Feasibility of esophagogastric junction distensibility measurement during Nissen fundoplication

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SUMMARY. Increased esophagogastric junction distensibility has been implicated in the development of gastroesophageal reflux disease (GERD). Previous authors have demonstrated a reduction in distensibility following anti-reflux surgery, but the changes during the operation are not clear. Our study aimed to ascertain the feasibility of measuring intraoperative distensibility changes and to assess if this would have potential to modify the operation. Seventeen patients with GERD were managed in a standardized manner consisting of preoperative assessment with symptom scoring, endoscopy, 24 hours pH studies, and manometry. Patients then underwent laparoscopic Nissen fundoplication with intraoperative distensibility measurement using an EndoFLIP EF-325 functional luminal imaging probe (Crospon Ltd, Galway, Ireland). This device utilizes impedance planimetry technology to measure cross-sectional area and distensibility within a balloon-tipped catheter. This is inflated at the esophagogastric junction to fixed distension volumes. Thirty-second median cross-sectional area and intraballoon pressure measurements were recorded at 30 and 40 mL balloon distensions. Measurement time points were initially after induction of anesthesia, after pneumoperitoneum, after hiatal mobilization, after hiatal repair, after fundoplication, and finally pre-extubation. Postoperatively, patients continued on protocol and were discharged after a two-night stay tolerating a sloppy diet. Patients with a hiatus hernia on high-resolution manometry had a significantly higher initial esophagogastric junction distensibility index (DI) than those without. Hiatus repair and fundoplication resulted in a significant overall reduction in the median DI from the initial to final recordings (30 mL balloon distension reduction of 3.26 mm²/mmHg ($P = 0.0087$), 40 mL balloon distension reduction of 2.39 mm²/mmHg ($P = 0.0039$)). There was also a significant reduction in the DI after pneumoperitoneum, hiatus repair, and fundoplication at 40 mL balloon distension. Two individual cases in the series highlight the utility of the system in potentially changing the operation. After fundoplication, patient 7 recorded a DI of 0.47 mm²/mmHg, the lowest in our series, and subsequently required reoperation because of significant symptoms of dysphagia. Patient 12 had a fundoplication that appeared visually too tight and was converted intraoperatively to a Lind 270° wrap resulting in a change in the DI from 0.65 to 0.89 mm²/mmHg. Laparoscopic Nissen fundoplication results in a significant reduction in the distensibility of the esophagogastric junction. The EndoFLIP system is able to demonstrate significant changes during the operation and may help guide intraoperative modification. Larger multicenter studies with long-term follow up would be beneficial to develop a target range of distensibility associated with good outcome.

KEY WORDS: distensibility, esophagogastric junction, functional luminal imaging, GERD (gastroesophageal reflux disease), Nissen fundoplication.

INTRODUCTION

Gastroesophageal reflux disease (GERD) can be regarded as a failure of the competency of the esophagogastric junction (EGJ) to resist abnormal flow. Established factors implicated in the development of GERD include transient lower esophageal sphincter relaxations and hiatus hernia. It has duplicate been proposed that increased distensibility or compliance may also be an important factor in the competence of the EGJ.$^{1,3}$ The distensibility of the EGJ can be described as the degree of distension of the EGJ in response to a radial force.
Patients with GERD have demonstrated a higher distensibility when compared with normal controls; this increase in distensibility allows for a greater volume of abnormal refluxate to pass through the EGJ and the EGJ to open at a lower intraluminal pressure. Outpatient measurement of EGJ distensibility in patients who have undergone anti-reflux surgery by both barostat devices and an experimental functional luminal imaging probe (FLIP) have revealed a reduction in distensibility when compared with normal controls.

Recently, a commercially available FLIP utilizing impedance planimetry technology originally described by McMahon et al. has been developed. The EndoFLIP EF-325 (Crospon Ltd, Galway, Ireland) has allowed simplified measurement of EGJ cross-sectional area (CSA) and distensibility, and its safe intraoperative usage has been demonstrated in both animal models and in normal control subjects undergoing laparoscopy.

The purpose of this study was to ascertain the feasibility of measuring intraoperative changes in the EGJ during the different stages of Nissen fundoplication and hiatus repair.

MATERIALS AND METHODS

Patients selection

Seventeen subjects were recruited from patients with GERD scheduled for laparoscopic Nissen fundoplication at a UK upper gastrointestinal surgical tertiary referral center. Patients were included if they had symptomatic reflux, heartburn, or regurgitation that was responsive to proton pump inhibitors (PPI). The diagnosis of reflux disease was confirmed with endoscopy and 24 hours pH studies. Patients also underwent esophageal manometry and were excluded in the presence of achalasia or other esophageal motility disorders, or if under the age of 18. Ethical approval was obtained from the East London Research Ethics Committee.

Symptom scoring

All patients submitted a validated symptoms scoring scale ERAFLUX. This assesses patient’s reflux symptoms of chest pain, heartburn, regurgitation, and dysphagia, and stratifies these individual component symptoms by frequency, duration, and perceived intensity. The total severity score is defined as the maximum of the symptom scores for each of the individual symptom domains. An ERAFLUX score of greater than 25 is regarded as severe. To ascertain patients quality of life related to their reflux, all patients also completed a EuroQoL EQ-5D-5L generic assessment tool.

Preoperative investigations

All patients had an endoscopic examination, and the presence of hiatus hernia or endoscopic Barrett’s esophagus was noted. Any esophagitis present was graded using the Los Angeles classification. All patients also underwent manometric examination and dual-channel 24 hour pH measurement. Four patients underwent standard manometric assessment to assess for esophageal motility disorders having been referred for surgery from outside of our institution. The remaining 13 patients underwent study with circumferential solid-state 36-sensor high-resolution manometry (HRM) (Manoscan 360-HRM, Sierra Scientific, Los Angeles, CA, USA) in the upright seated position.

Perioperative management

Patients were managed in the perioperative period using a standard pathway for laparoscopic anti-reflux surgery at our institution. Patients were admitted on the day of operation and were discharged on the 3rd day. Postoperative contrast imaging was not routinely performed. Patients were advised to start drinking clear fluids immediately postoperatively and follow a sloppy diet for the first week. This was then to progress to a soft diet for the first 6 weeks. All patients were advised to expect some degree of dysphagia in the initial period.

Laparoscopic Nissen fundoplication was performed in a standardized manner by one of the authors (AJB), an experienced esophagogastric surgeon. A five-port pneumoperitoneum of 15 mmHg was secured, and a Nathanson liver retractor was utilized. Initially, the crura was dissected, the EGJ fully mobilized, and if present, the hiatus hernia was reduced. Crural repair was with one to three posterior ‘O’ Ethibond sutures (Johnson and Johnson Ltd., Livingstone, UK) until the esophagus fitted comfortably in the hiatus. For large hiatus hernias, additional 1–3 anterior hiatal sutures were used. The hiatus repair was sized by comfortably opening a dissection forceps adjacent to the esophagus. A bougie was not utilized. A short floppy 360° Nissen fundoplication was performed after division of the superior short gastric vessels. The fundoplication was not sutured to the esophagus or crura.

Distensibility measurement

The intraoperative distensibility was measured using the EndoFLIP system comprising a recording and display unit (EndoFLIP EF-100, Crospon Ltd) into which is attached a pre-calibrated single-use imaging catheter (EndoFLIP EF-325 catheter).

Prior to use, the FLIP imaging catheter was required to undergo an automated purging test cycle.
to remove air from the balloon; intraballoon pressure was referenced to atmospheric pressure. The catheter was inserted transorally to 60 cm at the teeth so the balloon was placed intragastrically. The balloon was distended to 20 mL and the catheter withdrawn slowly through the EGJ. Correct positioning was confirmed by the characteristic ‘hourglass’ appearance in the display of the FLIP whereby the centre of the imaging sensors within the balloon was at the narrowest point of the EGJ, typically at the hiatus. If there was doubt about the positioning of the catheter, then this was confirmed by direct visualization with endoscopy.

CSA and distensibility measurement was taken at defined time points while the patient was under general anesthesia:

- Initial- after induction of anesthesia and muscle paralysis but preincision
- Pneumoperitoneum- after skin incision and insufflation of 15 mmHg pneumoperitoneum
- Hiatal mobilization- after full mobilization of the EGJ and/or reduction of hiatus hernia
- Hiatal repair- after repair of the hiatus
- Fundoplication- after formation of the 360° Nissen fundoplication
- Final- pre-extubation after release of pneumoperitoneum

At each of the measurement points, the catheter balloon was distended to fixed volumes of 30 and 40 mL as recommended by previous authors. For each distension, a 30-second recording of the electrode diameter and the intraballoon pressure was recorded.

Data processing and statistical analysis

The data were post-processed in FLIP Analytics (FLIP Analytics Rev. D, 2010). The median value of each 30-second recording was used to calculate the minimum diameter and CSA in mm² for that time point and balloon distension. The distensibility index (DI) in mm²/mmHg was calculated by dividing the CSA by the average intraballoon pressure over 30 seconds.

All data were expressed as median and interquartile range. Statistical comparisons were made using Spearman’s rank correlation for continuous variables and Mann–Whitney U test for binary outcome categorical variables. Intraoperative values were compared sequentially using a two-sided paired t-test. All statistical analysis was at 5% significance using GraphPad Prism version 5.00 (GraphPad Software, San Diego, CA, USA).

RESULTS

Patient demographics

Seventeen patients underwent EndoFLIP study during primary Nissen fundoplication, nine male and eight female. All patients had a documented symptomatic response to PPIs, and all patients were on PPI therapy preoperatively. The median age was 51.5 (45.3–56.3), median weight was 73.6 kg (69.6–91.4), and average body mass index (BMI) 26.0 kg/m² (24.8–30.4).

Symptom scoring

The median ERAFLUX heartburn score was 29.5, the overall median ERAFLUX score was 34.5. The mean EQ-5D-5 L visual analog score was 75.0 (50–80).

Endoscopy

All patients underwent esophagastroduodenoscopy, 13 patients (76.5%) had an apparent hiatus hernia, four patients had grade A esophagitis, two patients had grade B esophagitis, and three patients grade C.

Esophageal manometry and 24 hour pH measurement

There were no motility disorders detected in the study cohort. The median lower esophageal sphincter (LES) length on HRM was 2.40 cm (20.5–3.25), basal respiratory minimum pressure was 3.40 mmHg (2.50–5.95 mmHg), and basal respiratory mean pressure was 10.1 mmHg (8.90–16.3 mmHg). HRM was used as the preoperative diagnostic modality for the detection of hiatal hernia and of the 13 patients who had preoperative HRM; eight had a hiatus hernia on HRM criteria (61.5%).

The median 24 hour total acid exposure time was 9.85% (7.48–12.5%), and median DeMeester score was 38.4 (26.0–48.5). Only one patient had a normal DeMeester score but had esophagitis and a hiatus hernia visualized on endoscopy.

Distensibility measurement

Initial measurements

At 30 mL balloon distension, the initial median CSA was 75.1 mm², and DI was 4.23 mm²/mmHg (Fig. 2, Table 2). At 40 mL balloon distension, the median CSA was 124.2 mm², and DI was 3.75 mm²/mmHg. Patients with a hiatus hernia on HRM had a significantly higher initial EGJ DI at 40 mL balloon distension (Fig. 1, Table 1).

Initial CSA and DI did not correlate with weight or BMI, ERAFLUX or EQ5L score, endoscopic findings, LES length and pressure on HRM or acid exposure time, and DeMeester score on 24 hours pH measurement (Table 1).

Final measurements

At 30 mL balloon distension, there was a significant decrease in the final DI when compared with the initial DI with an overall decrease of 3.26 mm²/
mmHg ($P = 0.0087$) (Table 2). At 40 mL balloon distension, there was a significant decrease in both the CSA (initial 136 mm$^2$ to final 39.9 mm$^2$, $P = 0.0078$) and in the DI with an overall decrease of 2.39 mm$^2$/mmHg ($P = 0.0039$) (Table 2, Fig. 2).

Intraoperative measurements

At 30 mL balloon distension, there was a significant reduction in the DI after insufflation of 15 mmHg pneumoperitoneum and after hiatal repair when compared sequentially (Table 2, Fig. 3).

At 40 mL balloon distension, there were significant reductions in the DI after pneumoperitoneum, after hiatal repair, and a smaller reduction following fundoplication (Table 2, Fig. 3).

Short-term clinical outcome

The system proved safe with no patient complications as a result of its usage. On four occasions, the catheter proved difficult to place because of the flexible catheter tip not able to negotiate the EGJ. This resulted in the catheter kinking in the distal esophagus. Probe placement was facilitated by intraoperative endoscopy using a grasper to pull the catheter into the stomach.

There were no intraoperative complications and no conversions to open surgery. Postoperatively, all except for one patient were discharged after a two-night stay. All were free of reflux symptoms and were drinking at least thickened fluids as per protocol.

Patient seven in the series had a reoperation after 48 hours after suffering from profound postoperative nausea and retching for 24 hours. He became profoundly dysphagic after 48 hours. Interestingly, his post-fundoplication DI at operation was 0.47 mm$^2$/mmHg (Fig. 4). At re-laparoscopy, it was found that the cranial part of his fundoplication had become impacted in the hiatus. The fundoplication was repositioned in the abdomen, and the cranial fundoplication suture was removed. Unfortunately, EndoFLIP data were not available for the second operation.

Table 1 Initial distensibility at 30 and 40 mL balloon distensions and relationship to preoperative variable

<table>
<thead>
<tr>
<th>Patient demographics ($n = 17$)</th>
<th>Median IQR</th>
<th>$R$</th>
<th>$P$</th>
<th>$R$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>73.6 69.6–91.4</td>
<td>−0.195</td>
<td>0.438</td>
<td>−0.138</td>
<td>0.584</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>26.0 24.8–30.4</td>
<td>−0.133</td>
<td>0.589</td>
<td>−0.127</td>
<td>0.616</td>
</tr>
<tr>
<td>Symptom scoring ($n = 17$)</td>
<td>Median IQR</td>
<td>$R$</td>
<td>$P$</td>
<td>$R$</td>
<td>$P$</td>
</tr>
<tr>
<td>ERAFLUX heartburn</td>
<td>29.5 22.5–34.8</td>
<td>0.178</td>
<td>0.509</td>
<td>0.250</td>
<td>0.350</td>
</tr>
<tr>
<td>ERAFLUX total</td>
<td>34.5 29.3–37.5</td>
<td>−0.019</td>
<td>0.737</td>
<td>−0.093</td>
<td>0.733</td>
</tr>
<tr>
<td>EQ-5D-5 L VAS</td>
<td>75.0 50–80</td>
<td>−0.303</td>
<td>0.314</td>
<td>−0.128</td>
<td>0.677</td>
</tr>
<tr>
<td>Endoscopy ($n = 17$)</td>
<td>$n$</td>
<td>%</td>
<td>$P$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of hiatus hernia</td>
<td>13</td>
<td>76.5</td>
<td>0.394</td>
<td>0.789</td>
<td></td>
</tr>
<tr>
<td>Presence of esophagitis (any LA grade)</td>
<td>9</td>
<td>52.9</td>
<td>0.481</td>
<td>0.888</td>
<td></td>
</tr>
<tr>
<td>Presence of Barrett’s</td>
<td>2</td>
<td>11.8</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>High-resolution manometry ($n = 13$)†</td>
<td>$n$</td>
<td>%</td>
<td>$P$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of hiatus hernia</td>
<td>8</td>
<td>61.5</td>
<td>0.109</td>
<td>0.0295*</td>
<td></td>
</tr>
<tr>
<td>Basal resp. min pressure (mmHg)</td>
<td>3.40 2.50–5.95</td>
<td>−0.390</td>
<td>0.188</td>
<td>−0.489</td>
<td>0.090</td>
</tr>
<tr>
<td>Basal resp. mean pressure (mmHg)</td>
<td>10.1 8.90–16.3</td>
<td>−0.495</td>
<td>0.086</td>
<td>−0.544</td>
<td>0.055</td>
</tr>
<tr>
<td>LES length (cm)</td>
<td>2.40 2.05–3.25</td>
<td>−0.314</td>
<td>0.296</td>
<td>−0.317</td>
<td>0.292</td>
</tr>
<tr>
<td>24 hr pH ($n = 17$)</td>
<td>Median IQR</td>
<td>$R$</td>
<td>$P$</td>
<td>$R$</td>
<td>$P$</td>
</tr>
<tr>
<td>Total acid exposure time (%)</td>
<td>9.85 7.48–12.5</td>
<td>0.300</td>
<td>0.260</td>
<td>0.306</td>
<td>0.250</td>
</tr>
<tr>
<td>DeMeester Score</td>
<td>38.4 26.0–48.5</td>
<td>0.297</td>
<td>0.264</td>
<td>0.344</td>
<td>0.192</td>
</tr>
</tbody>
</table>

* $P < 0.05$. † Four patients had standard manometry and are not included here. Statistical evaluation was with Spearman’s Rank correlation for continuous variables and Mann–Whiney $U$ test for binary outcome variables. –, Not applicable; BMI, body mass index; DI, distensibility index; IQR, interquartile range; LA, Los Angeles esophagitis grade; LES, lower esophageal sphincter. Statistical comparison made with two-sided paired $t$-tests to the preceding value.
One further case in the series is of particular interest. Patient 12 underwent a 360° Nissen fundoplication; however, intraoperatively, the wrap appeared visually too tight (Fig. 5). Assessment with the FLIP revealed a DI of 0.65 mm²/mmHg, interestingly similar to patient seven (Fig. 4). The protocol was broken and a posterior 270° Lind fundoplication was formed increasing the DI to 0.89 mm²/mmHg. Intraoperative data for the fundoplication and final operative steps has not been included in the analysis.

**DISCUSSION**

Laparoscopic Nissen fundoplication aims to reverse the changes thought to contribute to gastroesophageal reflux by reduction and repair of hiatal hernia, repositioning the LES in the intra-abdominal compartment and adding a new anatomical component, the fundoplication. Pandolfino et al. have suggested that EGJ distensibility is an important factor in the development of GERD and have demonstrated that when compared with normal controls, patients who have undergone Nissen fundoplication have a reduced distensibility. This implies that distensibility may be a desirable variable to measure during fundoplication. Other methods have been proposed to attempt to standardize the operation for better results including forming the fundoplication with a rigid bougie, measurement with intraoperative manometry and direct visualization with endoscopy. However, none of these methods have gained universal acceptance, and there still exists a need for a safe, reproducible method of

**Table 2**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>DI (IQR)</th>
<th>P</th>
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<tbody>
<tr>
<td>Initial</td>
<td>4.23 (1.60–6.58)</td>
<td>NA</td>
</tr>
<tr>
<td>30 mL</td>
<td>4.53 (1.60–6.58)</td>
<td>0.0016</td>
</tr>
<tr>
<td>40 mL</td>
<td>3.75 (2.43–7.21)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Fundoplication</td>
<td>1.20 (1.17–4.66)</td>
<td>0.0006</td>
</tr>
<tr>
<td>3.59 (2.13–3.43)</td>
<td>0.0016</td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>0.834 (0.415–0.834)</td>
<td>0.170</td>
</tr>
<tr>
<td>0.972 (0.715–1.72)</td>
<td>0.087</td>
<td></td>
</tr>
<tr>
<td>1.36 (1.33–2.15)</td>
<td>0.087</td>
<td></td>
</tr>
<tr>
<td>2.02 (1.17–4.64)</td>
<td>0.0016</td>
<td></td>
</tr>
</tbody>
</table>

Statistical comparison made with two-sided paired *t*-tests to the preceding value. Bold values denote a statistically significant difference to the preceding value. DI, distensibility index; EGJ, esophagogastric junction; IQR, interquartile range; NA, Not applicable.

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calibrating the hiatal wrap and fundoplication to avoid complications.

Our results suggest that intraoperative distensibility measurement with the EndoFLIP system may help guide the surgeon during hiatus repair and fundoplication. Our study has demonstrated that a manometrically defined hiatus hernia is associated with an increased initial DI and that laparoscopic hiatus hernia repair and Nissen fundoplication results in an immediate significant reduction of the DI. The EndoFLIP system also proved capable of differentiating distensibility changes between individual operative steps, revealing a significant decrease in the DI following pneumoperitoneum, hiatal repair, and fundoplication (Fig. 3).

Furthermore, the special cases noted in the results show the potential of the EndoFLIP system to modify the operation. Patient seven had a comparatively low post-fundoplication distensibility of 0.47 mm²/mmHg; however, it is not clear whether this was the cause of his postoperative vomiting and subsequent dysphagia (Fig. 4). In the case of patient 12,
the fundoplication appeared visually too tight, and the EndoFLIP system confirmed a DI of 0.65 mm²/mmHg that is at the lower end of the DI range (Fig. 4). Two further patients are noted in Figure 4 (40 mL distension) to have a similarly low DI post-fundoplication; interestingly, one reported dysphagia postoperative and the other was unfortunately lost to follow up. Preoperative characteristics for patients 7 and 12 are detailed in Table 3. Two inferences can be made from this experience: that there may be a distensibility value that is predictive for postoperative dysphagia, and that the EndoFLIP system may be used to modify the operation.

Pandolfino et al. have pioneered the use of the EndoFLIP system in sedated patients at gastroscopy providing a distensibility measurement protocol that has been widely adopted.5,16 There is, however, limited data pertaining to intraoperative distensibility measurement.8,17 The most significant case series so far detailing EndoFLIP measurement during surgery has been in 50 patients undergoing laparoscopic intervention for conditions not related to GERD.9 Comparisons with our data reveal that the initial distensibility in our cohort of patients with GERD appears to be higher (4.23 vs. 1.1 mm²/mmHg) potentially because of the prevalence of hiatal hernia within the group. However, after fundoplication, the DI in our study is reduced when compared with that quoted by Nathanson et al. in normal control subjects (0.972 vs. 1.4 mm²/mmHg). This would be in keeping with previous authors observations in this regard.6,9

Our study only includes a small number of patients and does not include long-term follow up. It would be desirable to include EndoFLIP data when not under anesthetic, as postoperative distensibility measurement may be useful to demonstrate durability of surgical repair; however, our early experience with awake nasal intubation was unsatisfactory, with poor patient tolerance and measurement difficulty because of esophageal peristalsis. It is also possible that the two cases that we have demonstrated to potentially influence the operative outcome may have been adequately diagnosed using a rigid bougie. However, the flexible sensing catheter provides an objective value for the distensibility that provides extra information for the surgeon beyond simple visual cues.

Validation of final distensibility measurements with postoperative symptom scoring and 24 hours pH monitoring will be vital to ascertain the viability of EndoFLIP measurement. In order to achieve this larger, multicenter studies with standardized follow up are needed to help elucidate a potential range of distensibility associated with consistent successful patient outcome.

CONCLUSIONS

EndoFLIP technology can be safely used during Nissen fundoplication to measure the distensibility of EGJ. Laparoscopic Nissen fundoplication results in a significant immediate reduction in the distensibility of the EGJ. The EndoFLIP system is able to show a significant reduction in the DI following pneumoperitoneum, hiatus repair, and fundoplication. Importantly, FLIP technology may help guide anti-reflux surgery by prompting intraoperative modification and thereby ensuring a more reliable outcome for GERD sufferers undergoing anti-reflux surgery. Larger, multicenter studies with long-term follow up may result in the development of a safe range of distensibility associated with successful patient outcomes.

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AUTHOR CONTRIBUTIONS

AJB and AI were responsible for study design and manuscript preparation. AJB performed the surgical procedures. AI recorded the EndoFLIP measurements and analyzed the data.
References