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RESEARCH ARTICLE

Estimation of mechanical work done to open the esophagogastric junction using functional lumen imaging probe panometry

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Abstract

In this study, we quantify the work done by the esophagus to open the esophagogastric junction (EGJ) and create a passage for bolus flow into the stomach. Work done on the EGJ was computed using functional lumen imaging probe (FLIP) panometry. Eighty-five individuals underwent FLIP panometry with a 16-cm catheter during sedated endoscopy including asymptomatic controls (n = 14), 45 patients with achalasia (n = 15 each, three subtypes), those with gastroesophageal reflux disease (GERD; n = 13), those with eosinophilic esophagitis (EoE; n = 8), and those with systemic sclerosis (SSc; n = 5). Luminal cross-sectional area (CSA) and pressure were measured by the FLIP catheter positioned across the EGJ. Work done on the EGJ (EGJW) was computed (millijoules, mJ) at 40-mL distension. Additionally, a separate method was developed to estimate the "work required" to fully open the EGJ (EGJROW) when it did not open during the procedure. EGJW for controls had a median [interquartile range (IQR)] value of 75 (56–141) mJ. All achalasia subtypes showed low EGJW compared with controls ($P < 0.001$). Subjects with GERD and EoE had EGJW 54.1 (6.9–96.3) and 65.9 (10.8–102.3) mJ, similar to controls ($P < 0.08$ and $P < 0.4$, respectively). The scleroderma group showed low values of EGJW, 12 mJ ($P < 0.001$). For patients with achalasia, EGJROW was the greatest and had a value of 210.4 (115.2–375.4) mJ. Disease groups with minimal or absent EGJ opening showed low values of EGJW. For patients with achalasia, EGJROW significantly exceeded EGJW values of all other groups, highlighting its unique pathophysiology. Balancing the relationship between EGJW and EGJROW is potentially useful for calibrating achalasia treatments and evaluating treatment response.

NEW & NOTEWORTHY Changes in pressure and diameter occur at the EGJ during esophageal emptying. Similar changes can be observed during FLIP panometry. Data from healthy and diseased individuals were used to estimate the mechanical work done on the EGJ during distension-induced relaxation or, in instances of failed opening, work required to open the EGJ. Quantifying these parameters is potentially valuable to calibrate treatments and gauge treatment efficacy for subjects with disorders of EGJ function, especially achalasia.

distension-induced EGJ relaxation; energy; LES and EGJ opening; mechanical work; pressure-volume work

INTRODUCTION

The esophagogastric junction (EGJ) is a neurologically controlled valve between the stomach and esophagus that serves to facilitate entry of swallowed material into the stomach and protect the esophagus' mucosal lining from gastric juice. Swallowing induces relaxation of the lower esophageal sphincter (LES), assisting in the opening of this barrier (1–3), which is vital to the process of esophageal emptying (4). Significant deviations of EGJ compliance and degree of LES relaxation affect its opening and can lead to a range of disorders including gastroesophageal reflux disease (GERD) and achalasia (5, 6). High-resolution manometry (HRM) is the most widely used technique to assess LES relaxation. Recently, functional lumen imaging probe (FLIP) panometry (7) has also been used in the diagnosis and evaluation of achalasia (8) and GERD (9) as well as to assess EGJ compliance during surgical fundoplication (10–12) and myotomy (13–15).

Relaxation at the EGJ is most commonly assessed using the Integrated Relaxation Pressure (IRP) metric computed from HRM data. Although this quantifies the maximal relaxation after swallowing, it does not detect EGJ opening, which is an essential element of bolus transit. To define EGJ opening characteristics, it is necessary to obtain a relationship between lumen cross-sectional area (CSA) and intraluminal pressure. This information is readily available through FLIP panometry. Using FLIP, sustained distension

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of the esophagus is possible and luminal CSA is measured by impedance planimetry sensors housed within the device. Concurrent pressure measurements are also obtained and, combined with CSA, used to evaluate the esophageal response to distension (7) and EGJ compliance (9). However, current metrics that quantify EGJ compliance (e.g., the EGJ distensibility index) are "static" in that they do not consider the variation of pressure and CSA as the EGJ opens. We address this issue by computing the mechanical work done on the EGJ during opening under normal conditions (abbreviated as EGJW). Although relaxation is an integral part of EGJ opening, it is the esophageal contraction that generates the requisite energy to open the lumen (16). The dynamic nature of this process is evident by the large increase in EGJ CSA and pressure at this location within the FLIP. Additionally, it should be noted that relaxation of the sphincter alone is not a sufficient condition to facilitate EGJ opening. Relaxation has to be accompanied by some source of pressure rise (peristalsis or increasing bag volume). Otherwise, EGJ opening is impaired and mechanical work done on the EGJ remains low. Our hypothesis was that the work done on the EGJ is an indicator of not only the mechanical state of the EGJ but also the energy expended by the esophagus during opening. The aim of this study was to quantify the mechanical work done by the esophagus during EGJ opening and to see how it varied among normal individuals and various disease states. In addition to computing the work done on the EGJ, we developed a method to predict the "work required" to open the EGJ (EGJROW) in instances that it remained closed during the test protocol. This metric accounts for the EGJ's stiffness and estimates the work that would be required to completely open the EGJ. If the work required is greater than the work done, it implies that the EGJ has not opened. Consequently, it implies compromised trans-EGJ flow. This energetic perspective on the EGJ opening process can shed light on the work done by the esophagus, not only to propel the bolus, but also in overcoming resistance to trans-EGJ flow.

METHODS

Subjects

Adult patients presenting with esophageal symptoms were examined at the Esophageal Center of Northwestern between November 2012 and October 2018. FLIP panometry was conducted during upper endoscopy, and recorded data were indexed into a motility database. Representative patient cohorts with achalasia, GERD, systemic sclerosis (SSc), and eosinophilic esophagitis (EoE) were randomly chosen from this database. All but the patients with EoE were required to have also undergone HRM. The Chicago Classification v3.0 (17) was used to separate the patients with achalasia into types I, II, and III. Patients without hiatal hernia and a history of erosive esophagitis (Los Angeles grade A or B) or a positive ambulatory esophageal pH test performed off proton pump inhibitor (esophageal acid exposure time >6%) were classified as GERD. Patients with EoE not being treated with topical steroid or elimination diet [proton pump inhibitor (PPI) use was accepted] were identified based on having eosinophilic inflammation (>15 eosinophils per high power field) on esophageal biopsies and endoscopic findings of rings and/or furrows. Patients with SSc were identified based on a clinical-rheumatologic diagnosis of SSc. A cohort of healthy volunteers without esophageal symptoms were also included as controls. Informed consent was obtained from all subjects and control subjects were paid for their participation. There is overlap with previously described cohorts (18–20).

Study Protocol

After at least a 6-h fast, subjects were sedated during upper endoscopy done in the left lateral decubitus position. The 16-cm FLIP (EndoFLIP EF-322N; Medtronic, Inc, Shoreview, MN) was calibrated to atmospheric pressure and the probe was placed trans-orally after the endoscope was withdrawn. The FLIP was positioned such that one to three impedance sensors were beyond the EGJ, and this position was maintained throughout the FLIP study. With a starting volume of 20 mL, the FLIP was distended in 10-mL increments until a target volume of 70 mL was reached. At each increment, the volume was maintained for 30–60 s. A transient decrease in luminal diameter at 3 or more adjacent esophageal planimetry channels (axial length ≥ 2 cm) was considered a contractile event. Repetitive antegrade contractions (RACs) were defined as ≥6 consecutive antegrade contractions spanning ≥6 cm of axial length at a rate of 6 ± 3 per minute (21). HRM studies were conducted with ten 5-mL, liquid swallows in a supine position. The HRM catheter consisted of a solid-state assembly with 36 circumferential pressure sensors at 1-cm intervals (Medtronic, Inc.). Ambulatory esophageal pH-metry was done after withholding proton pump inhibitors for at least 7 days with either a wireless pH capsule (Bravo, Medtronic, Inc.) positioned 6 cm proximal to the squamocolumnar junction or a catheter-based antimony pH electrode positioned 5 cm proximal to the manometrically localized EGJ (Sandhill Scientific, Inc., Highlands Ranch, CO).

Collecting EGJ Opening Data

Planimetry and pressure data occurring at the 40-mL distension volume were used to compute work done on the EGJ. This volume was chosen because it generated sufficient distension to elicit contractions and was low enough to allow fluid movement in the bag without exceeding the bag's infinite compliance limit. Another issue was that at greater bag volumes, the EGJ was always partially open, compromising the calculation of EGJ work. To compute work done on the EGJ, we first identified the planimetry sensors localized within the EGJ evident as a "waist" in the distal segment of the bag. An example of the areas chosen for work computation is shown in Fig. 1. At each instant, candidate locations for the EGJ were identified by locating minima CSAs. These are marked with green diamonds in the figure. The distal-most candidate was then marked as the center of the EGJ. Data from planimetry sensors 2 cm proximal and distal to this location were considered as the EGJ segment and used for calculating work. These sensors have been highlighted by the blue box in Fig. 1.

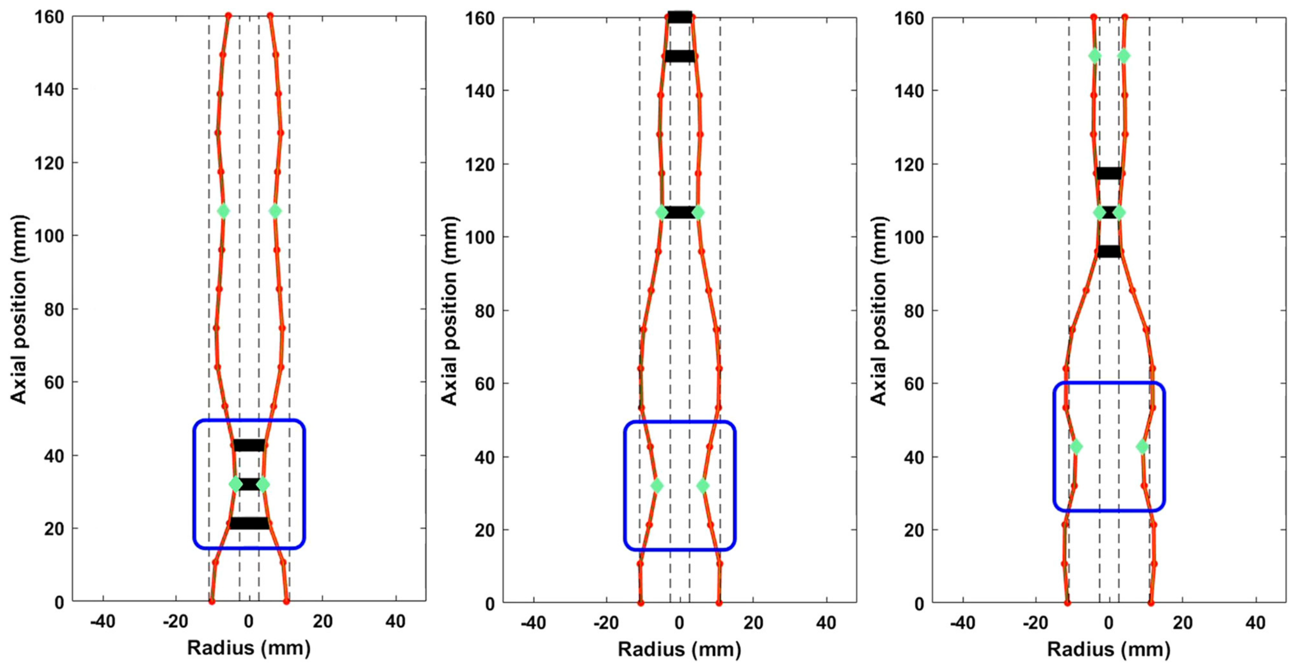

Figure 1. Real-time detection of planimetry sensors spanning the EGJ. Shown here are three snapshots of the esophageal lumen as detected by the FLIP. In the first panel, there is no contraction wave evident and the EGJ is closed. In the second panel, the contraction is at the proximal end of the FLIP and the EGJ is partially open. The third panel shows the bag profile when the contraction has traveled halfway along the bag length and the EGJ is almost fully open. Green diamonds represent local minimum values of the CSA. The blue box indicates the specific sensors chosen for the calculation of EGJ work metrics. The thick horizontal lines indicate the smallest luminal CSA at each instant and the vertical dotted lines represent the range of accurate CSA measurable by the FLIP (21–380 mm^2). CSA, cross-sectional area; EGJ, esophagogastric junction; FLIP, functional lumen imaging probe.

Computing Work Done on the EGJ and Work Required to Open the EGJ

To compute actual work done, pressure and planimetry data from the EGJ segment were combined based on the definition of mechanical work (the product of force and displacement in that direction). In the context of the FLIP, luminal pressure corresponds to force and change in EGJ area is equivalent to radial displacement. Thus, by systematically combining pressure and change in EGJ CSA, mechanical work done on the EGJ can be computed. For a detailed derivation of the pressure-volume version of mechanical work from the classical definition of force times displacement, see (22). Based on this explanation, it is clear that a large amount of force (or pressure) alone does not equate to a substantial amount of mechanical work done. The applied force has to result in wall displacement for work to be done. In the FLIP, displacement is indicated by substantial increase in luminal CSA at the EGJ.

During distension-induced contractility, the contraction wave moves fluid away from the proximal segment of the FLIP bag toward the EGJ, resulting in an increase in fluid pressure and causing it to open. We compute the work done on the EGJ during this process; henceforth referred to as EGJ work done (EGJW), expressed in units of millijoules. Under normal conditions, EGJW was computed for the interval beginning with a closed EGJ to the instant of maximal EGJ opening. An example is shown in Fig. 2, wherein the time interval under consideration starts at AA’ and ends at BB’. In controls, the diameter of the EGJ when fully open ranged from 20 to 25 mm. In patients with impaired EGJ opening (e.g., achalasia) a 5-s interval (approximately half the duration of a typical contraction wave or the time taken for full EGJ opening in a typical control) in which some increase in EGJ volume occurred was identified and used for EGJW computation. Derivation of the mathematical expression used to compute EGJW with pressure and planimetry data recorded by the FLIP is given in the APPENDIX.

In subjects with impaired EGJ opening due to absent relaxation or insufficient lumenal pressure, changes in EGJ CSA were negligible and work done on the EGJ was low. During impaired relaxation, however, EGJ opening might require a greater amount of work. Hence, an alternative method was developed to estimate the work required for EGJ opening in instances that opening was impaired. We computed this estimate, for EGJ opening from a 3 mm diameter to 22 mm; the former being the minimal diameter of the FLIP assembly and the latter being the average diameter of a fully opened EGJ in a typical control. Since pressure data corresponding to this range of EGJ area were unavailable in these patients, we assumed a linear relationship between EGJ CSA and FLIP pressure. The coefficients corresponding to this linear variation were found by fitting a straight line through the median EGJ CSA and median FLIP pressure for the five volumes of the distension protocol (30, 40, 50, 60, and 70 mL) and extrapolating to calculate the energy required to open the EGJ to 22 mm. Mathematical details and the derivation of this formula are given in the appendix. An

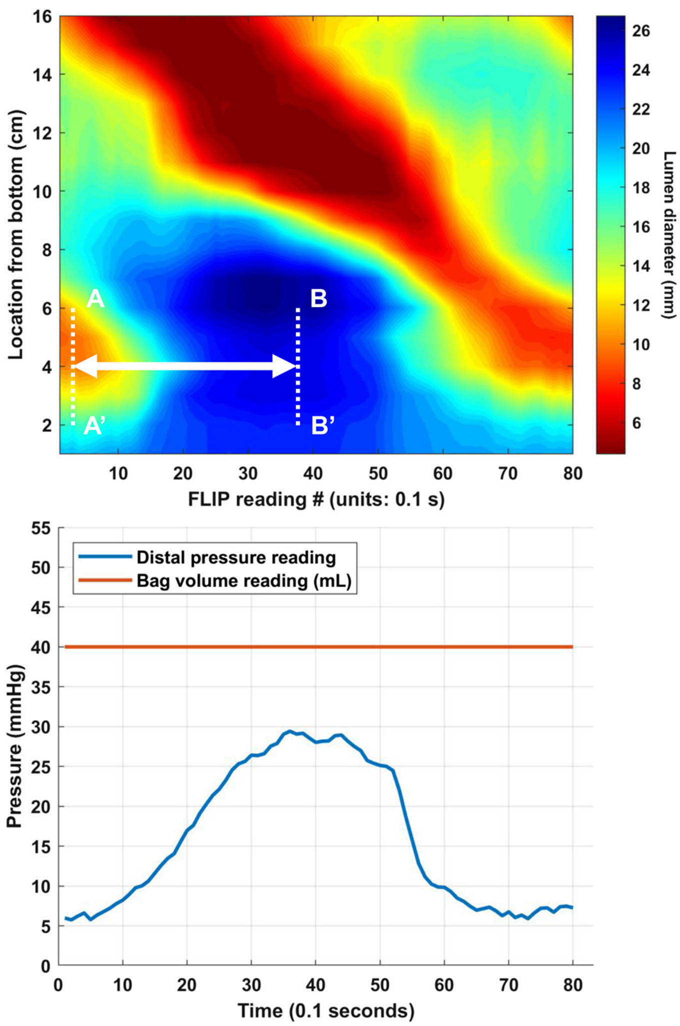

Figure 2. *Top*: a typical antegrade contraction observed in a control subject. The contraction begins at reading 0 and ends after 8 s. Maximum FLIP pressure and EGJ CSA were observed at around 4 s. The time interval considered for work calculation is shown by the solid white arrow. The approximate location of the EGJ is the length spanned by the white dotted lines. Contraction begins at time marked by AA' and max EGJ opening is marked by BB'. *Bottom*: the FLIP bag volume is shown to be 40 mL, and the variation of bag pressure for the entire duration is given by the blue curve. FLIP topography and pressure variation are plotted for the same time interval in both panels. CSA, cross-sectional area; EGJ, esophagogastric junction; FLIP, functional lumen imaging probe.

example of the pressure-CSA relationship is provided in Fig. 3.

In summary, we have two approaches for computing work done on the EGJ. In the first approach, EGJW is the actual work done on the EGJ computed at the 40-mL bag volume. Its value is strongly dependent on the increase in EGJ CSA during the interval of the calculation. The second approach, i.e., the EGJ opening work required or EGJROW, is an estimate of the amount of energy one would need to fully open the EGJ in a subject without EGJ opening.

Statistical Analysis

Work done on the EGJ (EGJW) has units of energy expressed in millijoules. Estimated work required to open the EGJ (EGJROW) has units of energy as well. For each subject group, the median values are provided along with interquartile ranges. Group comparisons were made using the Kruskal–Wallis test. The Mann Whitney *U* test was used for post hoc comparisons between pairs of groups. A $P < 0.05$ was used to indicate significance, and all computations were performed using the Statistics Toolbox within MATLAB.

RESULTS

Cohort Characteristics

Table 1 summarizes the demographics and esophageal motility characteristics of the six patient cohorts. All controls showed RACs, whereas no RACs were observed in the patients with achalasia. However, other contractile patterns were observed in 2 of 15 (13%) of type I, 9 of 15 (60%) of type II, and 15 of 15 of the type III achalasia patients. RACs were seen in 2 of 13 (14%) of patients with GERD, 1 of 8 (12%) patients with EoE, and none of the SSc group. Non-RAC contractile patterns were observed in 13 of 14 (93%) patients with GERD, all the 8 patients with EoE, and 3 of 5 (60%) patients with SSc.

Observed Values of EGJ Opening Work

All controls showed complete EGJ opening. As the contraction wave approached, the FLIP pressure and EGJ CSA maximized at approximately the same time with the contraction close to the midpoint of the FLIP. The EGJ CSA then decreased, and the EGJ returned to its baseline contracted state after the contraction wave passed. A typical antegrade contraction in a control is shown in Fig. 2. The large white arrow shows the time interval for the work calculation. The observed values for EGJW for all individuals are summarized in Fig. 4. Outliers are marked with red plus symbols.

As controls exhibited the greatest EGJ opening along with a significant rise in pressure, they showed the greatest values for EGJW. The EGJW for controls was 74.8 (56–141) mJ. Little to no change in EGJ CSA was observed in patients with type I and type II achalasia. Consequently, EGJW was very low: 3.02 (0.8–5.9) mJ for type I and 4.0 (1.9–7.1) mJ for type II. In contrast, some EGJ opening was observed in the type III achalasia group yielding greater values of EGJW at 22.0 (6.8–41.2) mJ.

Six of 13 patients with GERD exhibited large changes in EGJ CSA and FLIP pressure during contractility resembling RACs. The remainder exhibited minimal variations in EGJ diameter and pressure. For the group as a whole, EGJW was 54.1 (6.9–96.3) mJ. Four of 8 subjects with EoE exhibited significant pressurization along with a large increase in EGJ CSA. The remainder exhibited minimal variations in EGJ diameter and pressure. For the group as a whole, EGJW was 65.9 (10.7–102.2) mJ. All five individuals with SSc had negligible changes in EGJ CSA and FLIP pressure leading to low values for EGJW at 11.9 (3–20.2) mJ.

Estimated Values of Work Required to Open the EGJ

The EGJ did not open during the 40-mL distension period in most patients with achalasia resulting in low

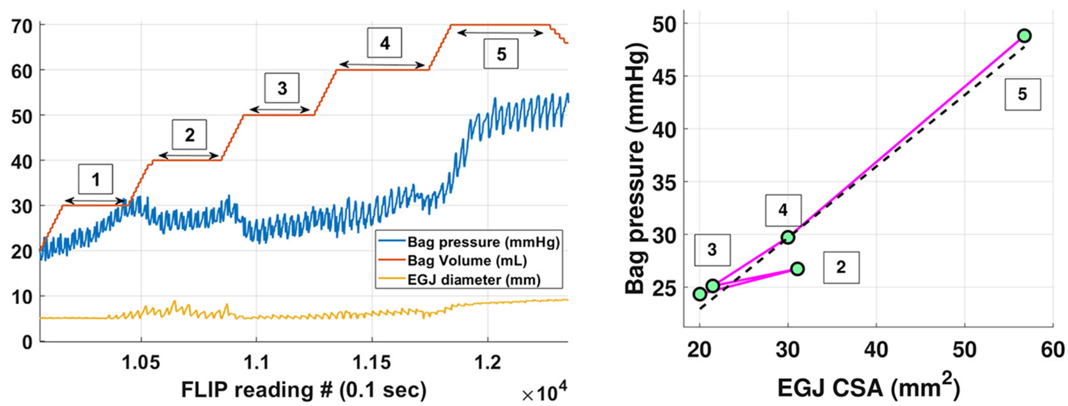

Figure 3. *Left*: distension protocol and variation of EGJ diameter and FLIP pressure in a typical patient with type I achalasia. Median of FLIP pressure and EGJ CSA was found for each of the highlighted intervals when the bag volume was fixed. Volume starts at 30 mL marked as (1) and was increased in steps of 10 mL till BV reached the maximum value of 70 mL, marked as (5). *Right*: plot of pressure vs. EGJ CSA. The *x*-coordinate of each point is the median EGJ CSA corresponding to the specific bag volume numbered on the left plot, and the *y*-coordinate is the median BP for that volume interval. BP, bag pressure; BV, bag volume; CSA, cross-sectional area; EGJ, esophagogastric junction; FLIP, functional lumen imaging probe.

EGJW. Figure 5 illustrates examples of the variation of median pressure versus EGJ CSA in selected studies across patient groups. Figure 6 summarizes the variation of pressure with EGJ CSA for each group. Median values of the fitting coefficients were used to create each line. The spread within each group was computed using first and third quartile values of the coefficients. Using the mathematical definition for work, the linear pressure-CSA relationship was used to calculate the work required to open the EGJ to a 22 mm diameter. This method was also applied to all other subjects to provide a comparison between opening work required for patients with achalasia and the other groups.

The work required to open the EGJ in type I, II, and III achalasics were 208.4 (115.7–328.7) mJ, 235.6 (141.7–802.1) mJ, and 159.6 (98.4–298.8) mJ, respectively. The estimated work required for EGJ opening in controls was 53.9 (47.6–63.5) mJ, considerably lower than the EGJW value, which was 74.8 (56.1–141.2) mJ. The reason for this discrepancy is discussed in the following section. Estimated values of work required to open the EGJ for each group are summarized in Fig. 7. EGJROW for the subjects with GERD and EoE were 100.3 (88.5–138.5) mJ and 55.6 (35.4–64.1) mJ, respectively. Table 2 summarizes EGJW and EGJROW values computed for each group. The last column of the table expresses the ratio of median EGJW to EGJROW, illustrating the sharp discrepancy between groups with severely impaired peristalsis (achalasia and SSc) versus those with relatively preserved peristalsis (controls, GERD, EoE).

DISCUSSION

EGJ opening occurs by the interplay of neurally mediated EGJ relaxation and distension generated by intrabolus pressure within the esophagus or proximal stomach (23, 24). Following EGJ relaxation, rising intrabolus pressure widens the lumen creating a path for trans-EGJ flow

Table 1. *Summary of cohort information*

	Type I	Type II	Type III	GERD	EoE	SSc	Control
n	15	15	15	13	8	5	14
Age, yr, median (IQR)	48 (43–59)	43 (31–59)	59 (55–65)	48 (28–58)	40.5 (31–46)	59 (37–65)	27 (23–31)
Female, *n*	9	7	4	7	1	3	13
HRM classification, *n* (%)					na		3 – no HRM
Type I achalasia	15 (100)						
Type II achalasia		15 (100)					
Type III achalasia			15 (100)				
Absent contractility						3 (60)	
IEM				2 (15)		1 (20)	
Normal motility				11 (77)			10 (77)
EGJOO				1 (8)*		1 (20)†	1 (8)*
IRP, mmHg, median (IQR)	28 (17–39)	35 (24–46)	23 (18–40)	12 (7–13)	na	12 (3–14)	12 (8–13)
Basal EGJ pressure, mmHg, median (IQR)	25 (15–39)	27 (20–36)	36 (13–39)	13 (8–24)		18 (5–25)	16 (11–24)

Basal EGJ pressure was measured at end-expiration. In addition to median IRP > 15mmHg yielding classification of EGJOO, *Patients had normal peristalsis and †patients had ineffective peristalsis. EGJ, esophagogastric junction; EGJOO, esophagogastric outflow obstruction; EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; HRM, high resolution manometry; IEM, ineffective esophageal motility; IQR, interquartile range; IRP, integrated relaxation pressure; na, not available; SSc, systemic sclerosis.

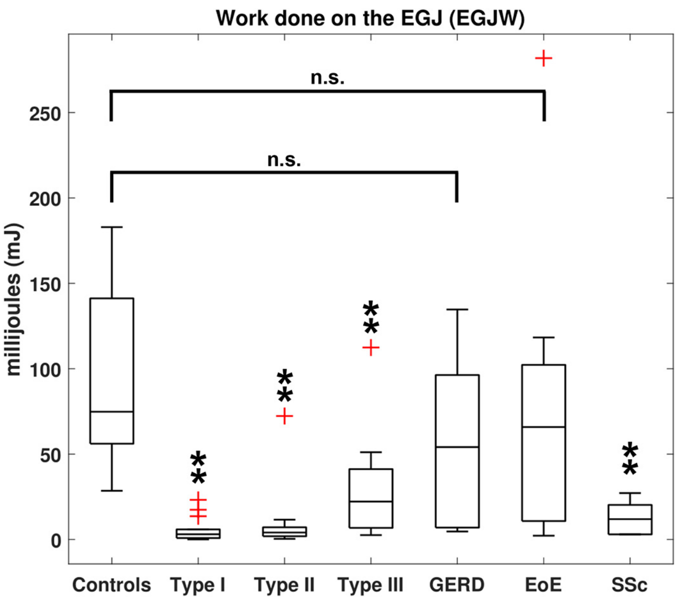

Figure 4. Variations of EGJ work done (EGJW) across disease groups compared with controls. The outliers are marked with red plus signs. Medians are shown along with IQR values and 5th, 95th percentile. EGJW was low in subjects with impaired EGJ opening and does not indicate resistance to flow at the EGJ. Rather, it indicates minimal EGJ opening at the 40-mL bag volume. **$P < 0.01$ compared with EGJW of controls. n.s.: no significant differences between groups. EGJ, esophagogastric junction; EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; IQR, interquartile range; SSc, systemic sclerosis.

with the direction of flow dependent on the prevailing pressure gradient. Thus, EGJ opening is a dynamic event requiring energy to increase EGJ CSA and overcome resistance to flow. This energy is temporarily stored in the walls of the EGJ as they distend and stretch during opening. The aim of this study was to compute work done on the EGJ and compare that value among normal controls and disease groups. As a result, we quantify the work done during EGJ opening in a biomechanically and clinically relevant way. The major findings of our analysis were the following: *1*) work done on the EGJ was greatest when it distended fully due to lumen pressurization generated by RACs, and *2*) the estimated work required to open the EGJ in patients with achalasia with impaired relaxation was significantly greater than the work done on the EGJ in the normal controls.

In control subjects, distension of the distal esophagus was associated with LES relaxation, and distension-induced RACs resulted in an increased FLIP pressure that caused the EGJ to fully open. This combination of pressurization and increased EGJ CSA resulted in a large amount of mechanical work done on the EGJ. Consequently, since every control subject exhibited this pattern, the control group exhibited the greatest median EGJW (Fig. 4). On the other hand, significantly lower median EGJW was exhibited in achalasia and SSc, and substantial overlap with the controls was observed in the EoE and GERD groups (Fig. 4). This illustrates the dependence of the EGJW metric on normal contractility, evident in a FLIP study by RACs. In the absence of RACs, EGJ opening was impaired and EGJW was low. EGJW in all achalasia subtypes was significantly reduced compared to controls ($P < 0.001$). Among subtypes, however, type III exhibited significantly greater values for EGJW compared with types I and II ($P < 0.005$ and $P < 0.03$, respectively), likely attributable to the persistent (disordered) contractility observed with type III achalasia (25–27).

Somewhat paradoxically, individuals with SSc showed similar EGJW values as achalasia subtypes I and II. Clearly, given the near absence of EGJ contractility in SSc, EGJW does not reflect resistance to flow at the EGJ or the amount of LES relaxation. Rather, when changes in EGJ CSA are negligible, the value of EGJW is low irrespective of the underlying reason. For achalasics, EGJ relaxation is impaired and peristalsis is absent, leading to minimal change in EGJ CSA and very low EGJW. Patients with scleroderma have a compliant EGJ; however, they exhibit inadequate luminal pressurization due to weak contractility, again resulting in negligible changes in EGJ CSA and a low value of EGJW (28). This motivates the need for a second work metric that incorporates EGJ stiffness and captures its resistance to trans-EGJ flow.

Unlike the achalasia and SSc disease groups, the motility patterns observed in the EoE and GERD groups were heterogeneous and displayed a wide range of contractile behavior at the EGJ. Individuals within these groups who had RACs and showed significant opening at the EGJ had EGJW values similar to controls. The remainder had poor EGJ opening. Consequently, these groups showed a wide range of EGJW values and, although the median EGJW values were lower, no significant differences were found in EGJW compared with controls. Previous reports have quantified the propulsive forces generated by esophageal contractions (29, 30). However, work done by propulsive forces generated during peristalsis is different from the work done on the EGJ to open it. The former is related to motion of fluid in the axial direction while the latter quantifies the energy needed to radially distend the sphincter. In previous studies (18, 31), we used FLIP measurements to quantify the propulsive work done by RACs and derived values that matched well with work estimated using traction force measurements in the distal esophagus (29, 30). It should also be noted that although luminal diameter proximal to the EGJ can vary substantially among disease groups, this has no direct effect on the value of EGJW because only planimetry sensors within the EGJ were used to compute EGJW. However, a widely dilated distal esophagus may well be associated with minimal or absent pressurization of the lumen, making it impossible to generate any intraluminal pressure and, hence, indirectly reducing EGJW. Previous studies have investigated the pressure-CSA relationship for the distal esophagus in great detail using the FLIP (20, 32).

Returning to the need for a second work metric, it is important to determine whether or not low EGJW was also associated with impaired LES relaxation as in achalasia. With impaired relaxation, one would expect that the energy required to achieve full EGJ opening would be greater than normal, but it is not possible to directly measure that in the absence of normal esophageal contractility. To address this issue, we developed the EGJROW metric using the pressure versus CSA measurements obtained during the full FLIP distention protocol up to the 70-mL fill volume and extrapolating to estimate the work required to completely open the

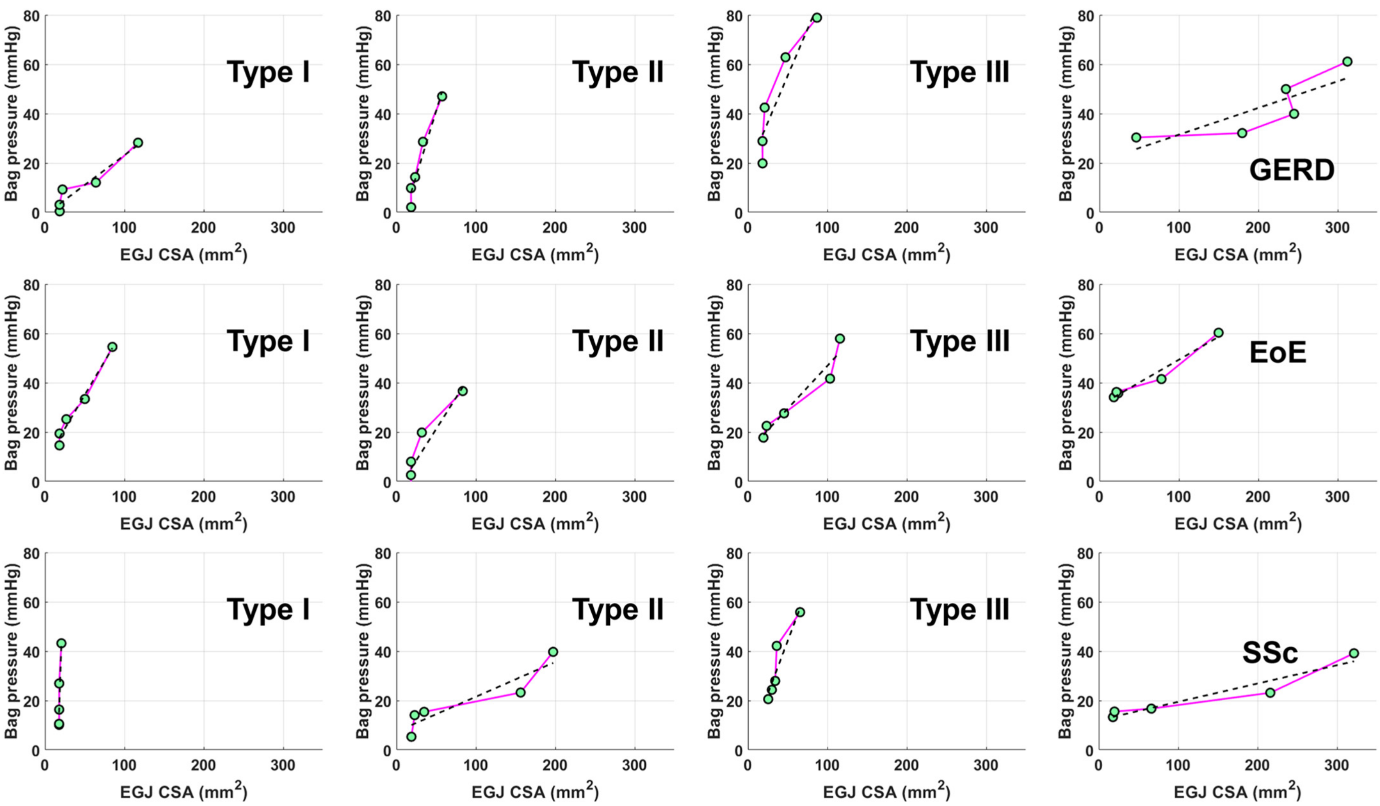

Figure 5. Plots showing the variation of median bag pressure vs. EGJ CSA for 12 randomly selected subjects across disease groups. Each plot shows five points corresponding to the five distension volumes. The slope and intercept of each fit line reveals the effective material properties of the subject's EGJ that were used to compute the work required to open it. The greater the slope, the stiffer the EGJ. CSA, cross-sectional area; EGJ, esophagogastric junction; EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; IQR, interquartile range; SSc, systemic sclerosis.

EGJ to a diameter of 22 mm, even though the EGJ never approached a 22 mm diameter in these patients. All achalasia subtypes showed greater EGJROW values compared with controls and other disease groups including SSc ($P < 0.001$). Among them, type II showed the greatest EGJROW with a maximum observed value of 970 mJ. Thus, although achalasia and scleroderma subjects both showed low values of EGJW, they present significantly different median values for EGJROW. In summary, EGJW is low when opening is impaired due to absent contractility or impaired relaxation. However, EGJROW is significantly greater when the EGJ fails to relax, differentiating absent contractility from impaired sphincter relaxation.

This study had some significant limitations. With respect to GERD, the exclusion of patients with hiatal hernia likely selected out individuals with severe disease. Subjects with significant hernia were not studied with FLIP panometry, as the presence of the hernia adequately explained their observed symptoms. Although some patients with a small hernia (<2 cm) were present in the cohort, the separation between the crural diaphragm and LES was too small to allow for a separate mechanical analysis of each component. Another limitation was the inherent heterogeneity of subjects with GERD and EoE who were studied in relatively small numbers without optimal phenotyping. Additionally, the algorithm used to track EGJ motion during work calculation was not 100% accurate. Tracking the EGJ during significant axial motion is a complex problem and, in situations in which the EGJ is fully effaced, it can be difficult to isolate the EGJ segment from the distal esophagus or stomach. Finally, as alluded to in the results section, EGJROW values were lower than EGJW values in the control subjects. A likely explanation for this is that controls exhibited greater pressurization with RACs than during the distension protocol leading to lesser EGJROW values. Of the two measures, EGJW is probably to be preferred in instances of normal EGJ opening, as it is more representative of normal physiology, but, on the other hand, the EGJROW did very effectively discriminate between SSc and achalasia, which is of great clinical importance. In a future work, we aim to study the relationship between EGJ CSA and pressure during opening to understand the effect of different parameters involving contraction and relaxation to achieve optimum sphincter opening.

In conclusion, this study used FLIP data to calculate the mechanical work done on the EGJ during normal opening or, in instances of impaired EGJ opening, work that would be required to fully open the EGJ. Two work metrics are proposed to summarize the mechanical behavior observed at the EGJ: EGJW when opening is normal and EGJROW when opening is abnormal. EGJW quantifies the work done by the esophageal contraction on the EGJ, causing it to open. EGJROW helps differentiate patients with achalasia from the other groups, as it identifies impaired LES relaxation as the most likely reason for negligible EGJ opening. This analysis is summarized using a decision tree shown in Fig. 8, which

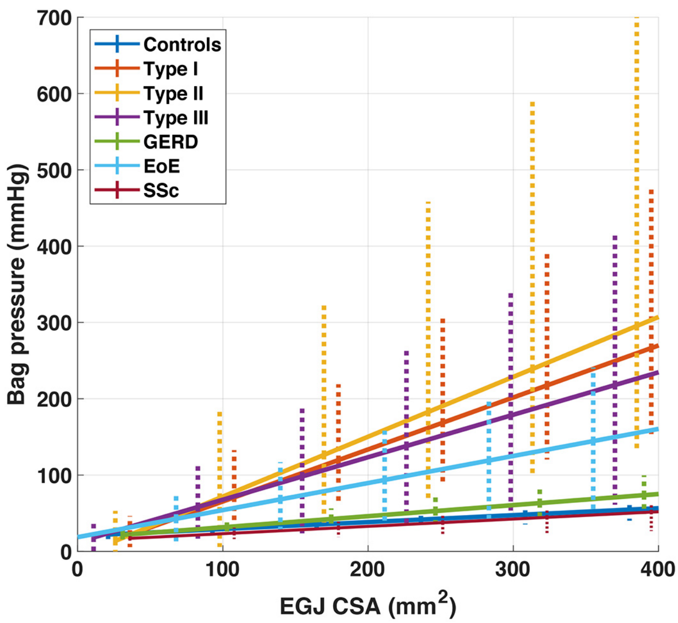

Figure 6. Summary of pressure vs. EGJ CSA variation observed in each group. A representative line (solid) for each group was constructed using the median values of the fitting coefficients obtained from each subject in the group. The spread (dotted) for each line was computed using the first and third quartile values of these coefficients. Estimated pressures for various EGJ CSAs were computed using the expression for pressure given in the appendix. The greater the slope, the stiffer the EGJ. CSA, cross-sectional area; EGJ, esophagogastric junction; EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; SSc, systemic sclerosis.

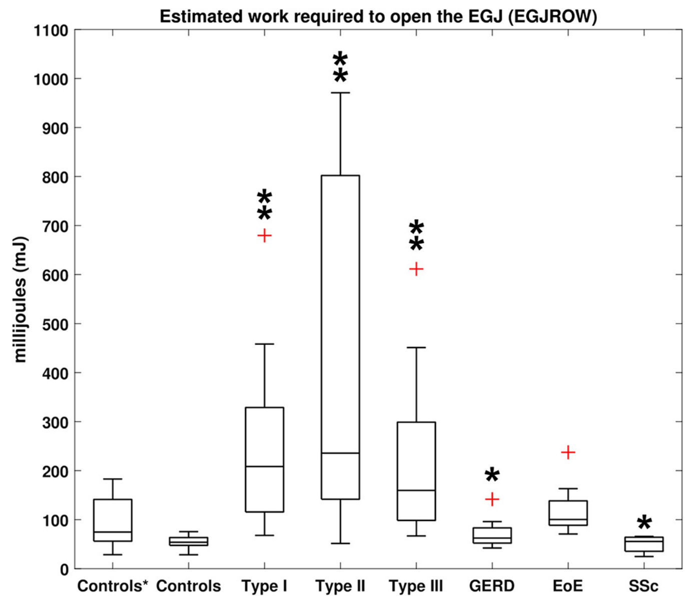

Figure 7. Variation of work required to open the EGJ among subject groups. Also shown is EGJW computed for controls (labeled as Controls*), which is greater than the estimated work required to open the EGJ using the full distension protocol (labeled as Controls). The outliers are marked with red plus signs. Achalasics show the greatest values for work required to open the EGJ indicating greater stiffness. Subjects that present substantial resistance to trans-EGJ flow are expected to require greater energy for complete EGJ opening. $^{**}P < 0.01$ compared with EGJW of controls. $^{*}P < 0.001$ compared with achalasia (all subtypes). EGJ, esophagogastric junction; EGJROW, work required to open the esophagogastric junction; EGJW, esophagogastric junction work done; EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; SSc, systemic sclerosis.

groups diagnoses based on the mechanical state of the EGJ and the ability of the esophagus to generate EGJW. For achalasics, although the work done on the EGJ was low due to negligible changes in its CSA, the EGJROW was much greater than observed in any other group. This suggests that the EGJROW is a suitable complement to IRP to characterize the contractile behavior of the EGJ. Although IRP quantifies the extent (or absence) of relaxation, computing the EGJROW reveals the sphincter's stiffness and the pressure required to open it. In addition to this insight, defining the pressure-CSA relationship might be useful to calibrate treatments and gauge treatment efficacy for individual subjects with disorders of EGJ function, especially achalasia.

APPENDIX

Mathematical Expression for Actual Work Done on the EGJ (EGJW)

The definition of mechanical work done by a fluid to move its boundary is given by

$$W = \int p \ \mathrm{dV}$$

Within the FLIP, the value of p is directly measured by the pressure sensor. The change in volume dV is computed from the changes in CSA recorded by the planimetry sensors. The above equation can be expanded as follows:

$$\int p \ \mathrm{dV} = \int\int p \ \mathrm{d}A \ \mathrm{d}x = \int\int p\frac{\partial A}{\partial t}\mathrm{d}t\mathrm{d}x = \int\left(\int p\frac{\partial A}{\partial t}\mathrm{d}x\right)\mathrm{d}t.$$

The term within the parentheses can be thought of as power at a specific instant. It is integrated over time to find work done on the EGJ. The limits for x are the upper (x_2) and lower margin (x_1) of the EGJ and the limits for time go from t_1 to t_2. These are marked as AA' and BB', respectively in Fig.

Table 2. *Summary of EGJW and EGJROW computed for each group*

	EGJW (mJ)	EGJROW (mJ)	EGJW/EGJROW
Controls	74.8 (56.1–141.2)	53.9 (47.6–63.5)	1.38
Type I	3.06 (0.84–5.9)	208.4 (115.7–328.8)	0.01
Type II	4.05 (1.9–7.1)	235.6 (141.7–802.0)	0.02
Type III	22.2 (6.8–41.2)	159.6 (98.4–298.9)	0.14
GERD	54.1 (6.9–96.3)	62.5 (52.2–83.2)	0.87
EoE	65.9 (10.8–102.3)	100.3 (88.5–138.5)	0.66
SSc	11.9 (2.97–20.2)	55.6 (35.4–64.1)	0.21

Median values are listed along with interquartile ranges. Compared with all other groups, controls show greater values of EGJW compared with estimated work required for EGJ opening because secondary peristalsis generated much higher bag pressures compared with pressurization due to passive dilation alone. Greater amounts of work was required to open the EGJ in patients with impaired relaxation (achalasia). EGJ, esophagogastric junction; EGJROW, estimated work required to open the esophagogastric junction; EGJW, work done on the esophagogastric junction; EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; SSc, systemic sclerosis.

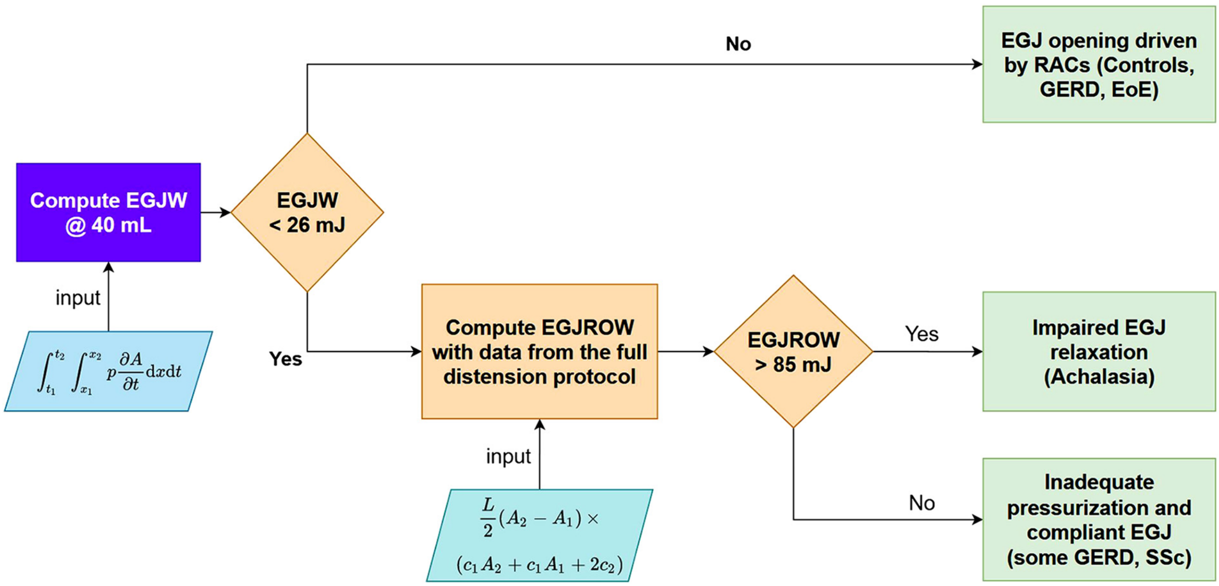

Figure 8. Decision tree that summarizes the use of both work metrics. The end-points of the decision tree correspond to a specific mechanical state of the EGJ and associated disease groups. An EGJ always shows lower values of EGJW, and further separation between causes for impaired opening was achieved by computing EGJROW. Values specified in the diamond decision boxes are based on results summarized in Figs. 4 and 7. Constants c_1 and c_2 are patient specific and are found from pressure-diameter data obtained from the FLIP distension protocol. EGJ, esophagogastric junction; EGJROW, work required to open the esophagogastric junction; EGJW, esophagogastric junction work done; EoE, eosinophilic esophagitis; FLIP, functional lumen imaging probe; GERD, gastroesophageal reflux disease; RAC, repetitive antegrade contractions; SSc, systemic sclerosis.

2 for a control. The integral is then converted to its discrete form, which is written in terms of quantities that are directly available from FLIP recordings. An example of this step is shown below:

$$\int_{t_1}^{t_2}\left(\int_{x_1}^{x_2} p\frac{\partial A}{\partial t}\mathrm{d}x\right)\mathrm{d}t \approx \sum_{n=t_1}^{t_2}\sum_{i=2}^{5} p_n\left(\frac{\partial A}{\partial t}\right)_{i,n}\Delta x\Delta t$$

$$\approx \sum_{n=t_1}^{t_2}\sum_{i=2}^{5} p_n\left(\frac{A_{i,n+1}-A_{i,n-1}}{2\Delta t}\right)\Delta x\Delta t$$

Here, i represents the identification number of the planimetry sensors that lie within the margins of the EGJ. In this example equation, sensors $i = 2$ to 5 measure the profile of the EGJ with $i = 1$ being the most distal planimetry sensor and $i = 16$ being the most proximal sensor in the bag. The FLIP reading numbers are represented with n. For example, $A_{i,n}$ is the area recorded by the planimetry sensor i at time recording n. The interval between readings is Δt = 0.1 s and distance between planimetry sensors is denoted by Δx = 1 cm.

Estimating Work Required to Open the EGJ (EGJROW)

As explained in the text, pressure and CSA variation corresponding to a fully opened EGJ was not available in patients with impaired EGJ opening. We assume that the following relationship holds between pressure p and EGJ area A

$$p = K\left(\frac{A}{A_0}-1\right) + \beta$$

Here, K is the stiffness coefficient of the EGJ and A_0 is the reference CSA of the EGJ when the transmural pressure difference is zero. β accounts for any offset in the pressure reading due to external influences or errors in measurement. The above relationship can simply be reframed as

$$p = c_1A + c_2$$

Where $c_1 = K/A_0$ and $c_2 = \beta - K$. The coefficients c_1 and c_2 are patient specific and can be found from the equation of the fit line as shown in Figs. 3 and 5. Using the definition of work, we have

$$W = \int p\ \mathrm{dV}$$

To calculate work required to open the EGJ, we assume that the EGJ has a length L and that its area increased from A_1 to A_2, which corresponds to EGJ diameters of 3 and 22 mm, respectively. Using these simplifications, we can rewrite W as

$$W = \int_{A_1}^{A_2}(c_1A + c_2)L\ dA = \frac{L}{2}(A_2 - A_1)(c_1A_1 + c_1A_2 + 2c_2)$$

The length of the EGJ is assumed to be 3 cm for all patients. Once the values of c_1 and c_2 are computed from a subject's FLIP data, the estimated work required to open the EGJ for this patient can be computed using the formula derived above.

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DISCLOSURES

D. A. Carlson, P. J. Kahrilas, and J. E. Pandolfino hold shared intellectual property rights and ownership surrounding FLIP panometry systems, methods, and apparatus with Medtronic Inc. D. A. Carlson: Medtronic (Speaking, Consulting). W. Kou: Crospon, Inc. (Consulting). P. J. Kahrilas: Ironwood (Consulting), R. Benckiser (Consulting). J. E. Pandolfino: Crospon, Inc. (stock options), Given Imaging (Consultant, Grant, Speaking), Sandhill Scientific (Consulting, Speaking), Takeda (Speaking), Astra Zeneca (Speaking), Medtronic (Speaking, Consulting), Torax (Speaking, Consulting), Ironwood (Consulting), Impleo (Grant). S. Acharya, S. Halder, and N. A. Patankar: None.

AUTHOR CONTRIBUTIONS

S.A., P.J.K., J.E.P., and N.A.P. conceived and designed research; D. A.C. performed experiments; S.A., S.H., D.A.C., W.K., P.J.K., J.E.P., and N.A.P. analyzed data; S.A., S.H., D.A.C., W.K., P.J.K., J.E.P., and N.A.P. interpreted results of experiments; S.A. prepared figures; S.A. and D.A.C. drafted manuscript; S.A., P.J.K., J.E.P., and N.A.P. edited and revised manuscript; S.A., S.H., D.A.C., W.K., P.J.K., J.E.P., and N. A.P. approved final version of manuscript.

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