Reflux disease and achalasia: Failure of the gatekeeper
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Chapter 12
Efficacy of Treatment for Patients with Achalasia Depends on the Distensibility of the Esophagogastric Junction
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ABSTRACT

Background & aims:
Many patients with persistent dysphagia and regurgitation after therapy have low or no lower esophageal sphincter (LES) pressure. Distensibility of the esophagogastric junction (EGJ) largely determines esophageal emptying. We investigated whether assessment of the distensibility of the EGJ is a better and more integrated parameter than LES pressure for determining efficacy of treatment for patients with achalasia.

Methods:
We measured distensibility of the EGJ using an endo functional luminal imaging probe (EndoFLIP) in 15 healthy volunteers (controls; 8 male, 40±4.1 y) and 30 patients with achalasia (16 male, age 51±3.1 y). Patients were also assessed by esophageal manometry and a timed barium esophagogram. Symptom scores were assessed using the Eckardt score, with a score below 4 indicating treatment success. The effect of initial and additional treatment on distensibility and symptoms were evaluated in 7 and 5 patients respectively.

Results:
EGJ distensibility was significantly reduced in untreated patients with achalasia, compared with controls (0.7±0.9 mm²/mmHg vs 6.3±0.7 mm²/mmHg; P<.001). In patients with achalasia, EGJ distensibility correlated with esophageal emptying (r=–0.72; P<.01) and symptoms (r=0.61; P<.01), and was significantly increased with treatment. EGJ distensibility was significantly higher in patients successfully treated (Eckardt score≤5) compared to those with an Eckardt score >3 (1.6 ± 0.3 vs 4.4 ± 0.5 mm²/mmHg; P=.001). Even when LES pressure was low, EGJ distensibility could be reduced, which was associated with impaired emptying and recurrent symptoms.

Conclusions:
EGJ distensibility is impaired in patients with achalasia, and in contrast to LES pressure, is associated with esophageal emptying and clinical response. Assessment of EGJ distensibility by EndoFLIP is a better parameter than LES pressure for evaluating efficacy of treatment for achalasia.
INTRODUCTION

Achalasia is a rare motility disorder of the esophagus, with an incidence of 1 per 100,000. Disappearance of neurons in the esophagus leads to loss of peristalsis and a defective relaxation of the lower esophageal sphincter (LES). The subsequent retention of food and saliva in the esophagus results in the typical symptoms of achalasia, i.e. dysphagia, regurgitation of undigested food, respiratory complications, chest pain and weight loss. As the neuronal loss is irreversible, treatment of achalasia is limited to disruption of the LES by pneumatic dilation or Heller myotomy, aiming to reduce LES tone and improve bolus transport across the esophagogastric junction (EGJ).

The clinical management of achalasia is challenging, especially as treatment success declines in the long term, leading to an increasing risk for retreatment. Identification of patients in need of retreatment may be difficult and is often delayed as symptoms are underreported or absent due to decompensation of the esophagus or impaired esophageal sensitivity. Moreover, patients get used to symptoms or adapt their diet. It should be emphasized though that timely recognition of functional obstruction and subsequent stasis of food in the esophagus is of importance for at least two reasons: first, decompensation of the esophagus must be prevented, as this can lead to mega-esophagus or sigmoid-like esophagus associated with higher morbidity and refractory symptoms. Second, esophageal stasis has been suggested to be a risk factor for the development of dysplasia and neoplasia, especially in patients with longstanding achalasia.

Several studies have proposed manometry to be a useful test to determine whether patients should be retreated. Reduction of LES pressure to less than 10 mmHg has been reported to be a good predictor for long-term treatment success. Based on these reports, patients with a LES pressure ≥ 10 mm Hg are therefore considered for additional therapy. However, several studies and clinical experience demonstrate that a significant proportion of patients with persistent symptoms has a low or even absent LES pressure. Interestingly, these patients often have incomplete esophageal emptying on a timed barium esophagogram. Moreover, despite absence of LES pressure, a significant proportion of these patients benefit from additional treatment with pneumodilation. These observations argue against LES pressure as a useful test to assess the need for treatment.

As shown by Pandolfino et al., flow across the esophagogastric junction (EGJ) is mainly determined by its distensibility in response to increased intraluminal pressure. Although LES pressure will definitely contribute, other factors such as fibrosis due to previous treatment or natural history of the disease may impair distensibility and subsequently EGJ opening. Reduced distensibility even in the absence of LES pressure may therefore explain why esophageal emptying on timed barium esophagogram may be impaired. In the present study therefore, we determined EGJ distensibility...
in patients with achalasia using the commercially available Endo functional luminal imaging probe (EndoFLIP) during volume controlled distensions. 20 We compared its ability to predict clinical success with that of LES pressure and esophageal emptying.

METHODS

Subjects
Fifteen healthy volunteers (8 males, 40 ± 4.1 years) and 34 patients with achalasia were included in the study. In 4 patients, the EGJ could not be passed, leaving 30 achalasia patients in which distensibility measurements could be performed (16 males, 51 ± 3.1 years, P<0.05 vs healthy volunteers). The diagnosis of achalasia was based on the absence of peristalsis and impaired LES relaxation (nadir pressure ≥ 10 mmHg during swallow-induced relaxation) assessed during esophageal manometry. Patients known with a sigmoid like esophagus (>6cm diameter) were excluded from the study. One patient was excluded for this reason.

Seven of the 30 patients were newly diagnosed and were measured before and 3 months after treatment. (Figure 1.) The rest of the patients (n=23) were diagnosed 5.4 ± 1.4 years earlier. Thirteen patients were initially treated with graded pneumodilation (PD), 7 patients with laparoscopic Heller myotomy (LHM) and 3 patients had undergone both treatments. In patients with newly diagnosed achalasia, PD was performed in 6 patients and LHM in 1. Treatment procedures were performed according to the protocol described earlier. 20 Briefly, PD is performed with Rigiflex balloons (Boston Scientific, Nanterre, France) positioned at the EGJ and dilated with 5 PSI during 1 min, followed by 8 PSI during 1 min. Two dilations are performed with 30 and 35 mm balloons respectively separated by 1-3 weeks. For LHM, a myotomy was performed extending 6 cm above the EGJ and 1.5 cm over the stomach. Subsequently a fundoplication according to Dor was performed. Each subject gave written informed consent, and the study was approved by the Medical Ethics Committee of the Academic Medical Centre.

Study design
Healthy volunteers underwent EndoFLIP measurement. Patients underwent esophageal manometry, EndoFLIP measurement of the EGJ and timed barium esophagogram. In addition, symptoms were assessed using the Eckardt score. Studies were performed after at least a 4 hr fast. First, esophageal manometry was performed, followed by the EndoFLIP measurement and timed barium esophagogram. Patients with additional treatment after the procedure were invited to undergo the study protocol 3 to 6 months after treatment.
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Figure 1 | A flowchart describes the patients groups in the study. Seven patients were studied before and after initial treatment. Thirty patients were studied after therapy, of which 18 were treated successfully (Eckardt score <4) and 12 patients were treated unsuccessfully. Eight of 12 patients unsuccessfully treated patients were additionally treated, of which 5 patients underwent an additional EndoFLIP measurement.

EndoFLIP measurement

Distensibility of the EGJ was determined using the commercially available EndoFLIP system (MMS, Enschede, the Netherlands). In this technique, a probe is inserted into the esophagus and placed at the level of the EGJ. The probe consists of a 240 cm catheter with a 14 cm bag attached to its distal end, which is compliant to a maximal diameter of 25 mm. Inside the bag 17 electrodes are placed at 4 mm intervals. An excitation current of 100 μA is generated between two adjacent electrodes at a frequency of 5 kHz. Using impedance-planimetry, cross sectional areas (CSAs) are determined for the 16 balloon cross sections during volume controlled distensions. Additionally two pressure sensors are located on the probe to determine intrabag pressure allowing assessment of EGJ distensibility.

The distension probe and the pressure transducers were calibrated by the manufacturer. The pressure sensor was zeroed prior to insertion of the catheter, and subsequently the deflated catheter was inserted through an anaesthesized nostril. Manometry readings were used to position the balloon. In our distension protocol, the balloon was inflated to a 20, 30, 40 and 50 mL volume. Pressures and CSAs are collected at a rate of 10 Hz. Distensibility was assessed using the median value over a 30s dynamic measurement of the narrowest CSA, which corresponds to the EGJ, and the median intrabag pressure.

Symptom scores

Symptom scores were assessed using the Eckardt score, which is the sum of the symptom scores for dysphagia, regurgitation and chest pain (0 = absent, 1 = occasional, 2 = daily, 3 = each meal) completed with the score of weight loss (0 = no weight loss, 1 = < 5 kg, 2 = 5-10 kg, 3 = > 10 kg), and thus ranges from 0 to 12. Treatment was considered as successful if the Eckardt score was below 4.
Esophageal manometry

Esophageal manometry was performed using a 10 lumen assembly (Dentsleeve, Missisauga, Ontario, Canada) with a sleeve incorporated at its distal end. The sideholes and the sleeve sensor were perfused at a rate of 0.6 mL min\(^{-1}\). The sleeve was positioned as such that it incorporated the EGJ. Data were stored on an MMS-solar system (MMS, Enschede, the Netherlands). End-expiratory LES resting pressure was determined after wet swallows and relative to intragastric pressure. A LES pressure \(\geq 10\) mm Hg was considered as elevated. Residual LES pressure was determined as the mean residual pressure after 10 water swallows of 5 mL.

Timed barium esophagogram

Esophageal stasis was determined on a timed barium esophagogram immediately after, 1, 2 and 5 minutes after ingestion of the maximal tolerable amount of low density barium sulphate over 30-45 s without regurgitation or aspiration, with the patient upright in a slight left posterior position. The distance from the tapered distal esophagus to the top of the barium column and the maximal diameter of the esophagus were measured. A maximal diameter of \(>3\) cm was considered enlarged.

Data analysis and statistics

Basal LES pressure was measured at end-expiration. Distensibility of the EGI was measured as the median cross sectional area at the narrowest point divided by the balloon pressure. Statistical analysis was performed using SPSS 16.0 (IBM corporation, Somers, NY, United States). Data are presented as mean ± SEM when parametric, and as median (IQR) when not parametric. Parametric data were tested using a Student’s t-test, with Bonferroni correction in case of multiple comparisons. Paired unparametric data were tested using the Wilcoxon signed ranks test. Chi-square was used to determine sensitivity and specificity. All reported P-values are 2 tailed, and a value of 0.05 is regarded as statistically significant.

RESULTS

Patients

To determine normal values, 15 healthy volunteers were invited to undergo an EndoFLIP procedure. Of the 30 patients that completed the protocol, 18 had an Eckardt symptom score of 3 or less, and were therefore regarded as successfully treated. (Figure 1.) Esophageal manometry, symptom evaluation and EndoFLIP procedure were performed in all patients. A timed barium esophagogram was performed in 24 patients. After inclusion, 8 patients with recurrent symptoms underwent additional treatment, of which 5 patients agreed to undergo additional EndoFLIP and manometry 3 to 6 months after additional treatment. The EndoFLIP procedure was well tolerated.
An hourglass shape of the bag was observed in all measurements, with the narrowest CSA at the level of the LES, as determined during esophageal manometry.

**EGJ distensibility**
Healthy volunteers had a mean EGJ distensibility of \(6.3 \pm 0.7 \text{ mm}^2 / \text{mmHg}\) using a 50 mL volume distension. Healthy volunteers had a significantly higher EGJ distensibility compared to untreated patients \((0.7 \pm 0.9 \text{ mm}^2 / \text{mmHg} \ P<0.001)\), unsuccessfully treated patients \((1.6 \pm 0.3 \text{ mm}^2 / \text{mmHg} \ P<0.01)\) and successfully treated patients \((4.4 \pm 0.5 \text{ mm}^2 / \text{mmHg} \ P=0.02)\) in a 50 mL volume distension. (Figures 2 and 3.) Unsuccessfully treated patients had a significantly lower EGJ distensibility compared to successfully treated patients, both at 40 mL \((P<0.01)\) and 50 mL distension \((P<0.01)\).

Next, we determined the cut-off value using the lower 90th percentile of EGJ distensibility in healthy volunteers. The cut-off for normality was \(2.9 \text{ mm}^2 / \text{mmHg}\). As demonstrated in Figure 2B, 4 of 18 (22%) successfully treated patients have an EGJ distensibility value lower than the 90th percentile value of healthy volunteers. This is in contrast to 11 of 12 (92%) unsuccessfully treated patients and 7 of 7 (100%) newly diagnosed patients. Using this cut-off value, the sensitivity and specificity of EGJ distensibility (50 mL) for treatment failure is 92% and 72% respectively (chi-square).

**Effect of treatment**
a) Newly diagnosed patients
Seven patients with newly diagnosed achalasia were included in the study, to verify the effect of initial treatment on EGJ distensibility. Before treatment, distensibility was significantly impaired compared to HV with a median distensibility of \(0.60 \text{ (IQR 0.37-0.94) mm}^2 / \text{mmHg}\) in a 50 mL volume distension. Treatment significantly improved distensibility to \(2.9 \text{ (IQR 1.2-7.4) mm}^2 / \text{mmHg}\) after treatment \((P=0.02\) compared to pre-treatment, Wilcoxon signed rank test). (Figure 4.) Interestingly, the increase in distensibility after treatment had an excellent correlation with the decrease in symptom score \((r=0.89 \ P<0.005\), Spearman’s rank). Distensibility did not increase above the \(2.9 \text{ mm}^2/\text{mmHg}\) cut-off value in three patients and was associated with persistent symptoms, as indicated by an Eckardt score above 3. These patients all underwent additional treatment: 2 patients underwent PD with a 40 mm balloon, whereas 1 patient underwent LHM. This led to a decrease in symptoms in all patients. In the single patient that underwent an additional EndoFLIP measurement, LHM resulted in an increase in distensibility to \(6.0 \text{ mm}^2/\text{mmHg}\).
FIGURE 2 | The EGJ opening is plotted against the intrabag pressure in figure 2A for healthy volunteers (n=15), patients with successful treatment (n=18), treatment failures (n=12) and newly diagnosed patients (n=7). Starting from a 40 mL volumetric distension, treatment failures have a clearly smaller EGJ opening at higher intrabag pressure, corresponding with a significantly lower distensibility compared to successfully treated patients and healthy volunteers. Newly diagnosed patients clearly have the most impaired EGJ distensibility. Figure 2B shows the separate measurements of the included groups at the maximal volumetric distension of 50 mL. The 90th percentile of healthy volunteers EGJ distensibility is marked. Open symbols are used in case values are below the 90th percentile. Of the successfully treated patients 78% is above the 90th percentile of healthy volunteers, in contrast to only 8% and 0% of treatment failures and newly diagnosed patients respectively. ***P<0.001 **P<0.01 *P<0.05 Test are performed with a Student’s T-test with Bonferroni correction.
FIGURE 3 | Examples of EndoFLIP measurement during volumetric distensions in a healthy volunteer (A), a patient with successful treatment (B), a patient with recurrent symptoms (C) and a patient before initial treatment (D) are depicted. The bag has a cylindrical shape, of which the varying diameter corresponds with the opening at that point, and the exact values can be observed in the right panel of each measurement. The narrowest diameter corresponds with the EGJ opening. The EGJ opening is clearly wider in the healthy volunteer and the patient with treatment success compared to the patient with treatment failure and the newly diagnosed patient. Additionally, bag pressures are lower in treatment success, indicating that less pressure is needed to open the EGJ, corresponding with a higher distensibility.
b) Previously treated patients
Five of the 12 patients with treatment failure/ recurrent symptoms were evaluated by EndoFLIP after additional treatment. Before treatment, patients had a median distensibility of 0.79 mm²/mmHg (IQR 0.58-1.2). Three patients were treated by PD (35 mm) and 2 by LHM. After a median of 6 months, distensibility increased significantly to 5.6 mm²/mmHg (IQR 3.7-6.6) (P=0.03 vs. before treatment, Wilcoxon signed rank test) and was above 2.9 mm²/mmHg in all patients. This was associated with clinical success and a reduction of the Eckardt score < 3 (median 1 (range 0-2)).

**EGJ distensibility, esophageal emptying and LES pressure in relation to treatment success**

As shown in Figure 2A, treatment failures had a significantly lower EGJ distensibility compared to successfully treated patients. Moreover, treatment failures had significantly more esophageal stasis after five minutes (4.5 ± 1.1 cm vs. 1.2 ± 0.7 cm, P=0.01), and a higher LES pressure (4.4 ± 1.1 mmHg vs 10 ± 3.0 mmHg, P=0.03) compared to successfully treated patients. (Figure 5.)

Although LES pressure > 10 mmHg is accepted to indicate inadequate treatment 6, 13, 14, LES pressure was < 10 mmHg in 7 of the 12 (58%) patients with treatment failure (Figure 5 panel B). Residual LES pressure after swallowing was >10 mmHg in only 5 of 12 in patients with treatment failure. In contrast, impaired distensibility as assessed with the EndoFLIP and residual stasis on timed barium esophagogram were present in 92% and 89% of patients with treatment failure respectively. (Figure 5, panels A and C) To define why patients are treatment failures even though LES pressure is < 10 mmHg, we compared LES pressure to EGJ distensibility and esophageal stasis.

**LES pressure in relation to esophageal emptying and EGJ distensibility**

Of the 22 patients with a low LES pressure, 8 patients had impaired distensibility on EndoFLIP. These patients had significantly more stasis on their timed barium esophagogram compared to patients with a normal distensibility (6.5 ± 0.6 cm vs. 1.2 ± 0.5 cm, P<0.01). Interestingly, 5 of these patients reported a symptom score of 4 or higher. Thus, even if LES pressure is low, distensibility can be impaired leading to impaired esophageal emptying and recurrent symptoms. In line with this, 7 of 14 (50%) patients with impaired esophageal emptying had a LES pressure <10 mmHg, whilst there was no significant relationship between LES pressure and the height of stasis (r=0.25, P=0.26 Spearman's rank).
Figure 4: The effect of initial treatment is depicted in Figure 4 (n=7), showing increased distensibility at the different volumetric distensions after treatment in Figure 4A, which is statistically significant at the largest volumetric distension (* P<0.05, Wilcoxon signed rank test). Additionally, Figures 4B and 4C demonstrate that the effect of treatment on distensibility differs, and that an increase correlates excellently with the decrease in symptoms (r=0.89, P<0.01 Spearman’s rank correlation). The 3 patients marked with an open symbol (o) in figure 3B and 3C have an impaired distensibility after therapy (<2.9mm²/mMg). All three patients needed additional therapy, due to persistent symptoms.

Figure 5: Values for EGI distensibility (A), LES pressure (B) and esophageal stasis (C) are compared for successfully treated patients (n=18) and treatment failures (n=12). Distensibility and LES pressure are higher in successfully treated patients, whereas the height of esophageal stasis 5 minutes after barium ingestion is lower in successfully treated patients compared to treatment failures. Although there are significant differences, the discriminatory value of the cut-offs (marked by a dotted line) differs between the 3 parameters. Open symbols are used in case values are below (EGI distensibility) or above (LES pressure and esophageal stasis) the cut-off value. Of treatment failures, 92% and 89% have an impaired EGI distensibility and impaired esophageal emptying respectively, whilst 42% have an elevated LES pressure. **P<0.01 *P<0.05, Student’s T-test.
**Esophageal emptying and EGJ distensibility**

In contrast to LES pressure, EGJ distensibility significantly correlated with the height of stasis \( r=0.72, \ P<0.001 \) Spearman’s rank. Patients with complete emptying indeed had a higher distensibility of the EGJ compared to patients with residual stasis (50 mL: 2.2 ± 0.40 vs. 4.7 ± 0.76 mm\(^2\)/mmHg \( P=0.006 \)). Furthermore, in patients with impaired EGJ distensibility after treatment (<2.9 mm\(^2\)/mmHg) the height of the barium column was significantly higher after 1, 2 and 5 minutes, compared to patients with a normal distensibility. (Figure 6.) Lastly, in 9 of 10 patients (90%) with a normal EGJ distensibility, emptying was complete after 5 minutes.

![Diagram showing the height of the barium column over time for patients with normal and impaired distensibility.](image)

FIGURE 6 | The height of the barium column is plotted at the different measurement times, for patients with a normal distensibility (n=10) and for patients with an impaired distensibility (n=14). Right after ingestion, there is no difference in column height. The height of the barium column is significantly lower after 1, 2 and 5 minutes in patients with a normal distensibility, corresponding with a significantly better esophageal emptying. * \( P<0.05 \) ** \( P<0.01 \) Student’s t-test.

**EGJ distensibility and esophageal width**

To assess the effect of esophageal width on EGJ distensibility, we used the maximal esophageal diameter of the barium column on the timed barium esophagogram. No correlation of esophageal width and EGJ distensibility was found \( r=-0.35 \ P=0.14 \), Pearson’s correlation). Furthermore, patients with a widened esophagus (>3cm) have comparable EGJ distensibility compared to patients with a normal esophageal width (2.6 ± 0.3 vs. 4.0 ± 0.7 mm\(^2\)/mmHg, \( P=0.08 \)). Therefore, the effect of esophageal width on EGJ distensibility is probably limited.

**DISCUSSION**

In the present study we showed that EGJ distensibility, but not LES pressure, strongly correlates with clinical response to treatment: impaired EGJ distensibility is observed in 92% of patients with
recurrent symptoms, whilst only 42% of these patients have an elevated LES pressure. Moreover, patients with impaired EGJ distensibility have recurrent symptoms and impaired esophageal emptying, even if LES pressure is low. Based on these findings, we conclude that EGJ distensibility is a better parameter to evaluate the efficacy of treatment in patients with achalasia compared to LES pressure.

Treatment of patients with achalasia aims at relieving functional obstruction at the level of the EGJ. This is mostly achieved by disruption of the LES circular muscle fibres, either by endoscopic pneumodilatation or surgical myotomy. \(^5, 20\) Although initial treatment success rates are high, recurrences may occur in up to 87% of patients especially when follow up is as long as 12 years. \(^6-8, 20\) Since previous studies have suggested that basal LES pressure ≥ 10 mmHg is a risk factor to develop recurrent symptoms, LES pressure is often used in current clinical practice to decide if patients require further treatment. \(^6, 13, 14\) In our study however, LES pressure did not discriminate patients with clinical success from those with persistent or recurrent symptoms: in 7 of 12 (58%) patients with recurrent symptoms, LES pressure was lower than 10 mmHg. Alternatively, one could reason that the residual LES pressure during swallowing is a more relevant parameter determining LES opening and subsequent passage of the bolus and esophageal emptying. Unfortunately, no data are available in literature evaluating the relationship between this parameter and clinical success. Nevertheless, we checked whether the residual LES residual pressure after swallowing would be an alternative parameter to discriminate patients with recurrent symptoms during manometry. However, comparable to basal LES pressure, only 5 of 12 (42%) treatment failures had a residual LES pressure > 10mm Hg. Similarly, Zaninotto et al. reported that following LHM LES pressure was comparable in treatment failures and successfully treated patients. \(^9\) Moreover, multiple studies have failed to confirm LES pressure as a risk factor for additional treatment. \(^9, 20, 22\) Taken together, these findings would argue against LES pressure as a clinically useful parameter to determine clinical management of patients with achalasia.

Impaired emptying of the esophagus is a major hallmark of achalasia and largely determines severity of clinical symptoms. Obviously, increased LES pressure and impaired LES relaxation upon swallowing result in increased resistance to flow across the EGJ. Conversely, however, it should be emphasized that flow across the EGJ, even when LES pressure is low or absent, is mainly determined by the distensibility of the EGJ. In a study evaluating the dynamics of gastroesophageal reflux, Pandolfino et al. indeed elegantly demonstrated that increase of EGJ opening leads to an increase of flow across the EGJ to the fourth power. \(^18\) In line with these findings, we observed that EGJ distensibility significantly correlated with esophageal emptying (correlation coefficient -0.72) and most importantly with clinical symptoms and treatment success. In 78% of successfully treated patients, EGJ distensibility was found to be within the normal range, compared to 8% of
patients with recurrent symptoms and none of the newly diagnosed patients. In a recent case report, clinical response to LHM was also associated with increased EGJ distensibility in a patient with achalasia. Moreover, we showed that failure of PD or LHM to increase distensibility led to incomplete symptom improvement and resulted in the need for additional treatment, even if LES pressure was reduced to less than 10 mmHg. Similar to our findings, previous studies reported that low LES pressure does not necessarily lead to complete esophageal emptying and prolonged clinical success. For instance, in a study by Guardino et al., patients who failed to respond to LHM had a significant reduction in LES pressure but no improvement in esophageal emptying. Our finding that esophageal emptying and EGJ distensibility can be abnormal even though LES pressure is low, suggests that other factors contribute to the impaired distensibility observed in achalasia. One potential explanation could be fibrosis of the LES or the surrounding tissue resulting from previous treatment(s) or progression of the disease. Histopathological evaluation of LES specimens from achalasia patients indeed reveals extensive fibrosis, especially after disappearance of myenteric neurons. In contrast to EGJ distensibility, we did not find any correlation between LES pressure and esophageal emptying or treatment success. Taken together, these data indicate that EGJ may be a better parameter than LES pressure to evaluate the efficacy of treatment or the need for retreatment.

Previously, Vaezi et al. elegantly demonstrated that patients with incomplete esophageal emptying have a four-fold increased risk for retreatment, even in the absence of symptoms at the time of assessment. Since then, multiple studies have confirmed that incomplete esophageal emptying is an important predictor of the need for retreatment. Based on our results, we hypothesize that assessment of EGJ distensibility can also timely diagnose incomplete therapeutic response. As demonstrated, EGJ distensibility correlates well with esophageal emptying, and has a high sensitivity to detect patients with current treatment failure. Therefore, impaired EGJ distensibility might eventually be helpful to detect patients with incomplete therapeutic response, but yet without symptoms, comparably to incomplete emptying as demonstrated by Vaezi et al. Early additional therapy in these patients might reduce morbidity and avoid esophageal decompensation in the long term. Further studies are needed however to confirm this hypothesis.

Based on our data, we propose to use either EndoFLIP or timed barium esophagogram instead of esophageal manometry as clinical useful tools in the management of achalasia patients. Obviously, esophageal manometry, preferentially high resolution manometry, remains the most important tool to diagnose achalasia. However, measurement of esophageal emptying using timed barium esophagogram or assessment of EGJ distensibility by EndoFLIP are superior to manometry when it comes to evaluate the effect of therapy and to assess the need for retreatment. The choice between these two techniques is determined by several factors. EndoFLIP has the advantage
that it can be performed intra-operative.\textsuperscript{24} However, the test is invasive and requires expertise. Hence, this technique will probably be reserved for research purposes in tertiary care referral centers. In contrast, a barium esophagogram is a non-invasive, simple and widely available tool and is repeatedly demonstrated to be predictive for treatment failure, and only involves a low dose of radiation.\textsuperscript{4, 20, 25} Our data confirm that this technique is indeed an important tool to assess treatment success, and in view of its simplicity very well suited for routine clinical practice.

A possible limitation of our study is the small number of patients in each category and the relatively short follow up. Potentially, a longer follow up period could demonstrate that patients with an impaired distensibility but a symptom score of 3 or lower will indeed need additional therapy with prolonged follow-up. Additional larger studies with longer follow up period are therefore warranted.

In conclusion, improved esophageal emptying and EGJ distensibility rather than low LES pressure is associated with clinical success. In patients with low LES pressure, delayed esophageal emptying results from impaired distensibility, probably resulting from fibrosis due to earlier treatment or progression of the disease. From these data, we conclude that a timed barium esophagogram or EndoFLIP are better tools to evaluate treatment in achalasia than LES manometry.


