REGURGITATION?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

6. How often during the past week has HEARTBURN OR ACID REGURGITATION KEPT YOU FROM DOING THINGS WITH FAMILY OR FRIENDS?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

7. How often during the past week did you have A LACK OF ENERGY BECAUSE OF HEARTBURN OR ACID REGURGITATION?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

8. How often during the past week have you had "DIFFICULTY GETTING A GOOD NIGHT'S SLEEP BECAUSE OF HEARTBURN OR ACID REGURGITATION?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

9. How often during the last week has HEARTBURN OR ACID REGURGITATION MADE IT DIFFICULT TO EAT ANY OF THE FOODS OR SNACKS YOU LIKE?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

10. How often during the past week did you FEEL TIRED OR WORN OUT DUE TO LACK OF SLEEP BECAUSE OF HEARTBURN OR ACID REGURGITATION?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

11. How often during the past week did HEARTBURN OR ACID REGURGITATION WAKE YOU UP AT NIGHT AND PREVENT YOU FROM FALLING ASLEEP AGAIN?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

12. How Often during the past week have you felt DISCOURAGED OR DISTRESSED BECAUSE OF HEARTBURN OR ACID REGURGITATION ?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

13. How often during the past week has HEARTBURN OR ACID REGURGITATION MADE FOOD SEEM UNAPPEALING TO YOU?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

14. How often during the past week have you FELT FRUSTRATED OR IMPATIENT BECAUSE OF HEARTBURN OR ACID REGURGITATION?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

15. How often during the past week have you been ANXIOUS OR UP OF HEARTBURN OR ACID REGURGITATION?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

16. During the past week, how much HEARTBURN OR ACID REGURGITATION HAVE YOU HAD BECAUSE OF HAVING EATEN FOODS OR SNACKS YOU COULD NOT TOLERATE?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | A great deal | A great deal |
| ❑ | A lot | A lot |
| ❑ | A moderate amount | a moderate amount |
| ❑ | Some | Some |
| ❑ | A little | A little |
| ❑ | Hardly any | Hardly any |
| ❑ | None at all | None at all |

17. How often during the past week have you had ANY WORRIES OR FEARS ABOUT YOUR HEALTH BECAUSE OF HEARTBURN OR ACID REGURGITATION?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

18. How often during the past week did you FAIL TO WAKE UP IN THE MORNING FEELING FRESH AND RESTED BECAUSE OF HEARTBURN OR ACID REGURGITATION?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

19. How much during the past week has HEARTBURN OR ACID REGURGITATION MADE YOU FEEL IRRITABLE?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

20. How often during the past week have you had to AVOID CERTAIN FOOD, BEVERAGES OR DRINKS BECAUSE OF HEARTBURN OR ACID REGURGITATION?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

21. How often during the past week did you HAVE TROUBLE GETTING TO SLEEP BECAUSE OF HEARTBURN OR ACID REGURGITATION?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

22. How often during the past week did you FEEL FRUSTRATED BECAUSE THE EXACT CAUSE OF YOUR SYMPTOMS IS NOT KNOWN AND YOU STILL HAVE SO MUCH HEARTBURN OR ACID REGURGITATION?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

23. How often during the past week did you have DIFFICUL IN SOCIALIZING WITH FAMILY OR FRIENDS BECAUSE OF HEARTBURN OR ACID REGURGITATION?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

24. How often during the past week were you UNABLE TO CARRY OUT YOUR DAILY ACTIVITIES (INCLUDING BOTH WORK OUTSIDE THE HOME AND HOUSE WORK) DUE TO HEARTBURN OR ACID REGURGITATION ?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

25. How often during the past week were you UNABLE TO CARRY OUT YOUR NORMAL PHYSICAL ACTIVITIES (INCLUDING SPORT, LEISURE ACTIVITIES AND MOVING AROUND OUTSIDE THE HOME) DUE TO HEARTBURN OR ACID REGURIGITATION?

| Pre Op | | Post Op |
|---|---|---|
| ❑ | All of the time | All of the time |
| ❑ | Most of the time | Most of the time |
| ❑ | Quite a lot of the time | Quite a lot of the time |
| ❑ | Some of the time | Some of the time |
| ❑ | A little of the time | A little of the time |
| ❑ | Hardly any of the time | Hardly any of the time |
| ❑ | None of the time | None of the time |

**26** Answer the following question whether or not you answered BETTER or WORSE and what your response was. Note if you have improved, the change will be important since you likely will be able to carry out your responsibilities with greater ease and comfort compared to before the operation. If on the other hand you are worse, then you will have more difficulty carrying out your responsibilities; this will also be important for you as you have more difficulty with your activities.

Is this change (BETTER/WORSE) important to you in carrying out your daily activities?

- ❑ Not important
- ❑ Slightly important
- ❑ Somewhat important
- ❑ Moderately important
- ❑ Important
- ❑ Very important
- ❑ Extremely important

A..Heartbutn frequecy;
How often would you experience heartburn?

| **Before your operation?** | **After your operation?** |
|---|---|
| ❑ None | None |
| ❑ Mild episodes (less than 3/week) | Mild episodes (less than 3 /week) |
| ❑ Moderate (more 3/wk) | Moderate (more 3/wk) |
| ❑ Daily pain ( 6-7dys/wk) | Daily pain ( 6-7dys/wk |

b. On a SCALE OF 0 TO TEN ( TEN BEING MOST SEVERE) , HOW WOULD YOU RATE YOUR HEARTBURN ?

**Before your operation?**

0_----------2.5 ----------5----------7.5 ---------- 10

**After your operation, today?**

0_----------2.5 ----------5----------7.5 ---------- 10

c..Regurigitation Score:
How often would you experience regurgitation?

| **Before your operation?** | **After your operation?** |
|---|---|
| ❑ None | None |
| ❑ Mild episodes (less than 3/week) | Mild episodes (less than 3 /week) |
| ❑ Moderate (more 3/wk) | Moderate (more 3/wk) |
| ❑ Daily pain ( 6-7dys/wk) | Daily pain ( 6-7dys/wk |

**A3: The Gastroesophageal Reflux Disease-Health-Related Quality of Life Questionnaire:** GORD-HRQL score [142] consists of 10 questions rated from 0-5 with a score of zero representing no problem and a score of 5 indicating a severe problem. Symptoms of heartburn include severity in relation to posture, post-prandially, sleep disturbance, swallowing difficulty and bloating.

**A4: Reflux Symptom Index:** ENT symptom scoring was by the reflux symptom index (RSI) [261] which consists of a nine-item questionnaire. RSI questions are scored from 0-5, zero score indicating no problem and a score of 5 indicating severe problem. Symptoms include hoarseness, swallowing, cough, breathing problems and heartburn, the cut-off value for the questionnaire being 13.0.

**A5: Regurgitation Scoring:** Regurgitation was also assessed and was scored from 0-3 with a score of zero being no regurgitation, and a score of 3 representing daily pain.

| Please circle the appropriate number which matches your symptoms. | 0= No problem<br>5= Severe problem |
|---|---|

## Symptoms in relation to your Gullet

| | | | | | | |
|---|---|---|---|---|---|---|
| 1. How bad is the heartburn? | 0 | 1 | 2 | 3 | 4 | 5 |
| 2. Do you have heartburn when lying down? | 0 | 1 | 2 | 3 | 4 | 5 |
| 3. Have you Heartburn when standing up? | 0 | 1 | 2 | 3 | 4 | 5 |
| 4. Do you have heartburn after meals? | 0 | 1 | 2 | 3 | 4 | 5 |
| 5. Does your diet affect your heartburn? | 0 | 1 | 2 | 3 | 4 | 5 |
| 6. Does heartburn wake you from your sleep? | 0 | 1 | 2 | 3 | 4 | 5 |
| 7. Do you have difficulty swallowing? | 0 | 1 | 2 | 3 | 4 | 5 |
| 8. Do you have pain while swallowing? | 0 | 1 | 2 | 3 | 4 | 5 |
| 9. Do you have bloating or gassy feelings? | 0 | 1 | 2 | 3 | 4 | 5 |
| 10. Do you have any heartburn while on stomach medication, if so, how severe is it? | 0 | 1 | 2 | 3 | 4 | 5 |

**A3:**

## Symptoms in relation to your throat

Do you have?

| | | | | | | |
|---|---|---|---|---|---|---|
| 1. Hoarseness or a problem with your voice | 0 | 1 | 2 | 3 | 4 | 5 |
| 2. Clearing your throat | 0 | 1 | 2 | 3 | 4 | 5 |
| 3. Excess throat mucus or postnasal drip | 0 | 1 | 2 | 3 | 4 | 5 |
| 4. Difficulty swallowing food, liquids or pills | 0 | 1 | 2 | 3 | 4 | 5 |
| 5. Coughing after you ate or lying down | 0 | 1 | 2 | 3 | 4 | 5 |
| 6. Breathing difficulties or choking episodes | 0 | 1 | 2 | 3 | 4 | 5 |
| 7. Troublesome or annoying cough | 0 | 1 | 2 | 3 | 4 | 5 |
| 8. Sensation ofsticking or lump in throat | 0 | 1 | 2 | 3 | 4 | 5 |
| 9. Heartburn, chest pain, or stomach acid | 0 | 1 | 2 | 3 | 4 | 5 |

**A4:**

## Heartburn frequency:

How often would you experience heartburn?

Never
Mild episode (less than 3/week)
Moderate (more than 3/week)
Daily pain (6-7days/week)

B. On a scale of 0 to ten ( ten being most severe), how would you rate your heartburn?

0----------2.5----------5----------7.5----------10

## Regurgitation Score:

How often would you experience regurgitation?

Never
Mild episodes ( less than 3/week)
Moderate (more than 3/week)
Daily Pain (6-7days/week)

**A5:**