Official Title: Esophagogastric junction distensibility during hiatal hernia repair

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Background and Significance:

The esophagogastric junction (EGJ) has two distinct functions, to remain closed during periods of rest providing a barrier to prevent reflux and to open during periods of deglutination to allow for movement of contents between esophagus and stomach. As opposed to the contractile force of the lower esophageal sphincter (LES) complex, the degree to which the EGJ resists changes in distention is referred to as distensibility. While high resolution manometry directly measures closure forces, the opening force or compliance, is less accurately assessed via this modality. Conversely, functional lumen imaging probe (FLIP) utilizes impedance planimetry to measures the cross-sectional area as a relation of pressure within the EGJ, thus calculating the distensibility at the EGJ called the distensibility index (DI).(1)

Patients with gastroesophageal reflux have abnormally increased distensibility at the EGJ.(2) The result is an incompetent EGJ, with decreased resistance to distention, allowing for inappropriate reflux of gastric contents and exposure of the esophageal mucosa. Hiatal repair and fundoplication have been demonstrated to improve the distensibility of the EGJ.(3) As such, intraoperative measurements of EGJ distensibility via impedance planimetry may be a helpful intraoperative guide in foregut surgery.(4)

Long-term patient reported outcome measures after anti-reflux surgery demonstrate encouraging results with 95% of patients reporting improvement in postoperative reflux symptoms.(5) Despite the improvement in symptoms of GERD, new onset or worsened dysphagia after anti-reflux procedures occurs in up to 14% of patients.(6) The etiology of postoperative dysphagia is likely complex and multifactorial. Furthermore, a lack of standardization of the surgical procedure likely contributes to reported variability in incidence rate, suggesting that differences in operative technique drive postoperative dysphagia after anti-reflux surgery.(7–9) However, with use of an intraoperative tool to calibrate the crucial aspects of the hiatal repair, outcomes may be improved or more predictable.

Previous studies have demonstrated intraoperative impedance planimetry may help in identifying patients with overly corrected distensibility.(10) It has been suggested that for a modest increase in procedural time, the addition of impedance planimetry can add valuable information that, in a majority of cases, can augment management decisions.(11) However, there are yet to be clear reference ranges establishing normal and pathologic ranges of distensibility especially pre and post-op. Complicating matters further, patients who undergo anti-reflux procedures demonstrate marked drops in distensibility similar to those seen in patients with achalasia, presumably with only a subset demonstrating dysphagic symptoms.(12) As such, it is unclear if there is a correlation between postoperative symptoms after anti-reflux procedures and the DI at the EGJ or crural closure.

The EndoFLIP catheter (Medtronic, MN, USA) is designed to take real-time measurements of the lower esophagus during endoscopy, thus providing an internal dynamic view of the EGJ anatomy. Utilizing impedance planimetry, the cross-sectional area along an 8 or 16cm segment is obtained.(13,14) The pressure within the balloon is measured and correlated to the cross-sectional area, determining the ratio of area to pressure, or the DI. Use of EndoFLIP in patients who undergo hiatal hernia repair is able to distinguish components of the EGJ, including

crural diaphragm from LES.(15) In addition, unrecognized patterns of esophageal dysmotility can be identified using this technology.

The Gastroesophageal Reflux Disease-Health Related Quality of Life survey (GERD-HRQL) is a well validated and widely used disease-specific quality of life measure. Since its introduction it has been translated into several languages and demonstrated reliability, responsiveness, and validity in the assessment of symptom severity in patients with gastroesophageal reflux. The measure consists of 10 questions including queries about heartburn, swallowing, gas-bloat symptoms, as well as medication related symptoms, and overall satisfaction. Importantly, its sensitivity to detect changes in symptomatology (e.g. responsiveness) make it an adequate QOL measure to assess the effects of surgical treatments.(16) The Mayo Dysphagia Questionnaire is another validated survey that can further asses dysphagia in this patient population. The questionnaire comes in a short 14 question version addressing specific symptoms related to dysphagia.(17)

Purpose:

We aim to ascertain the effects of hiatal hernia repair and fundoplication on the distensibility of the esophagogastric junction (EGJ) as measured by FLIP topography/impedance planimetry. We also aim to assess for any correlation between values of EGJ distensibility and GERD related quality of life (QOL) and dysphagia scores.

Study Design:

Patients referred for antireflux surgery and/or hiatal hernia repair will be considered for enrollment. Standard preoperative evaluation will include esophagogastroduodenoscopy (EGD) to assess for intraluminal pathology including esophagitis, columnar lined esophagus suggestive of Barrett's esophagus, intraluminal masses, and to measure hernia size. Patients will also undergo preoperative high resolution esophageal manometry testing with impedance as clinically indicated to evaluate esophageal motility as assessed by standardized Chicago Classification V3.(18) Manometry will occasionally be avoided in patients with paraesophageal hernias without substantial dysphagia or those not amenable to manometry, with appropriate upper gastrointestinal radiology imaging (UGI), who will be having partial fundoplications. UGI is also a routine preoperative evaluation. Furthermore, pH testing for evaluation of acid reflux will be performed in patients without LA grade C or D esophagitis, paraesophageal hernia, or pathologic confirmation of Barrett's esophagus.

Patients appropriate for enrollment will be consented in the office setting or via telephone by a member of the research team. Preoperative baseline evaluations of symptom severity will be assessed via the GERD-HRQL survey and Mayo Dysphagia Questionnaire. Surgery will be scheduled and patients will undergo intraoperative impedance planimetry with EndoFLIP obtaining measurements of the cross-sectional area, balloon pressure, minimum diameter, compliance, length of high pressure segment, and distensibility index of the EGJ using an 8cm EndoFLIP balloon. Sequential assessments will be performed to 30ml and 40ml for up to a minute for each volume of distension. An initial baseline measurement will be obtained after establishment of pneumoperitoneum. A second measurement will occur following hiatal

dissection and mobilization but prior to crural closure. Two additional measurements will be obtained after hiatal closure and after fundoplication.

Surgeons will be blinded to EndoFLIP results for 25 cases. An analysis will be performed to determine goal impedance planimetry values based on patient postoperative symptom scores. The EndoFLIP catheters and pump will be provided by Medtronic, at no cost to the patient. Medtronic will also cover the fees associated with the EndoFLIP procedure (CPT 91040 is used).

Postoperative clinical care will proceed as per standard protocol for foregut surgery, with 1 additional office visit. Reports of postoperative symptomatology and QOL will be performed, via GERD-HRQL and Mayo Dysphagia Questionnaire during follow-up clinic appointments at 2 weeks and 6 weeks postoperative, and with additional long-term follow-up of at 6 months. Long-term follow-up will again assess for QOL symptoms via GERD-HRQL and the Mayo Dysphagia Questionnaire. The 6-month follow-up visit is not our typical practice and the patients cost for this visit will be covered by Medtronic. Per our standard clinical care, recurrence of symptoms or dysphagia at any point may lead to additional postoperative testing, including UGI, EGD, pH testing, esophageal manometry, CT scan, or EndoFLIP. Postoperative GERD-HRQL and Mayo Dysphagia score results will be compared to intraoperative EndoFLIP measurements in our interim and final analysis.

A total of 25 patients will be included. In the blinded group, operating surgeons will be blinded to the intraoperative EndoFLIP results, performed by a separate endoscopist. These values will be compared to scores based on the questionnaires in the analysis. At study completion, EndoFLIP values will again be analyzed in comparison to scores on the GERD HRQL and Mayo Dysphagia Questionnaires to assess for correlation between distensibility and symptomatology.

Patient Selection

- Inclusion Criteria
    - Patient undergoing hiatal hernia repair (types I-IV included) and fundoplication
    - Absence of spastic esophageal disorders (i.e. jackhammer esophagus, achalasia types I-III) assessed by preoperative high-resolution manometry
    - Adult patients ≥18 years
    - Elective repairs
- Exclusion Criteria
    - Redo hiatal hernia repairs
    - Emergent repairs
    - Patients with contraindication to surgery or endoscopy(13)
    - Patients with esophageal varices(13)
    - Cases with insufficient esophageal length in which fundoplication is unable to be performed or a Collis gastroplasty is required.
    - Connective tissue diseases such as scleroderma or lupus
    - Diameter measurements less than 5 mm as the EF-325N catheter is not suitable

Endpoints

- Primary
    - Change in distensibility index of EGJ as measured by EndoFLIP after hiatal hernia repair

- Secondary
    - Postoperative symptoms as measured by GERD-HRQL and Mayo Dysphagia Score

Variables

Preoperative	Intraoperative	Postoperative
Demographic data	Impedance planimetry values(Volumes, 30 and 40 ml with each measured over 1 minute): balloon pressure, Cross-sectional area, minimum diameter, distensibility, length of narrow segment, compliance	QOL (GERD-HRQL) and Mayo Dysphagia Questionnaire
Comorbidities	OR Time	Results of postoperative testing (e.g. any indicated studies based on symptoms: UGI, EGD, pH testing, manometry). No routine studies are planned for asymptomatic patients
Manometric and pH findings		
Upper GI series findings		
Endoscopy findings		
Baseline EndoFLIP measurements if performed (not part of proposed study)		
Baseline QOL (GERD-HRQL) and Mayo Dysphagia Score		

Data Collection:

Research fellows, data analysts, and clinical research team will be responsible for tracking subject enrollment and compliance with protocol. Patient outcomes and quality of life will be entered under a deidentified patient key in the surgical outcomes database which is prospectively maintained.

Statistical Analysis:

Data will be analyzed using standard statistical methods utilizing SAS System version 9.4 (Cary, NC, USA). Descriptive statistics will be used to define the study population on all

variables, utilizing mean and standard deviation or median and interquartile range where appropriate. Categorical variables will be compared with Chi-square and Fisher's exact tests. Continuous variables will be compared using Students t-tests or Wilcoxon-Mann-Whitney test when needed for nonparametric data. A statistical significance level will be set at $p<0.05$ for all statistical analysis.

Data Security Plan:

The patient key containing PHI will be stored in a password accessed digital file on a limited access folder on a secure network. Access to this folder is only available to researchers, and password access to this file will be granted only to sub-investigators. Computer access to this network is in an office space limited to employees during the working hours and requires badge access granted by security during after-hours. Data of interest will be recorded on a deidentified spreadsheet with no linking patient information. The spreadsheet will be kept on a limited access folder on a secure network. Following data collection period, all variables and data will be deidentified including during any subsequent data analysis or publication.

Benefit to Subjects:

Subjects may not benefit from participation. The patients in the blinded group will have standard preoperative work-up and intraoperative care.
There will be no monetary compensation for the patients who enroll, but Medtronic will cover the costs of the impedance planimetry procedure and the 6month follow-up visit. In addition, Medtronic is providing the 8cm EndoFLIP balloons for the study at no charge, as well as the EndoFLIP system.

Risk to Subjects:

The risks associated with this study revolve around the use of intraoperative EndoFLIP. First there are inherent risks associated with esophagogastroduodenoscopy (EGD) such as injury to the mouth, nasopharynx, esophagus, stomach and duodenum. EGD will be performed by experienced endoscopists. All patients with contraindications to EGD will be excluded from the study. With EndoFLIP there is a risk of esophageal injury with overdistention. All patients in which EndoFLIP is contraindicated in will also meet our exclusion criteria. The EndoFLIP catheter and software will be used as per the published instructions.(13,14). Notably, the diameter of the 8cm balloon that will be used (2cm) is similar to the diameter of bougie dilators that are routinely used in these procedures (1.85-2cm, based on surgeon selection).

An additional risk to is the release of information from the patient's health records. The research physician/institution will protect records so that patient name, address, and phone number will be kept private. HIPAA compliance in clinical and pathologic data handling will ensure protection of patients' rights to privacy. Data access will be restricted to those involved in data collection or analysis. Study-related records identifying the subject will be kept confidential and, to the extent permitted by applicable laws and/or regulations will not be made publicly available.

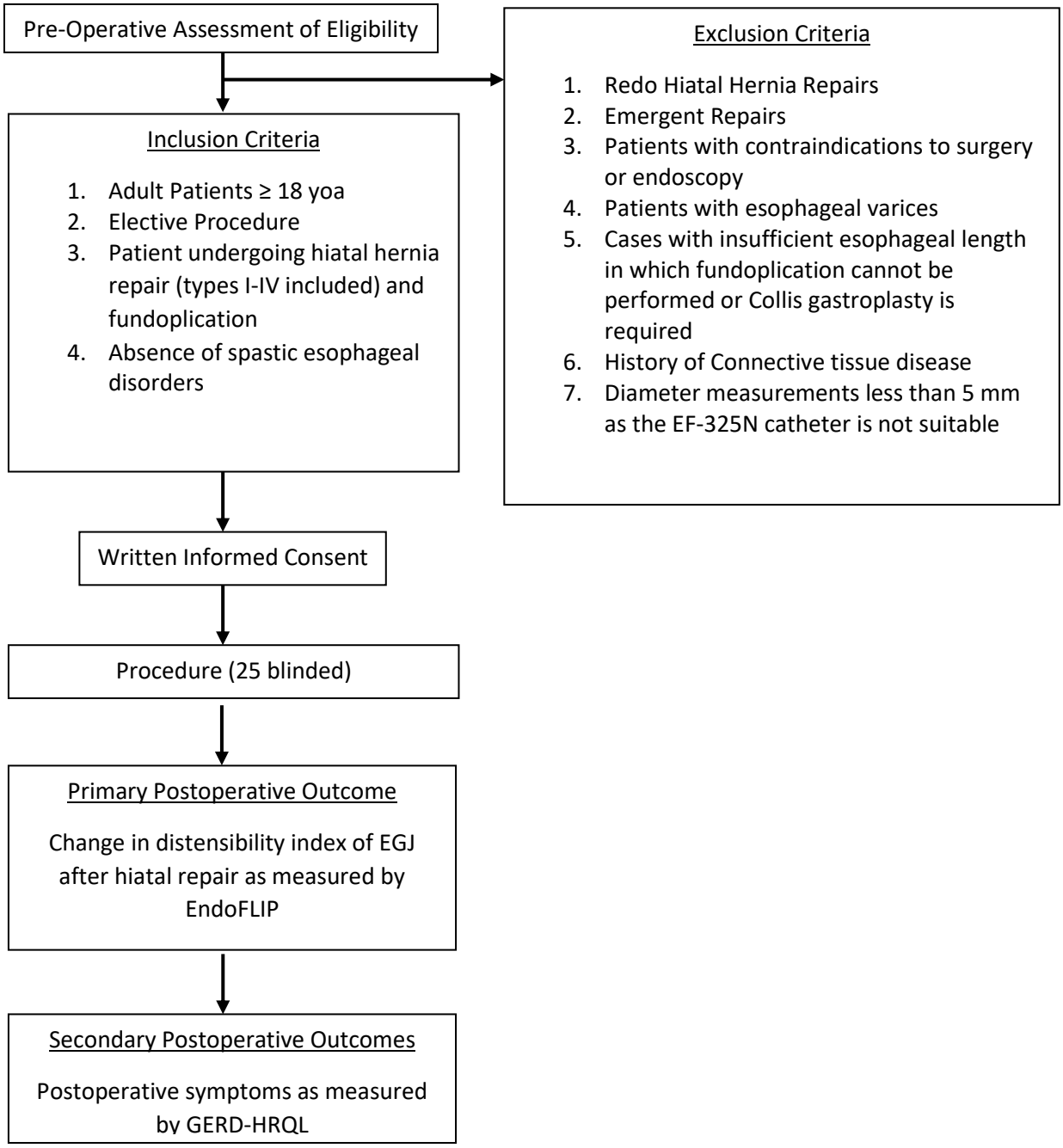
Safety issues that may terminate a patient's enrollment are significant differences in 30-day mortality, and unplanned operative interventions. A safety monitor will be appointed to monitor and track untoward complication. Should any complications that are directly attributed to the study arise, they will be reported to the IRB for review, as will any unexpected mortality.

Safety Monitoring:

The safety monitor will provide a professional opinion and review of any adverse events potentially related to the intervention. The co-investigators and research staff will regularly review and document the operative and postoperative course of patients enrolled in the study. The patient will be seen daily by the surgical team monitoring their care and wellbeing. The patient will also be seen or reviewed daily by an attending surgeon or resident involved in the study while they are in hospital. Residents will be instructed in the details of the protocol by the research attending. The research staff will document adverse events as follows:

1. Any adverse events potentially related to the intervention (EnodoFLIP) will be reported to the safety monitor, the principal investigator, and the IRB within 48 hours of discovery.
   Events potentially associated with the intervention include but are not limited to:
   i. Esophageal injury from balloon distention.
2. All adverse events not potentially related to the intervention will be recorded and reviewed per Clavien-Dindo complication classifications. A list of adverse events will be emailed to the principal investigator and the safety monitor every 6 months for review. Upon review by the principal investigator and safety monitor, any adverse events potentially associated with the interventions performed (as listed above) will be submitted to the IRB within 48 hours of discovery.
3. Any patient who is withdrawn from the study for any reason will be reported to the principal investigator and safety monitor every six months for review. Reasons for withdrawal include but are not limited to patient preference, physician judgment, anesthesiologist judgment, adverse event not related to intervention, adverse event related to intervention.
4. The study will be stopped if
   a. The intervention is deemed unsafe by the safety monitor, the principal investigator, or the IRB committee.
   b. The intervention is deemed significantly superior, rendering further utilization of the alternate intervention unethical.
5. A monitor, auditor, IRB and/or other regulatory authorities will have access to study-related medical records.

Figure 1. Protocol Flow Chart Including Patient Inclusion/Exclusion Criteria



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