The acid pocket, hiatal hernia and TLESRs: essential players in the pathogenesis of gastro-esophageal reflux disease
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Differences in compliance of the esophagogastric junction between healthy subjects, GERD patients and patients after a Nissen fundoplication

Submitted

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**Abstract**

**Introduction:** Increased distensibility or compliance of the esophagogastric junction (EGJ) plays an important role in the pathogenesis of gastroesophageal reflux disease (GERD). However, to measure EGJ distensibility, radiographic imaging involving radiation is required limiting its application in research protocols. Therefore, a functional lumen imaging probe (FLIP) was constructed measuring eight cross sectional areas (CSA) at 4mm intervals inside a saline-filled bag using impedance planimetry and containing two pressure side holes allowing assessment of EGJ compliance. The present study was designed to evaluate whether this technique could be used to detect changes in EGJ compliance between healthy volunteers, untreated GERD patients and patients who had a laparoscopic Nissen fundoplication (LNF).

**Methods:** 10 GERD patients (20-74 yrs), 6M), 9 post Nissen patients (35-67 yrs), 5M) and 10 HV (19-58), 7M) were evaluated. They underwent a compliance measurement using the FLIP, esophageal manometry and 24 hrs pH metry. The FLIP was positioned with the bag straddling the EGJ under guidance of manometry readings and point of respiratory inversion. The bag was filled with saline at a rate volume of 25 ml/min to a maximum of 60 ml. Bag pressure and CSA were recorded. A pH below 4 > 5.78% of total time was considered to be pathological. For statistical analysis of pH and manometry, unpaired Student’s t-tests were used and data is presented as mean ± SE.

**Results:** GERD patients have significant more pathological acid reflux 5 cm above the lower esophageal sphincter (LES) compared to HV, but not to LNF patients (GERD patients: 8.4 ± 2.3 %, P < 0.04; LNF: 4.3 ± 2.3 %; HV: 2.7 ± 0.7 %). Compliance was increased in GERD patients compared to HV; at a distension of 50ml CSA in HV was 92.4 ± 8.5 mm², compared to 122.9 ± 15.5 mm² in GERD patients. A Nissen fundoplication restored compliance to even lower levels than HV (83.8 ± 6.4 mm² at 50ml distension). Compliance between HV and Nissen patients was not significantly different. The basal LES pressure did not significantly differ between the three groups (GERD patients: 5 ± 1 mmHg; LNF: 10 ± 2 mmHg; HV: 9 ± 2 mmHg (ns)).

**Conclusion:** FLIP studies showed a greater distensibility in GERD patients compared to HV, accompanied by an increased esophageal acid exposure. Conversely, we showed that FLIP detects a significant decrease in compliance after LNF accompanied by a decrease in acid exposure. These results suggest that FLIP may offer a direct method to assess changes in compliance of the EGJ.
Introduction

Reflux of gastric contents into the esophagus is a physiologic phenomenon, but becomes pathological when it causes troublesome symptoms or complications.\(^1\) Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal disorders, with typical symptoms as heartburn, regurgitation or retrosternal pain reported by 15-20% of the general population at least once a week.\(^2\) \(^3\)

The esophagogastric junction (EGJ), a dynamic high pressure zone consisting of the lower esophageal sphincter (LES) and the crural diaphragm, provides an important barrier to flow of gastric contents into the esophagus. Failure of this functional barrier will lead to increased reflux of gastric contents into the esophagus and GERD. The most common mechanism underlying incompetence of the EGJ are transient lower esophageal sphincter relaxations (TLESRs), periods of prolonged absence of LES pressure in the absence of swallowing.\(^4\) Interestingly, the number of TLESRs is not different between GERD patients and healthy controls, but instead, acidic reflux occurs twice as often during a TLESR in GERD patients.\(^5\) \(^6\) Several factors, such as the presence of a hiatal hernia\(^7\) and the localisation of the postprandial acid pocket\(^8\) \(^-\)\(^10\) may contribute. Alternatively, differences in compliance of the EGJ may result in more liquid reflux in patients compared to healthy subjects.\(^11\) \(^12\) Indeed, a high compliance at the EGJ will lead to increased reflux of liquids 1) by lowering the intra-abdominal pressure required to open the EGJ, and 2) by the fact that the EGJ will have a wider diameter at a given pressure resulting in reduced resistance to flow. In line with this, previous studies have shown that GERD patients, and especially patients with hiatal hernia, have an increased distensibility or compliance of the EGJ compared to healthy subjects, resulting in exacerbation of liquid reflux.\(^11\) \(^-\)\(^13\) In these studies, distensibility of the EGJ was however assessed using a radiological technique, requiring radiation exposure, making this technique less suitable for research purposes.

Recently, a new technique has been developed and validated to measure the compliance upon radial expansion of the esophagus.\(^14\) \(^15\) Based on the impedance planimetry technique, an already established method for performing balloon distensions in the gastrointestinal tract, a functional lumen imaging probe (FLIP) was developed which measures the cross sectional areas (CSA) in a radial direction, using a saline-filled bag in the luminal organs. Previous studies have shown FLIP to be useful in measuring changes in distensibility of the EGJ in healthy volunteers and 2 patients with achalasia.\(^16\) In the present study, we further evaluated the use of FLIP as a radiation-free technique to assess changes in compliance, in particular in GERD patients. In addition, we hypothesized that anti-reflux surgery would restore compliance, contributing to the reduction in acid exposure observed after this procedure.\(^17\)
Material and Methods

Subjects
Studies were performed in 10 healthy volunteers (7 males, 19-58 years of age), 10 GERD patients (6 males, 20-74 years of age), and 9 GERD patients who had undergone a Nissen fundoplication (5 males, 35-67 years of age). All HV were free of any gastrointestinal symptoms, had no history of gastrointestinal surgery and did not take any prescribed medication. All GERD patients were using standard doses of proton pump inhibitors (PPIs), had no history of gastrointestinal surgery and were otherwise healthy. Administration of PPIs was discontinued 5 days before the study. Postoperatively, fundoplication patients had a good response to surgery with improvement of GERD symptoms and were not taking any acid suppressant medication, except for 1 subject whose symptoms relapsed 3 months postoperatively. All fundoplication patients postoperatively reported a period of self-limiting dysphagia during a few weeks. Fundoplication patients were evaluated 6 to 28 months (median 8 months) after surgery. Each subject gave written informed consent, and the study was approved by the Medical Ethics Committee of the Academic Medical Centre.

Study design
All subjects were invited to undergo an esophageal manometry, 24 hour pH metry, and compliance measurement of the EGJ. Studies were performed after a four hour fast. Manometry and pH metry were performed at the same day, whereas the compliance measurement was done the next day, after removing the pH catheter. The manometric and pH catheter were introduced through an anaesthetised nostril and positioned so that the sleeve straddled the LES. During manometry, ten wet water swallows of 5 ml each were given to the subject using a 20 ml syringe. In between each wet swallow, subjects were not allowed to swallow for 20 s. The pH catheter was placed with the pH electrode located 5 cm above the proximal margin of the LES, and subjects went home. The FLIP was inserted orally, after anaesthetising the throat, and positioned so that the bag straddled the EGJ. Two preconditioning distensions were performed for accommodation of the esophagus and to check the position of the probe. In addition, two volume controlled distensions were performed.

Recording methods
Manometry
Oesophageal manometry was performed using a 10 lumen assembly (Dentsleeve, Adelaide, Australia) with a sleeve sensor incorporated at its distal end to monitor LES pressure. Side holes monitored pressure in the stomach (1 cm below the distal margin of the sleeve) and at 2, 5, 8, 11, 14, 17 and 20 cm above the LES. A side hole in the pharynx monitored swallows. The sideholes and the sleeve were perfused with degassed distilled water at 0.6 ml min⁻¹, using a pneumohydraulic capillary perfusion pump (Dentsleeve Pty, Belair, South Australia).
Pressures were sensed by external transducers connected to a polygraph (Synectics Medical, Stockholm, Sweden).

24 hour pH metry
To measure acid reflux, pH was recorded for 24 hours with an antimony electrode with built-in reference, positioned 5 cm above the proximal margin of the LES. The catheter was connected to an ambulatory device (Digitrapper MK III; Synectics Medical AB, Stockholm, Sweden). Before the study, the pH electrode was calibrated at 37 °C using pH 1.0 and 7.0 buffer solutions (Medtronic, Skovlunde, Denmark). Both manometry and pH signals were digitalised, computer-processed, stored and analysed using commercially available software (Polygram, Synectics Medical, Stockholm, Sweden).

Compliance measurement
Distensibility of the EGJ was measured using a functional lumen imaging probe (FLIP). The FLIP catheter was custom designed to measure 8 cross sectional areas (CSAs) and contained 2 manometric pressure side holes. The length of the probe was 72 cm, with the proximal 60 cm constructed from a polyurethane tube with an outer diameter of 6 mm. The distal 12 cm of the probe, lying inside and distal to the bag, was constructed of a polyethylene tube with an outer diameter of 1.6 mm. An excitation current of 100 µA at a frequency of 5 KHz, was generated between two excitation electrodes located on each side of the multiple detection electrodes. Voltage measurements were made across 8 electrode pairs. Each electrode in the pair was 1 mm apart and the distance between the centres of the electrode pairs, i.e. the distance between the measurements, was 4 mm. The voltage measured was proportional to the impedance between the detection electrodes, which decreased as the bag filled with saline. This impedance change was therefore proportional to the CSA change at each detection electrode pair in the bag. The bag was infinitely compliant up to its maximum distending volume, so that any pressure increase recorded in the bag did not reflect distensibility of the bag. When mounted on the probe, the cylindrical bag length was 10 cm. The bag ends were folded in before being fixed to the probe, creating a rolling-bag effect, which allowed some longitudinally movement of the bag without dislodging the bag. Pressure measurements were performed proximal to and inside the bag, using a low compliance saline perfused system connected to external transducers. Pressure and CSA were recorded at a rate of 10Hz.
A set of perspex cylindrical tubes with CSAs of 38.5 mm², 73.8 mm², 132.7 mm², 201 mm², 283.5 mm² and 572 mm² was used to calibrate the FLIP, as previously described. Calibration was performed with 0.225 g/l saline at body temperature. The pressure system was calibrated at 0 and 100 cm H2O respectively.
The FLIP was inserted orally and positioned with the bag straddling the distal esophagus, using manometry readings of the proximal side hole and point of respiratory inversion as a guide. At least two preconditioning distensions were performed by infusing the bag with 0.225 g/l saline. In addition, two volume controlled distensions at 25 ml/min were
carried out to a maximum of 60 ml or stopped earlier in the case of discomfort. During the
distensions, patients were asked to refrain from swallowing.
Since the EGJ is very dynamic and the data scattered, an exponential curve fitting technique
was used to get an impression of the changes in pressure and CSA during the distensions.

**Data analysis and statistics**
LES length was determined manometrically using the station pull through technique. Basal
LES pressure was measured at end-expiration relative to intragastric pressure. Compliance
of the EGJ was measured as cross sectional area at the narrowest point plotted against
balloon pressure. This compliance data was captured during the balloon distension at 25ml
per minute. For every 10ml-step volume, the narrowest CSA and its corresponding pressure
were assessed. Manometry and compliance data are presented as mean ± SEM. Statistical
analysis was done using the Student’s T-tests. A P-value < 0.05 was regarded as statistically
significant.

**Results**
Manometry data of 8 HV could be analysed. Two healthy subjects refused to undergo
manometry and 24 hours pH metry. In two GERD patients, pH metry was not performed
due to comparable reasons. Data from all post Nissen patients could be analysed.

**LES pressure**
In HV, basal LES pressure was 8.9 ± 1.6 mmHg. This was decreased in GERD patients 5.1 ±
0.9 mmHg (ns), whereas LES pressure was increased after a Nissen fundoplication to 10.4 ±
2.0 mmHg (ns compared to HV, P < 0.04 compared to GERD patients) (Figure 1).

**Acid exposure**
In HV, total acid exposure time during 24 hr pH metry was 2.7 ± 0.7 %. Acid exposure
was significantly increased in GERD patients (8.4 ± 2.3 %, P < 0.04) but not in post Nissen
patients (4.3 ± 2.3 %, ns) (Figure 2).
In HV, acid reflux mostly occurred in the upright position (upright: 4.0 ± 1.3 %; supine: 1.1 ± 0.6 %), whereas in GERD patient and in patients after a Nissen fundoplication acid reflux occurred mostly during the supine position (GERD, upright: 7.8 ± 1.7 %; supine 10.8 ± 8.4 %; Nissen, upright: 1.5 ± 0.6 %; supine: 6.2 ± 5.2 %).

**Compliance**

For each group the mean and SEM of two distensions was included at distension volumes of 30ml, 40ml, 50ml and 60ml, except for the Nissen patients where there was only a complete set of data to 50ml.
Data on compliance in HV, GERD patients and post-Nissen fundoplication patients are shown in Figure 3. Compliance of the EGJ was increased in GERD patients compared to HV and post Nissen patients. A Nissen fundoplication restored compliance to even lower values than measured in HV. For example, at a distension of 50ml with a pressure of 29 cm H₂O in all three groups, the CSA in HV was 92.4 ± 8.5 mm². This was increased to 122.9 ± 15.5 mm² in GERD patients, and decreased to 83.8 ± 6.4 mm² in post Nissen patients.

**Discussion**

Distensibility or compliance of the EGJ is an important determinant of the luminal diameter of a given hollow organ and may significantly affect its function. In case of the EGJ, increased compliance may contribute to increased gastroesophageal reflux. Indeed, increased compliance at the EGJ will result in a greater change in diameter at a given intraluminal distending pressure, leading to a reduction in the resistance to flow and subsequently allowing a larger volume of liquid refluxate to enter the esophagus. Recent insights indeed clearly indicate that the compliance of the esophagogastric junction largely determines the probability for reflux to occur. For example, Pandolfino et al. demonstrated that the compliance of the esophagus is increased in GERD patients, contributing to an increased risk to have liquid reflux during sphincter opening. In line with this, Nissen fundoplication yields its anti-reflux effect by restoring EGJ compliance. These data indicate that distensibility of the distal esophagus provides important additional information on EGJ and esophageal competence. So far, it was difficult to measure compliance as it is very invasive and involves a large burden of radiation, limiting its application in research settings. With the introduction of the FLIP, a newly developed tool measuring multiple cross-sectional areas with concurrent pressure in a saline-filled bag during volume controlled distensions, it is possible to evaluate the compliance of the distal esophagus in a more elegant and less invasive manner.

In the present study we confirmed that compliance is increased in GERD patients compared to HV. At a given pressure, the EGJ opening is indeed wider in GERD patients compared to healthy controls. One possible explanation for the increased compliance in GERD, could be the presence of hiatal hernia. In this case, the sphincter complex is anatomically disrupted leading to a different pressure profile, possibly contributing to the observed increase in compliance. In the present study, however, we did not determine the presence of a hiatal hernia and thus can not evaluate its role in the observed changes in compliance. We did demonstrate though that increased compliance was indeed accompanied with increased acid reflux. Conversely, we demonstrated that anti-reflux surgery, aimed at restoring EGJ function, restored the compliance at the EGJ and reduced acid reflux.

Complications after a Nissen fundoplication, such as bloating, the inability to vomit and dysphagia are often mild and short-lasting, but may be troublesome in a small group of patients. Most likely, the cause of these postoperative symptoms are related to the fundoplication itself. Although high LES pressures and ramp pressures were manometrically
found in some post-fundoplication patients, this was poorly correlated with clinical outcome.\textsuperscript{20} Therefore, resistance to distension may be a better parameter to define the elasto-mechanical properties of the EGJ. In the present study, compliance was even lower in patients after a Nissen fundoplication compared to HV. This was, however, not associated with an increased prevalence of dysphagia in these patients (unpublished results). Previous studies revealed possible other underlying mechanisms for the action of anti-reflux surgery, such as incomplete LES relaxation and a reduced rate of TLESRs due to a reduced gastric accommodation.\textsuperscript{21}

A possible shortcoming of our study is that we could only measure compliance at 8 points over a segment length of 3.5 cm. The FLIP technique would benefit by increasing the number of detecting points and therefore the number of CSAs measured through the EGJ. Optimizing the technique and increasing the number of patients and patients groups are needed to confirm the usefulness of FLIP in defining changes in compliance before and after anti-reflux treatments.

In summary, using a novel technique to measure EGJ compliance, insight in the opening function of the EGJ can be obtained without the need for radiation. Compared to healthy subjects, compliance of the EGJ is increased in GERD patients, resulting in a reduced resistance for reflux to occur and an increased acid exposure time. Anti-reflux surgery, like a Nissen fundoplication, restores EGJ compliance and acid exposure to normal values, illustrating the importance of EGJ compliance in the pathogenesis of GERD.

### Reference List

Chapter 2


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