Achalasia: A New Clinically Relevant Classification by High-Resolution Manometry

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Background & Aims: Although the diagnosis of achalasia hinges on demonstrating impaired esophagogastric junction (EGJ) relaxation and aperistalsis, 3 distinct patterns of aperistalsis are discernable with high-resolution manometry (HRM). This study aimed to compare the clinical characteristics and treatment response of these 3 subtypes. Methods: One thousand clinical HRM studies were reviewed, and 213 patients with impaired EGJ relaxation were identified. These were categorized into 4 groups: achalasia with minimal esophageal pressurization (type I, classic), achalasia with esophageal compression (type II), achalasia with spasm (type III), and functional obstruction with some preserved peristalsis. Clinical and manometric variables including treatment response were compared among the 3 achalasia subtypes. Logistic regression analysis was performed using treatment success as the dichotomous dependent variable controlling for independent manometric and clinical variables. Results: Ninety-nine patients were newly diagnosed with achalasia (21 type I, 49 type II, 29 type III), and 83 of these had sufficient follow-up to analyze treatment response. Type II patients were significantly more likely to respond to any therapy (BoTox [71%], pneumatic dilation [91%], or Heller myotomy [100%]) than type I (56% overall) or type III (29% overall) patients. Logistic regression analysis found type II to be a predictor of positive treatment response, whereas type III and pretreatment esophageal dilatation were predictive of negative treatment response. Conclusions: Achalasia can be categorized into 3 subtypes that are distinct in terms of their responsiveness to medical or surgical therapies. Utilizing these subclassifications would likely strengthen future prospective studies of treatment efficacy in achalasia.

A major objective of clinical esophageal manometry studies is to diagnose achalasia, a well-defined esophageal motor disorder with effective treatments. Conventional diagnostic criteria for achalasia are impaired esophagogastric junction (EGJ) relaxation, absence of normally propagated peristaltic contractions, and absence of a structural explanation (e.g., tumor, stricture) for these abnormalities. However, there is substantial variability in the peristaltic abnormalities and esophageal pressure dynamics encountered in achalasia, making these criteria less straightforward than they seem at first glance. Furthermore, there is wide variability among centers in reported treatment response in achalasia, raising the possibility that clinically relevant subtypes might exist, with some subtypes more responsive to therapy than others.

Efforts to identify achalasia subgroups have previously focused on the variant of “vigorous” achalasia. This entity was differentiated from the classic version of achalasia in that the esophageal body exhibits simultaneous pressurizations. These pressurizations were thought indicative of simultaneous contractions of the tubular esophagus, and vigorous achalasia was presumed to represent an early form of the disease and/or a more treatable subgroup. However, evidence supporting this hypothesis is scant, and no consensus currently exists on either the definition or the prognostic implications of vigorous achalasia. These limitations are at least partly attributable to the variability of manometric technique among centers and to the lack of any obvious consistency among (or even within) centers in the criteria used to define “vigorous” achalasia. Most notably, “simultaneous contractions” at adjacent intraesophageal recording sites is the defining criterion for both vigorous achalasia and distal esophageal spasm in conventional manometric classification. However, conventional classification makes no distinction between “simultaneous contractions” attributable to rapidly propagated, lumen-obliterating, spastic contractions and those attributable to compartmentalized intraesophageal pressurization between loci of a lumen-obliterating contraction proximally and a downstream obstruction distally. High-resolution manometry (HRM) with pressure topography plotting easily resolves this distinction. Consequently, HRM may provide a means to subtype achalasia in a more consistent and functionally relevant way.

Abbreviations used in this paper: EGJ, esophagogastric junction; HRM, high-resolution manometry; IRP, integrated relaxation pressure; PFV, pressurization front velocity.

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We recently reported an initial clinical experience with HRM and pressure topography plotting in 400 consecutive patients. In that series, we recognized 3 distinct manometric patterns of esophageal body contractility in achalasia: (1) no significant pressurization; (2) rapidly propagated compartmentalized pressurization, either localized to the distal esophagus or present across the entire length of the esophagus; and (3) rapidly propagated pressurization attributable to spastic contractions. Although all 3 subtypes had impaired EGJ relaxation and aperistalsis, they each represent a distinct pathophysiologic scenario and possibly an explanation for some of the observed variability in treatment response. Thus, our goal in this follow-up investigation was to test that hypothesis in a large series of achalasia patients. Achalasia patients were classified into these 3 subtypes to determine what differences exist in clinical characteristics and treatment response among subtypes.

**Patients and Methods**

**Patients**

HRM studies performed on 1000 consecutive patients (39.7% male, ages 13 to 94 years) between February 2004 and January 2007 at Northwestern Memorial Hospital were reviewed. Each study was analyzed for impaired EGJ relaxation to identify potential achalasia patients. Impaired EGJ relaxation was defined as an average 4-second integrated relaxation pressure (IRP) greater than 15 mm Hg. A total of 207 patients had impaired EGJ relaxation and were identified for further analysis. The study protocol was approved by the Northwestern University Institutional Review Board.

**Manometry Protocol**

After a brief interview and examination to assess symptoms and to make anthropometric measurements, all subjects presenting to the motility laboratory at Northwestern Memorial Hospital underwent a standardized protocol. A solid-state manometric assembly with 36 pressure sensors spaced at 1-cm intervals (outside diameter, 4.2 mm) was used (Manoscan; Sierra Scientific Instruments Inc, Los Angeles, CA). The pressure sensing elements are accurate to approximately 1 mm Hg after thermal correction with Manoview software (Sierra Scientific Instruments Inc, Los Angeles, CA). The pressure sensing elements are calibrated at 0 and 100 mm Hg using externally applied pressure. Each of the 36 pressure-sensing elements is circumferentially sensitive with the extended frequency response characteristic of solid-state manometric systems. The HRM assembly was placed transnasally and the manometric catheter positioned to record from the hypopharynx to the stomach with approximately 5 intragastric sensors. Studies were performed in a supine position after at least a 6-hour fast. The manometric protocol included a 5-minute period to assess basal EGJ pressure; 10 water swallows of 5 mL; and 1 water swallow each of 1 mL (dry), 10 mL, and 20 mL.

**Manometry Analysis**

All manometric analysis was done using Manoview software applied to the data tracings viewed in the color pressure topography mode and referenced to intragastric pressure. The main software tool utilized was the isobaric contour tool. The isobaric contour tool allows the user to select any pressure for identification on the pressure topography plots of the manometric study. Areas on the pressure topography plots at which the pressure is equal to the selected pressure are then indicated in black, thereby forming isobaric contour lines that circumscribe the pressure domains equal to or greater than the predefined pressure and excluding all areas with a pressure less than the specified set point (Figure 1).

Patients were first categorized as having normal or impaired EGJ relaxation (mean IRP >15 mm Hg). This was ascertained by scrutinizing the EGJ relaxation window beginning with upper esophageal sphincter (UES) relaxation and extending at least 10 seconds forward or to the point at which the peristaltic contractile wave front intersects the proximal aspect of the EGJ. The spatial limits of the EGJ were defined by identifying the crural contraction and the proximal and distal aspects of the lower esophageal sphincter (LES). The IRP was then
determined by scrolling up the pressure on the isobaric contour tool to the lowest value at which no isobaric area was identified within the distal esophageal segment. This value was recorded as the IRP for that swallow. The axial position change of the LES was also measured both to determine the magnitude of swallow-induced esophageal shortening and to ensure that the sphincter was not mislocalized in the relaxation analysis.

Patients with impaired EGJ relaxation were then further categorized by the dominant characteristics of distal esophageal pressurization after swallows. This analysis was also performed using the isobaric contour tool, now set at 30 mm Hg to determine the pressurization front velocity (PFV) in the distal esophageal segment. The PFV is the slope of the line connecting the distal temporal margin of the transition zone with the superior proximal margin of the EGJ on the 30-mm Hg isobaric contour line, expressed in centimeters/seconds. Each swallow was characterized as normal (intact isobaric contour and a PFV <8 cm/s), failed (complete failure of contraction), hypotensive (>2-cm break in the 30-mm Hg isobaric contour between the distal segment and the EGJ), rapidly conducted (PFV ≥8 cm/s) spastic contractions, or pansophageal pressurization with simultaneous esophageal pressurization extending from the UES to the EGJ (Figure 2). Finally, each swallow was scored for the maximal pressure observed in the distal segment. This was done by scrolling up the isobaric contour tool to the pressure value at which no isobaric area was identified within the distal esophageal segment.

Examples of the 3 subtypes of achalasia are illustrated in Figure 2. In type I (classic) achalasia, there was no distal esophageal pressurization to >30 mm Hg in ≥8 of the 10 test swallows (Figure 2A and B). In type II achalasia (with compression), at least 2 test swallows were associated with pansophageal pressurization to greater than 30 mm Hg (Figure 2C and D). Type III patients (spastic) had 2 or more spastic contractions with or without periods of compartmentalized pressurization (Figure 2E and F). If patients were found to have more than 2 swallows with compression, but also had 2 or more spastic contractions, they were categorized as type III because this was their more unique feature. Patients with some preserved peristaltic activity in the distal esophagus manifest by an intact 30-mm Hg isobaric contour bridging between the distal propagated contraction and a poorly relaxing EGJ were classified as EGJ obstruction. Although some of these patients may represent an achalasia variant, others clearly had a mechanical obstruction. Given the heterogeneity of the group, they were excluded from further analysis in this series.

Basal EGJ pressure, axial LES movement during swallowing, and maximal intraesophageal pressure were also measured using the isobaric contour tool and the Manoview smart mouse tool in the achalasia patients. End-expiratory EGJ pressure was measured during a 3-minute baseline period by scrolling the isobaric contour tool to determine the nadir value during expirations and calculating the mean value. Axial LES movement was measured using the isobaric contour tool to first define the proximal margin of the LES high-pressure zone. The Manoview basic smart mouse tool was used to measure the distance between the baseline position of the proximal margin of the LES just prior to each swallow and its maximal axial position during the postswallow period (10 seconds maximum). Axial LES movement was measured for each swallow and presented as a mean value. Maximal intraesophageal pressure was measured by using the smart mouse tool to define the maximal pressure in a spatial domain extending from the area starting temporally at the transition zone and extending 10 seconds forward. The maximal pressure was measured for each swallow and presented as a mean value for each patient.

**Clinical Variables**

The medical records of each patient were reviewed by an investigator blinded to the manometric analysis to determine their dominant symptoms at presentation, the number and type of therapeutic interventions they underwent, and whether or not they had a good treatment response. Successful treatment response was defined as at least 1 postintervention clinic visit documenting sufficient improvement such that no further intervention was recommended for a minimum 12-month follow-up after the last intervention. Unsuccessful response was defined as the need for further intervention or poor subjective improvement as assessed during the most recent encounter. In addition, preintervention endoscopy reports were evaluated to grade the presence or absence of esophageal dilatation. Although contrast studies may be a more objective method to measure dilatation, we were limited in using this variable because fewer than 50% of patients had contrast studies performed. Dilatation was graded as normal (score, 0) if there was no mention of dilatation or retained secretions, mild (score, 1) if the endoscopist described possible dilatation, and severe (score, 2) if the endoscopist described obvious dilatation and the presence of retained secretions or food.

**Statistical Analysis**

The manometric parameters and clinical variables obtained from the medical records were summarized using mean and standard error (SE). ANOVA was used to compare the mean values of manometric parameters and clinical variables among the achalasia group types, and χ² analysis was used to compare categorical variables among the 3 achalasia subtypes. Logistic regression analysis was performed using successful treatment response as a dichotomous dependent outcome in the model. Independent variables assessed in the logistic regression model...
Figure 2. Achalasia subtypes. The subtypes are distinguished by 3 distinct manometric patterns of esophageal body contractility. Type I is illustrated in both a color pressure topography plot (A) and as a 3-dimensional plot to illustrate the pressure gradients spanning the esophagus and proximal stomach (B). In panel a, there is no significant pressurization within the body of the esophagus, and this would be classified as failed peristalsis with an IRP of 42 mm Hg. The 3-dimensional rendering of these pressure data in B clearly illustrates that esophagogastric flow cannot occur because the esophageal pressure is too low to overcome the EGJ high-pressure zone. C represents a swallow from a type II achalasia patient with compartmentalized pressurization spanning the entire length of the esophagus. The 3-dimensional rendering of these pressure data (D) illustrates that the isobaric column within the esophagus equals the EGJ pressure and would likely be associated with esophagogastric flow. E illustrates a pressure topography plot of a spastic contraction in a type III achalasia patient. Although this swallow is also associated with rapidly propagated pressurization, the pressurization is attributable to an abnormal lumen obliterating contraction. The 3-dimensional rendering of these pressure data (F) illustrates the peaks and valleys of that spastic contraction, and this swallow would likely appear as a rosary-bead pattern on fluoroscopy.
were age, sex, body mass index, number and type of therapeutic interventions, esophageal dilatation, achalasia subtype, IRP, basal LES pressure, and axial movement of the LES.

Results

Of the 1000 patients referred for manometry, a total of 213 patients had impaired EGJ relaxation; 4 studies were excluded because of technical limitations, whereas another 2 were excluded because of a diagnosis of esophageal cancer (Figure 3). The medical records of the remaining 207 patients (20.7%) were reviewed to exclude patients with a preexisting diagnosis of achalasia who had already undergone therapy (n/H11005 30). Of the remaining 177 patients, 78 were classified as having functional obstruction on the basis of preserved peristalsis, leaving 99 achalasia patients for analysis. Thus, 99 patients (9.9%) were newly diagnosed with achalasia based on having impaired EGJ relaxation, aperistalsis, and absence of a structural lesion to account for these abnormalities. Of these, 83 had follow-up information of sufficient detail and duration (at least 12 months) to assess response to therapy.

Achalasia Classification

Of the 99 patients included in the analysis, 21 were classified as type I, 49 as type II, and 29 as type III (Figure 3). The mean age of the patients was similar among the 3 subtypes (Table 1). Although the male to female ratio was similar overall (47/42), there was a difference in the sex ratio within subtypes. Type II was predominantly female (70%), whereas type I and type III had a male predominance. Type I patients were more likely to present with endoscopic evidence of dilatation, represented as a higher endoscopy grade in Table 1. Although all 3 subtypes presented with severe dysphagia, chest pain was significantly more common in types II and III compared with type I (Table 1).

Manometric Variables

There were significant differences in a number of manometric parameters among achalasia subtypes (Table 2). Type I was associated with a lower basal LES pressure and diminished axial LES proximal movement after swallowing compared with subtypes II and III. The EGJ relaxation pressure was significantly greater for type II compared with type I. Maximal esophageal pressurization was greater in type II than type I and greater in type III than in type I or II. However, there was overlap in the maximal esophageal pressurization values between types II and III, making this metric by itself inadequate to distinguish between types (Figure 4).

The individual swallows among the achalasia subtypes are provided in Table 3. Type I patients by definition had predominantly failed swallows. Ninety-one percent (19/21) of type I patients had 10 failed swallows, whereas 1 patient had 8 failed and 2 hypotensive contractions, and another had 9 failed swallows and 1 swallow associated with compression. The type II patients also presented with a very consistent swallow profile. Ninety-two percent (45/49) of the type II patients had 8 or more swallows associated with compression. The remaining 4 patients had at least 4 swallows with compression, and the other swallows in these patients were predominantly failed (4 or 5 swallows). The type III patients were more heterogeneous; however, the dominant swallow pattern was spastic contraction with an average of 8 spastic swallows per patient. There was not a single type III patient who had fewer than 4 spastic contractions and not a single type II patient who had a single spastic contraction. Thus, these contractile patterns appear to be quite consistent within the groups as defined.

Clinical Outcome of Achalasia Subtypes

Follow-up information of sufficient detail and duration to assess treatment outcome was available for 83 of the 99 achalasia patients (Table 4). Type I patients underwent a mean number of 1.6 therapeutic interventions during a mean follow-up period of 19 months and experienced a response rate of 56% after their most recent therapy. Type II patients underwent an average of 1.2 interventions during a mean follow-up period of 20 months and had an excellent response to all 3 therapies. Type III patients had the worst response to therapy; despite having a signifi-

Table 1. Demographic and Clinical Data Among Achalasia Subtypes

<table>
<thead>
<tr>
<th>Achalasia subtype</th>
<th>Type I (n = 21)</th>
<th>Type II (n = 49)</th>
<th>Type III (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) mean (SD)</td>
<td>58 (16.9)</td>
<td>53.4 (19.6)</td>
<td>63.5 (15.6)</td>
</tr>
<tr>
<td>Male/female</td>
<td>12/9</td>
<td>15/34</td>
<td>19/10</td>
</tr>
<tr>
<td>Dilatation grade</td>
<td>1.5 (0.70)</td>
<td>0.6± (0.7)</td>
<td>0.4± (0.6)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia (%)</td>
<td>100</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>Chest pain (%)</td>
<td>19</td>
<td>41±</td>
<td>54±</td>
</tr>
</tbody>
</table>

*P < .05 vs type I.
significantly greater number of therapeutic interventions during a mean follow-up of 20 months, they exhibited the worst overall treatment response (29%). Overall response rates to BoTox (Allergan Inc, Irvine, CA), pneumatic dilation, and Heller myotomy during the first intervention differed, but this difference seemed to be attributable to differential response in the type I and type III patients. Type I patients responded best to Heller myotomy, whereas type III patients had a poor response to all therapies.

**Predictors of Response**

From the comparison analysis among the 3 groups in Table 4, it appeared that the achalasia subtype was an important predictor of clinical outcome. This was tested in a logistic regression model in which clinical outcome was the dependent variable and achalasia subtype was the independent categorical variable while controlling for age, sex, presence or absence of dilatation on index endoscopy, and EGJ basal and relaxation pressure (4-second IRP). For the calculation of odds ratio (OR), achalasia subtype I was considered the control because this represents the classic definition of achalasia. The results indicated that achalasia subtype II was much more likely to respond to therapy compared with subtype I (OR, 11.2 (95th percentile CI, 2.4–35.6); \( P < .002 \)). In contrast, achalasia type III was much less likely to respond to therapy than subtype I (OR, 0.24 (95th percentile CI, 0.06–0.92); \( P = .044 \)). Severe esophageal dilatation (grade 2) was also shown to have a significant negative effect on treatment response when compared with patients with no evidence of dilatation (grade 0) (OR, 0.2 (95th percentile CI, 0.05–0.60); \( P = .005 \)).

**Reproducibility of HRM Findings Posttherapy**

Eighteen achalasia patients (type I, 5; type II, 3; type III, 10) had a repeat manometry from 1 to 36 months postintervention. The manometric achalasia subtype classification did not change after therapy regardless of whether the patients were asymptomatic at follow-up studies (n = 6) or experiencing continued symptoms (n = 12). In fact, the overall distribution of postdeglutitive contraction pattern in the follow-up manometry did not differ from the index manometry by more than 2 swallows in each category. In particular, the average number of spastic contractions on follow-up (average, 8.3; SE, 0.4) did not change from baseline (average, 7.4; SE, 0.95).

**Discussion**

The aim of this study was to determine whether subtypes of achalasia discernible in HRM studies ex-

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### Table 2. Manometric Variables Among Achalasia Subtypes

<table>
<thead>
<tr>
<th>Achalasia subtype</th>
<th>Type I (n = 21)</th>
<th>Type II (n = 49)</th>
<th>Type III (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal EGJ pressure (mm Hg), mean (SD)</td>
<td>24.7 (13.5)</td>
<td>33.2a (13.9)</td>
<td>40.5a (15.1)</td>
</tr>
<tr>
<td>EGJ relaxation pressure (IRP, mm Hg), mean (SD)</td>
<td>26.6 (11.8)</td>
<td>34.9a (10.1)</td>
<td>31.2 (10.6)</td>
</tr>
<tr>
<td>Maximal esophageal pressurization (mm Hg), mean (SD)</td>
<td>31.7 (7.5)</td>
<td>60a (15.6)</td>
<td>190.3a (100)</td>
</tr>
<tr>
<td>Axial LES movement after swallow (cm), mean (SD, range)</td>
<td>0.6 (0.5, 0–1.6)</td>
<td>1.2a (0.7, 0.2–3.6)</td>
<td>1.5a (0.7, 0.7–3.0)</td>
</tr>
</tbody>
</table>

*aP < .05 vs type I.

*bP < .05 vs type II.

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### Table 3. Characterization of Individual Swallows Among the 3 Achalasia Subtypes

<table>
<thead>
<tr>
<th>Achalasia subtype</th>
<th>Type I (n = 210)</th>
<th>Type II (n = 490)</th>
<th>Type III (n = 290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact peristalsis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypotensive contraction</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Failed peristalsis</td>
<td>207</td>
<td>58</td>
<td>21</td>
</tr>
<tr>
<td>Panesophageal pressurization</td>
<td>1</td>
<td>427</td>
<td>30</td>
</tr>
<tr>
<td>Spastic contraction</td>
<td>0</td>
<td>0</td>
<td>232</td>
</tr>
</tbody>
</table>
In summary, achalasia can be categorized into 3 subtypes that are distinct in terms of their responsiveness to medical or surgical therapies. Types I and II probably represent a continuum of the natural history of the disease, but, ultimately, we need to learn more about the underlying pathophysiology of achalasia to improve diagnostic and therapeutic strategies.

Table 4. Response to Therapeutic Interventions Among Achalasia Subtypes

<table>
<thead>
<tr>
<th>Achalasia subtype</th>
<th>Type I (n = 16)</th>
<th>Type II (n = 46)</th>
<th>Type III (n = 21)</th>
<th>All (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of interventions, mean (SD)</td>
<td>1.6 (SD, 1.5)</td>
<td>1.2a (SD, 0.4)</td>
<td>2.4abc (SD, 1.0)</td>
<td>1.8 (SD, 0.7)</td>
</tr>
<tr>
<td>Success with BoTox (first intervention) (%)</td>
<td>0 (0/2)</td>
<td>86 (6/7)</td>
<td>22 (2/9)</td>
<td>39 (7/18)</td>
</tr>
<tr>
<td>Success with dilation (first intervention with 30-mm balloon) (%)</td>
<td>38 (3/8)</td>
<td>73 (19/26)</td>
<td>0 (0/11)</td>
<td>53 (24/45)</td>
</tr>
<tr>
<td>Success with myotomy (first intervention) (%)</td>
<td>67 (4/6)</td>
<td>100 (13/13)</td>
<td>0 (0/1)</td>
<td>85 (17/20)</td>
</tr>
<tr>
<td>Success with first intervention (total) (%)</td>
<td>44 (7/16)</td>
<td>83 (38/46)</td>
<td>9 (2/21)</td>
<td>56 (47/83)</td>
</tr>
<tr>
<td>Success with last intervention (%) (last intervention type)</td>
<td>56 (B-0, P-10, M-6)</td>
<td>96 (B-6, P-25, M-15)</td>
<td>29abc (B-8, P-8, M-5)</td>
<td>71 (B-14, P-43, M-26)</td>
</tr>
</tbody>
</table>

NOTE. Pneumatic dilation was initially done with a 30-mm Microvasive balloon in all instances. If this failed, it was usually followed by a 35-mm dilation accounting for the difference in success rate for pneumatic dilation when applied as an initial or as the last intervention. Overall, type II patients exhibited better response to all therapies: Botox (B), pneumatic dilation (P), or surgical myotomy (M).

ap < .05 vs type I.
bP < .05 vs type II.
about the natural history. Similarly, more needs to be learned about the functional obstruction group of patients, some of whom might represent an even earlier stage in the natural history of achalasia. Type III patients seem distinct from the others in that they are more akin to distal esophageal spasm, perhaps representing a variant of that disease that involves the LES. The distinct clinical behavior of these 3 achalasia subtypes suggests that utilizing these HRM subclassifications is clinically useful and would likely strengthen future prospective studies of treatment efficacy in achalasia.

References