TITLE: ESOPHAGOGASTRIC JUNCTION CONTRACTILITY FOR CLINICAL ASSESSMENT IN PATIENTS WITH GERD: A REAL ADDED VALUE?

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KEY MESSAGES

- Esophagogastric junction (EGJ) plays an important role in defense mechanisms against reflux. Defining EGJ vigor with high-resolution manometry (HRM) may be useful to predict an abnormal impedance-pH testing in reflux disease.
- This study aims to establish a correlation between EGJ-contractile integral (EGJ-CI) and different reflux parameters, detected during impedance-pH monitoring in GERD patients.
- The EGJ-CI is calculated at HRM enclosing the upper and lower margins of the EGJ in a DCI toolbox, during three consecutive respiratory cycles and referenced to gastric pressure. The value computed with the DCI tool in mmHg*s*cm is then divided by the duration of the three respiratory cycles (in seconds) yielding EGJ-CI units of mmHg*cm. The value below 13 is established in a series of normal volunteers as a defective EGJ-CI. Reflux parameters determined at impedance-pH monitoring are total number of refluxes, total esophageal acid exposure time (AET), and symptom association.
- Our findings show that, when a defective EGJ-CI is present, a gradual and significant increase in reflux can be present.

ABSTRACT

Background. The role of esophagogastric junction contractile integral (EGJ-CI) as assessed by high-resolution manometry (HRM) is unclear. We aimed to correlate the EGJ-CI with impedance-pH findings in gastro-esophageal reflux disease (GERD) patients.

Methods. Consecutive patients with GERD symptoms were enrolled. All patients underwent upper endoscopy, HRM, and impedance-pH testing. The EGJ-CI was calculated using the distal contractile integral tool-box during three consecutive respiratory cycles. The value was then divided by the duration of these cycles. A value below 13 was considered as a defective EGJ-CI. We also assessed EGJ morphology, esophageal acid exposure time (AET), number of reflux episodes (NRE), and symptom association analysis (SAA). A positive impedance-pH monitoring was considered in case of abnormal AET and/or NRE and/or positive SAA.

Key Results. Among 130 patients we enrolled, 91 had GERD (abnormal AET and/or elevated NRE and/or positive SAA) and 39 had functional heartburn (FH) (negative endoscopy, normal AET, normal NRE, and negative SAA). The GERD patients had a lower median value of EGJ-CI (11 [3.1–20.7] vs 22 [9.9–41], $p < 0.02$) compared to FH patients. Patients with a defective EGJ-CI had, more frequently, a positive impedance-pH monitoring or esophageal mucosal lesions at endoscopy ($p < 0.05$ and $p < 0.05$, respectively) than patients with a normal EGJ-CI. An EGJ-CI cut-off value of 5 mmHg cm yielded the optimal performance in identifying GERD at impedance-pH (sensitivity 89%–specificity 63%).

Conclusions & Inferences. A defective EGJ-CI at HRM is clearly associated with evidence of GERD at impedance-pH monitoring. Evaluating EGJ-CI may be useful to predict an abnormal impedance-pH testing.

Keywords. EGJ contractile integral, esophagogastric junction, GERD, high-resolution manometry, impedance-pH monitoring.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most common diseases in Western Countries.(1–3) Different mechanisms have been involved in its pathogenesis and their specific roles are still under investigation.(4–6) In particular, the esophagogastric junction (EGJ) contraction at rest is considered a major defense against gastro-esophageal reflux (GER). An anatomically normal EGJ is constituted by the lower esophageal sphincter (LES) superimposed by the crural diaphragm (CD). The lateral fibers of each hiatal limb are inserted into the central tendon of the diaphragm and collaborated with phreno-esophageal membrane to maintain the fixation of the EGJ on the diaphragm.(7,8) Esophagogastric junction competence depends on the integrity and interaction among all these elements.

High-resolution manometry (HRM) is characterized by a higher number of pressures recording sites and a lower distance between them compared with traditional manometry. This technique has helped to define and standardize clinically relevant esophageal motility disorders.(9,10) In particular, vigor of esophageal peristaltic movements was introduced as a new metric (the so-called distal contractile integral, DCI) and it is currently used to discriminate among a normal, weak, or hypercontractile esophageal contraction. In addition, the EGJ can be investigated regarding its morphology in order to verify the presence of an axial separation between LES and CD, as indicative of hiatal hernia presence, and its capacity of relaxation in response to swallows. Recently, new HRM metrics were proposed to quantify the vigor of EGJ, trying to assess a correlation between the contractility strength and acidic reflux exposure. Hoshino et al.(11) first described the LES pressure integral (LES-PI), trying to discriminate patients by the severity of distal esophageal acid exposure. However, this metric had the limitation of a fixed 10 s recording box that could be impaired by the contribution of the diaphragm on EGJ contractility., Nicodeme et al. then modified this concept introducing a metric independent of respiration. Authors calculated the DCI value at the EGJ during three complete respiratory cycles with a threshold of 2 mmHg above the gastric baseline, they then divided the recorded value by the duration of complete respiratory cycles.(12) The new metric, termed the EGJ-contractile integral (EGJ-CI), resulted to be useful in distinguishing PPI refractory patients with functional heartburn (FH) from those with PPI resistant GERD, as defined by abnormal pH-impedance studies. However, the study of Nicodeme et al. was mainly focused on the development of this new HRM metric in comparison with LES-PI and, therefore, endoscopy findings were poor in their study.(12) Hence, our study aimed to correlate the EGJ-CI values with impedance-pH and endoscopic findings in patients with GERD. Moreover, we assessed the predictive value of the EGJCI in diagnosing GERD at impedance-pH and we correlated this metric with different EGJ morphological subtypes.

METHODS

Subjects

We prospectively enrolled consecutive patients referred to four different motility laboratories in Italy (Academic Hospitals of Padua, Naples, Genoa and Pisa) between March 2013 and January 2014 and presenting typical GERD symptoms (e.g., heartburn and regurgitation) lasting for more than 6 months and occurring at least three times per week. At first visit, demographics (including height and weight), medications, and response to PPI therapy (double dose PPI for at least 8 weeks), tobacco use, alcohol consumption, and clinical history were reviewed and recorded. A structured questionnaire to assess the presence of gastroesophageal reflux symptoms was administered.(13) The exclusion criteria were: a history of thoracic and gastro-esophageal surgery; primary or secondary severe esophageal motility disorders; pregnancy; use of non-steroidal anti-inflammatory drugs and aspirin; presence of peptic stricture and duodenal or gastric ulcer and inability to pass through the EGJ. All patients who agreed to participate in our study underwent upper endoscopy, HRM, and impedance-pH monitoring.

They were asked to stop any medication that would influence esophageal motor function (5–7) prior to motility testing, whereas patients treated with antisecretory drugs were asked to discontinue them at least 30 days before reflux testing. During the washout period, the use of antacid, on as needed basis, for the relief of heartburn was permitted.(14)

The study protocol was approved by the local Internal Revision Boards and performed according to Declaration of Helsinki. All patients gave written informed consent before the start of the study.

Symptom severity assessment and upper endoscopy

Patients were invited to define their symptoms using the validated GerdQ score.(15) It consists in a four-graded Likert scale (0–3, where 0 = never, 1 = 1 day, 2 = 2–3 days, and 3 = 4–7 days during the previous week) to score the frequency of four positive predictors of GERD (heartburn, regurgitation, sleep disturbance due to nocturnal reflux symptoms, or use of over-the-counter medications for controlling reflux symptoms) and a reversed Likert scale (3–0) for two negative predictors of GERD (epigastric pain and nausea), giving a total GerdQ score range of 0–18. A positive GerdQ was considered when equal or >9. Upper gastrointestinal endoscopy was performed according to international guidelines.(16) Esophagitis was staged according to the Los Angeles classification, Barrett's esophagus was defined as a detectable upward displacement of the squamocolumnar junction at endoscopy, confirmed by intestinalmetaplasia at histology.(16) Based on endoscopic features, patients were classified as (i) endoscopy negative, (ii) erosive esophagitis, and (iii) Barrett's esophagus.

High-resolution manometry

Esophageal pressure topography studies were carried out with a 4.2-mm outer diameter solid-state assembly with 36 circumferential sensors spaced at 1-cm intervals (Manoscan; Given Imaging, Los Angeles, CA, USA). Before recording, transducers were calibrated at 0 and 300 mmHg using externally applied pressure. Studies were done in a supine position after at least a 6-h fasting period and the manometric assemblies were positioned with at least five intragastric sensors. The manometric protocol included a 5-min baseline recording to assess the EGJ and at least ten single water swallows (5 mL) at 30-s intervals to evaluate the esophageal peristalsis.(17)

Data acquisition, display, and analysis were performed using dedicated software (Manoview analysis software; Given Imaging), after a proper thermal compensation. Lower esophageal sphincter was localized and its pressure and relaxations (using the integrated relaxation pressure) evaluated; proximal and distal borders were marked according to pressure difference related to intraesophageal and intragastric pressure marks. Crural diaphragm was marked as the axial level characterized by maximal inspiratory pressure augmentation. In individuals with normal anatomy, LES and CD were superimposed and indistinguishable. Three morphological types of EGJ were defined based on the presence of axial cranial separation between LES and CD, measured in cm: Type I, no separation between the LES and the CD; Type II, minimal separation (>1 and <2 cm); Type III, >2 cm of separation.(4)

Other measured parameters included the DCI and the distal latency as previous defined.18 The individual swallow type was categorized and the diagnosis of the esophageal pressure topography plots was made according to the Chicago Classification v.3.0.(8) Esophagogastric junction contractile integral was calculated according to Nicodeme et al.(12) The upper and lower margins of the EGJ were enclosed in a DCI toolbox. The duration of the box was exactly three consecutive respiratory cycles and the threshold of isobaric contour was set at 2 mmHg above the gastric pressure.

The value computed with the DCI tool in mmHg*s*cm was then divided by the duration of the three respiratory cycles (in seconds) yielding EGJ-CI units of mmHg*cm. We considered an EGJ-CI as defective when the value was below 13 (5th percentile among healthy volunteers in Nicodeme's study).

Esophageal impedance and pH monitoring

Esophageal impedance-pH monitoring was performed off-therapy using an ambulatory multichannel intraluminal impedance (MII) and pH monitoring system (ZepHr; Sandhill Scientific, Inc., Highland Ranch, CO, USA). The methodology of probe calibration, catheter placement, patient instruction, and performance has been previously described.(19) On the monitoring day, each subject ate three standard meals of a Mediterranean diet, as previously reported.(20) Multichannel intraluminal impedance -pH data were collected and analyzed with the Bioview GERD Analysis Software (Sandhill Scientific Inc.). Meal periods were excluded from the analysis. The following variables were assessed: distal esophageal acid exposure as percentage (%) of time (acid exposure time, AET) with pH <4 (abnormal if total time with pH <4 was greater than 4.2%), number and quality (acid, weakly acid, and weakly alkaline) of reflux detected at MII (normal value <54). Analysis of correlation between reflux and reported symptoms were evaluated using symptom index (SI, positive if >50%) and symptom association probability (SAP, positive if >95%), as previously described in details.(21) Patients were classified as having a positive MII-pH monitoring if at least one of the three parameters considered (total AET, total number of reflux at MII, SI and/or SAP) was abnormal/positive.

All HRM and MII-pH tracings were reviewed manually by two expert investigators (ES, ST), independently and in a blinded manner in order to ensure accurate detection and classification of EGJ-CI, EGJ morphology, motility, and reflux patterns. Any discrepancy in the assessment was further discussed and a consensus was reached.

Statistical analysis

Data were collected and analyzed using statistical software Statistical Package for the Social Sciences version 22 (SPSS, Chicago, IL, USA). Data for categorical variables are expressed as proportions and frequencies and data for continuous variables are expressed as median (interquartile range), unless otherwise specified. Receiver operating characteristic (ROC) curves with associated 95% confidence intervals (CI) were used for estimating the optimal cut-off value for a GERD diagnosis and its associated sensitivity (SE) and specificity (SP), and for estimating the optimal cut-off for presence of abnormal number of reflux, abnormal AET, and positive symptom association. As data were not normally distributed, we used a non-parametric test (Mann–Whitney test) when comparing continuous parameters and Fisher’s exact test and Kruskal–Wallis test were performed for comparison of categorical variables. Univariate and multivariate analysis were performed for testing the predictive potential of EGJ-CI in terms of positivity at impedance-pH monitoring. A two-sided p value of 0.05 was considered statistically significant.

RESULTS

We enrolled 130 (65M/65F; median age 53 [21–76]) consecutive patients with GERD symptoms. Subjects were stratified into FH (39, 30%) and GERD patients (91, 70%), according to medical literature.(22,23) The two groups were matched for sex and age. The baseline characteristics of these individuals are displayed in **Table 1**.

EGJ-CI values at baseline and their association with symptom severity

The overall median EGJ-CI was 13.6 (4.3–29.4). Sixtyfour (49.2%) patients had a defective EGJ-CI (<13 mmHg*s*cm), whereas 66 (50.8%) had a normal value. A defective EGJ-CI was present in 50 (54.9%) GERD vs 14 (35.9%) FH patients ($p < 0.05$). Moreover, GERD patients have a lower median value of EGJ-CI (11 [3.1–20.7] vs 22 [9.9–41], $p < 0.02$) compared to FH patients (**Fig. 1**).

Mean GerdQ score was greater in patients with a defective EGJ-CI vs those with a normal EGJ-CI (15 vs 8, $p < 0.02$). Moreover, mean GerdQ score resulted significantly higher in GERD vs FH patients (15 vs 7, $p < 0.02$). A positive GerdQ (equal or >9) was more common in patients with a defective than normal EGJCI (54.9% vs 35.9%, $p < 0.05$).

EGJ-CI and endoscopy features

At upper endoscopy, 22 (16.9%) patients had erosive esophagitis (Grade A, n = 16, Grade B, n = 6), 10 (7.7%) had short segment Barrett's esophagus and 98 (75.4%) had no mucosal breaks (non-erosive reflux disease [NERD] = 59/130, 64.8%). In particular, patients with negative endoscopy showed the higher median value of EGJ-CI (16.7 [7.4–33] vs 4 [0.2–14.5], $p < 0.001$, vs 7.8 [2.1–14.6], $p = 0.06$) than erosive reflux disease (ERD) and Barrett's esophagus. A significant difference was not reached between the latter two groups ($p = 0.381$).

At logistic regression, normal EGJ-CI patients had higher probability of presenting with no mucosal breaks ($p < 0.001$, $r2 = 0.108$, 95% CI: 0.073–0.469), and a lower probability of erosive esophagitis ($p < 0.007$, $r2 = 0.109$, 95% CI: 0.575–0.192) and Barrett's esophagus ($p < 0.05$, $r2 = 0.033$, 95% CI: 0.932–2.427) than defective EGJ-CI patients.

EGJ-CI and reflux features

Overall, patients with a defective EGJ-CI had more often a positive MII-pH monitoring, or an abnormal total number of reflux, or a pathologic AET ($p < 0.05$, $p < 0.001$, $p < 0.002$, respectively) than patients with a normal EGJ-CI, whereas no significant difference was recorded when comparing positive symptom association frequency ($p = 0.146$). In addition, all patients with abnormal total number of reflux, or total AET or positive symptom association showed a significantly decreased values of EGJ-CI. Comprehensive data on EGJ-CI characteristics and reflux parameters are summarized in **Table 2**. At linear regression, low value of EGJ-CI was correlated with abnormal number of reflux and abnormal AET ($p < 0.001$, $r = 0.298$, 95% CI: 0.906–0.255, and $p < 0.0001$, $r = 0.364$, 95% CI: 0.291–0.111), respectively.

EGJ-CI and EGJ morphology and motility patterns

At HRM, the study of LES-CD position allowed us to classify as Type I EGJ 60 (46.2%) patients, as Type II EGJ 50 (38.5%) patients and as Type III EGJ 20 (15.4%) patients. Type I showed the higher median value of EGJ-CI (20 [12.5–36] vs 10.6 [3.9–17.9], $p < 0.001$, vs 2.95 [0.2–8.4], $p < 0.001$) than Type II and III. A significant difference was also recorded between these latter two groups ($p < 0.008$). Based on the Chicago Classification, the most frequent motility patterns were represented by Normal peristalsis (75/130, 57.7%), Ineffective motility (30/130, 23.1%), and Fragmented peristalsis (11/130, 8.5%). Absent peristalsis, EGJ outflow obstruction, Jackhammer esophagus, and distal Esophageal Spasm were infrequent (0.8%, 3.8%, 1.5%, and 4.6%, respectively). Analyzing EGJ-CI subgroups, patients with a defective EGJ-CI showed a lower frequency of Normal motility (57.7%) in favor of Ineffective motility (32.3%), whereas outflow obstruction pattern was present only in normative EGJ-CI patients. However, significant differences were not reached among the various groups.

Presence of LES-CD separation (Type II + Type III EGJ morphology) correlated with an abnormal impedance-pH monitoring in 67%, whereas a defective EGJ-CI correlated with an abnormal test in 54.9% ($p < 0.02$). Patients with a defective EGJ-CI without a LES-CD separation correlated with an abnormal impedance-pH monitoring in 9.9%, those with a LES-CD separation without EGJ-CI correlated with an abnormal test in 22%, whereas patients with both defective EGJ-CI and LES-CD separation correlated in 76.9% of cases ($p < 0.0001$).

Diagnostic accuracy of EGJ-CI

Kappa interobserver agreement in calculating EGJ-CI was optimal (0.88). We analyzed three cut-off values of EGJ-CI (13, as the 5th percentile in healthy volunteers, 10 and 5) with ROC analysis in order to provide the optimal balance between diagnostic sensitivity and specificity for GERD, abnormal number of reflux, pathologic AET, and positive symptom association (**Fig. 2A–D**). The proposed cut-off value of 13 resulted to have a sensitivity and specificity too low for GERD, abnormal number of reflux, abnormal AET, and positive symptom association as shown in Table 3. The proposed cut-off value of 10 resulted to have a moderate sensitivity and specificity for GERD, but a low specificity for abnormal number of reflux, abnormal AET, and positive symptom association (**Table 3**). The proposed cut-off value of 5 yielded the optimal performance in identifying GERD, abnormal number of reflux, abnormal AET, and positive symptom association (**Table 3**).

DISCUSSION

Recently, new metrics based on esophageal pressure plot topography, such as DCI, have been evaluated to calculate esophageal body vigor., Attention was then focused on applying this metric on EGJ, in order to quantify its activity as a valid anti-reflux barrier.(12) In particular, esophagogastric junction contractile integral (EGJ-CI) has been proposed as a valid parameter in discriminating patients with different degrees of EGJ dysfunction.(12) Thus, we decided to apply and to validate this novel metric in a large group of GERD patients in order to correlate the EGJ-CI values with impedance-pH, HRM and endoscopic findings, and to assess the predictive value of the EGJ-CI in diagnosing GERD. The major novel findings of our study are that, with the lowering of EGJ-CI values, patients have a significant rise of reflux exposure in terms of AET, reflux episodes, and mucosal injuries; moreover, as an additional new parameter, a cut-off value of 5 has the highest sensitivity (89%) and specificity (63%) in distinguishing GERD from FH.

The EGJ is a complex entity and its pathology is tridimensional: dysfunction in terms of deglutitive relaxation, anatomical disruption typified by hiatus hernia, and competence in preventing gastroesophageal reflux. The role of LES resting pressure in determining or favoring reflux disease was extensively investigated in the past. Indeed, several studies in medical literature identified the low LES pressure (together with a short intrabdominal LES and presence of hiatal hernia) as a key determinant of GERD development in patients with reflux symptoms.(24–26) However, those studies did not take into account that the competence of EGJ is mediated by both LES pressure and CD contraction, as highlighted by the most recent studies.(18,27,28) Despite these advances in terms of EGJ pathology that were allowed by the widespread application of HRM technique, to date, data about EGJ function and their relation with GERD development is limited. Hoshino et al. first proposed the use of a new metric to estimate the vigor of LES, called LES pressure integral (LES-PI).(11) These Authors calculated LES-PI as for DCI (mmHg*cm*s) in a window of 10 s enclosing the LES. The LES-PI metric was calculated in 108 patients that underwent HRM and pH monitoring. Interestingly, a LES-PI value <400 mmHg*cm*s was more sensitive (79%) than the conventional cut-off (9%) for LES pressure (<10 mmHg) in predicting a positive pH monitoring. However, the use of LES-PI metric can be negatively influenced by the choice to use a 20 mmHg set for reference and not the intragastric pressure that varies between subjects (e.g., the pressure increases with abdominal obesity), and by the pressure induced by diaphragmatic pinch respiratory movements.

These two limitations were recently overcome by Nicodeme et al.(12) who proposed a new metric, the EGJ-CI, to calculate the vigor of EGJ, referenced to intragastric pressure, in a set of three respiratory cycles, then dividing the value for the time of their length. These Authors investigated a group of healthy volunteers and set the upper (95th percentile) and lower value (5th percentile) of EGJ-CI at the values of 116 and 13, respectively. They then applied the metric on a group consisting of 88 PPI non-responder patients, to test its performance in predicting reflux identified at impedance-pH monitoring. The Authors concluded that the EGJ-CI may be useful in distinguishing PPI non-responders between patients with FH and those with refractory GERD. This study is consistent with the observations reported by Nicodeme et al., highlighting a more frequent GERD diagnosis when patients had a defective EGJ-CI. Moreover, we were able to document for the first time that patients with defective EGJ-CI (defined as a value lower than 13, which is the 5th percentile previously reported in healthy volunteers) had an higher frequency of abnormal AET and impedance-detected reflux episodes and, thus, an increased probability to be distinguished as FH.(3,27) Thus, our data support the role of the EGJ-CI metric in evaluating EGJ vigor as an effective antireflux barrier and its usefulness as complementary measure of EGJ integrity, potentially useful in identifying patients likely to benefit from antireflux surgery. Interestingly, we also tested for the first time the relationship between the EGJ vigor, the EGJ morphology, and the esophageal mucosal damage. As we currently know, HRM provides the opportunity to assess the EGJ morphology, discriminating a possible axial separation between LES and CD. This event can be interpreted as the presence of hiatal hernia, or, more precisely, as an anatomical disruption of EGJ, leading to a reduction in its physiological anti-reflux barrier activity.(28) Our study confirms the hypothesis that, by increasing separation between LES and CD, patients have a gradual and significant reduction of the EGJ-CI, that can favor the rise of reflux episodes and esophageal acid exposure. In 2007, Pandolfino et al. (18) found a correlation between HRM characterizations of EGJ morphology and the objective demonstration of GERD (endoscopy and/or pH-metry). In that study, mean LES-CD separation was similar between control subjects and FH patients, whereas NERD and ERD patients had significantly greater LES-CD separation. In addition, these Authors found that end-expiratory EGJ pressure, LES-CD separation, and inspiratory EGJ augmentation were all significantly associated withGERDat logistic regression. This study is consistent with the latter, but in particular it addresses a new pathophysiological element, the loss of an objectively measured vigor when EGJ is disrupted. In fact, patients with Type III EGJ had a significantly decreased median EGJ-CI than patients with Type II and I. This difference is likely due to the lost contiguity between LES and CD and the exposure to the negative thoracic pressure, further supporting the idea that the EGJ is a unique entity, including both LES and CD, and that its physiological function requires a normal morphology. In addition, we correlated the defective EGJ-CI with a lack of macroscopicmucosal integrity. Indeed, we found a significant difference in frequency of ERD and Barrett's esophagus among our patients, with higher rate incidence in patients with a low value of EGJ-CI. These results emphasize the role of EGJ vigor, in combination with EGJ morphology, in preventing reflux and the development of mucosal injuries.

Finally, our study showed that a defective EGJ-CI is frequently correlated with a positive impedance-pH monitoring. Up to date, esophageal manometry has been solely used for evaluating motor function of the esophagus and has played a marginal role in diagnosing GERD. With the advent of HRM, instead, a quantum leap forward regarding not only motility but also the knowledge of GERD pathophysiology has been made. In fact, in this study, we highlighted a possible role of HRM in supporting GERD diagnosis, when a careful investigation of EGJ anatomy and vigor is performed. Indeed, we found an optimal cut-off of EGJCI in order to estimate a positive diagnosis of GERD at impedance-pH monitoring. We investigated three set of values, (13) (the 5th percentile we used as definition for a defective EGJ-CI), 10, and 5. The latter two showed a good-to-optimal sensitivity (74% and 89%, respectively) and a moderate-to-good specificity (54% and 63%, respectively) in identifying GERD patients. Overall, these observations further sustain the concept of the pathophysiological significance of perturbations of EGJ vigor in GERD, with the recognition that the EGJ plays a major role as anti-reflux barrier.

One of the limitations of this study was that EGJ-CI assessment was performed at the beginning of the recording period during the resting state, and thus given the instability of EGJ, it is possible that its value may vary with the time and movement, passing from a defective EGJ-CI to a normal one and vice versa.(29,30)

However, our focus was to investigate the role of an HRM metric, like EGJ-CI, which is easy to calculate and does not require prolonged recording or additional invasive tests.(29) Moreover, we aimed to quantify barrier function of the EGJ at rest as a complementary measure of EGJ integrity. Second, we did not include a control subjects group and, so far, the normal values adopted in our study were from a single published series of healthy subjects.(12) Further studies in healthy volunteers assessing the reproducibility of those values are necessary.

In conclusion, the results of our study suggest that patients with a defective EGJ-CI had a significant increase in reflux episodes and esophageal acid exposure, thus making the diagnosis at impedance-pH monitoring, while off-PPI therapy, more reliable. Thus, given the relatively easy feasibility of EGJ-CI assessment during HRM, these findings emphasize the utility of performing EGJ vigor assessment during manometry protocol and describing its value, in particular in patients undergoing reflux monitoring as preoperative assessment for endoscopic or surgical procedures or after surgery in order to evaluate the continence of the new valve. Further studies of temporal variability in the EGJ-CI are necessary to better understand its utility in the management of GERD patients.

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TABLE PAGES

Table 1. Baseline characteristics of patients with symptoms of gastro-esophageal reflux disease classified according to impedance-pH monitoring and response to therapy.

Features	Whole population	GERD patients	Functional heartburn patients	*p* value
Patients, *n*	130	91	39	
Male patients, *n* (%)	65 (50%)	44 (48%)	21 (53%)	N.S.
Mean age (range)	53 (21–78)	50 (38–60)	48 (40–57)	0.043
Mean BMI (range)	25 (17–33)	25 (19–32)	24 (18–23)	N.S.
Alcohol consumption, *n* (%)	30 (23%)	19 (21%)	11 (28%)	N.S.
Coffee consumption, *n* (%)	47 (36%)	32 (35%)	15 (38%)	N.S.
Smoking, *n* (%)	14 (11%)	9 (10%)	5 (13%)	N.S.
H. pylori infection, *n* (%)	12 (9%)	7 (8%)	4 (10%)	N.S.
Patients having previously received PPIs, *n* (%)	118 (91%)	79 (87%)	39 (100%)	N.S.
Positive (>50%) symptom response, *n* (%)	65 (50%)	65 (71%)	0 (0%)	0.02

Legend: GERD, gastro-esophageal reflux disease; FH, functional heartburn; BMI, body mass index; PPIs, proton pump inhibitors.

Table 2. Impedance-pH feature distribution between patients classified on the basis of a defective or normal EGJ-CI.

	EGJ-CI value (median + IQR)	Patients with normal EGJ-CI (n = 66)	Patients with defective EGJ-CI (n = 64)
Patients with GERD	11 (3.1–20.7)	41 (62%)	50 (78%)
Patients with FH	22 (9.9–41)	25 (38%)	14 (22%)
Patients with esophagitis	4 (0.2–14.5)*,†	2 (3%)	20 (31%)
Patients with NERD	16.7 (7.4–33)	17 (26%)	42 (65%)
Patients with abnormal NRE	6.4 (1.9–12.3)‡,†	9 (13%)	28 (44%)
Patients with normal NRE	17.8 (8.9–34.4)	57 (87%)	36 (56%)
Patients with abnormal AET	7 (0.7–18.2)§,†	21 (32%)	38 (59%)
Patients with normal AET	18.5 (9.9–36.1)	45 (68%)	26 (41%)
Patients with positive SAA	11.6 (2.6–20.1)¶,†	35 (53%)	42 (66%)
Patients with negative SAA	16.3 (9–33.5)	31 (47%)	22 (34%)

Legend: *p < 0.001 vs patients with NERD; †p < 0.001 vs patients with FH; ‡p < 0.001 vs patients with normal NRE; §p < 0.002 vs patients with normal AET; ¶p = 0.146 vs patients with negative SAA.

EGJ-CI, esophagogastric junction contractile integral; GERD, gastroesophageal reflux disease diagnosed by impedance-pH monitoring; FH, functional heartburn; NERD, non-erosive reflux disease; NRE, number of reflux episodes; AET, acid exposure time; SAA, symptom association analysis.

Table 3. Diagnostic sensitivity and specificity of three different cut-off values (13, 10, and 5) for EGJ-CI in identifying patients with GERD, abnormal number of reflux, pathological esophageal acid exposure time, and positive symptom association, determined at impedance-pH monitoring.

	EGJ-CI cut-off value 13 (sens [95 CI] to spec [95 CI])	EGJ-CI cut-off value 10 (sens [95 CI] to spec [95 CI])	EGJ-CI cut-off value 5 (sens [95 CI] to spec [95 CI])
Patients with GERD	64 (49–80) to 46 (35–56)	74 (60–88) to 54 (42–63)	89 (72–94) to 63 (53–73)
Patients with abnormal NRE	63 (53–73) to 24 (12–41)	72 (62–83) to 29 (16–35)	79 (69–85) to 51 (42–63)
Patients with abnormal AET	66 (56–79) to 35 (24–49)	74 (64–85) to 42 (29–55)	87 (59–92) to 54 (45–63)
Patients with positive symptom association	58 (42–66) to 48 (36–56)	70 (53–81) to 53 (45–64)	87 (58–91) to 61 (49–67)

Legend: AET, acid exposure time; NRE, number of reflux episodes; sens, sensitivity %; spec, specificity %; 95 CI, 95% confidence interval; EGJ-CI, esophagogastric junction contractile integral; GERD, gastro-esophageal reflux disease.

FIGURE PAGES

Figure 1. Box plot showing difference in esophagogastric junction contractile integral (EGJ-CI) values in patients with GERD vs Functional Heartburn, as determined by means of impedance-pH monitoring.

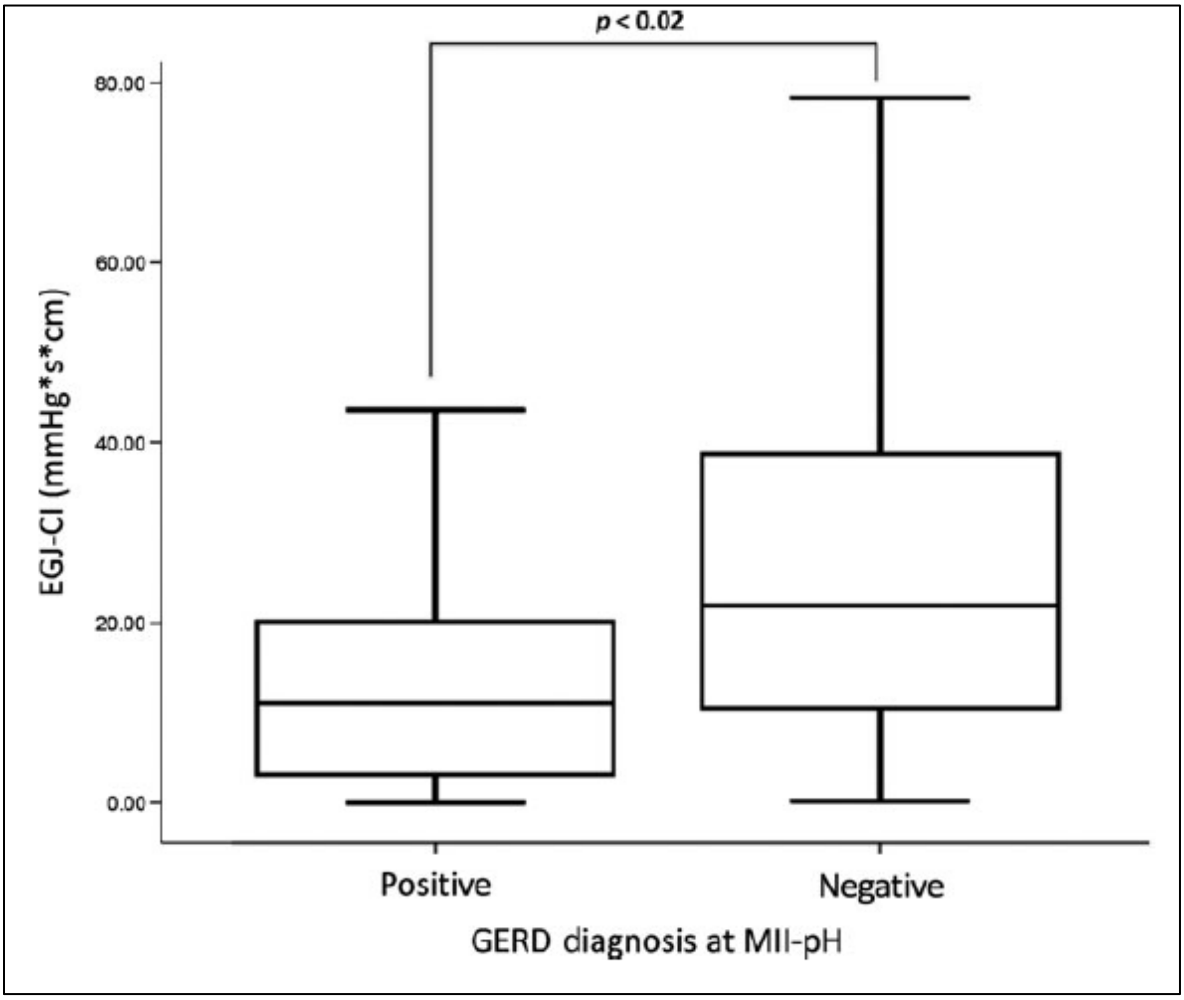

Figure 2. Receiver operating characteristics (ROC) for the esophagogastric junction contractile integral (EGJ-CI) value:

(A) ROC sensitivity and specificity of EGJ-CI for diagnosis of GERD presence determined by impedance-pH monitoring;

(B) ROC sensitivity and specificity of EGJ-CI for diagnosis of abnormal total number of reflux determined by impedance-pH monitoring;

(C) ROC sensitivity and specificity of EGJ-CI for diagnosis of abnormal acid exposure time (AET) presence determined by impedance-pH monitoring;

(D) ROC sensitivity and specificity of EGJ-CI for diagnosis of a positive symptom association determined by impedance-pH monitoring.