Complete lower esophageal sphincter relaxation observed in some achalasia patients is functionally inadequate

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Mearin, Fermín, and Juan-R. Malagelada. Complete lower esophageal sphincter relaxation observed in some achalasia patients is functionally inadequate. Am. J. Physiol. Gastrointest. Liver Physiol. 278: G376–G383, 2000.—Generally accepted manometric criteria for the diagnosis of achalasia are absent peristalsis and incomplete lower esophageal sphincter (LES) relaxation. However, in some patients with otherwise typical features of achalasia, esophageal manometry shows complete LES relaxation during swallowing. To establish whether such apparently complete LES relaxations are functionally adequate, we quantified changes in resistance to flow at the esophagogastric junction (EGJ) during wet swallowing. We studied seven achalasia patients with manometrically complete (>80%) LES relaxation, eight achalasia patients with incomplete (<40%) LES relaxation, and eight healthy volunteers. Complete LES relaxation on standard manometry (open-tip catheters) was confirmed in five of the seven achalasia patients by a Dentsleeve. Changes in EGJ resistance to flow were quantified using a pneumatic resistometer. Manometrically, the relaxation time span was significantly longer in patients with complete LES relaxation than in those with incomplete relaxation (7.3 ± 0.5 vs. 4.4 ± 0.7 s; P < 0.05). The fall in EGJ resistance from basal values during swallowing was markedly reduced in both achalasia groups (21 ± 8% in those with manometrically complete relaxation and 4 ± 2% in those with incomplete relaxation) by comparison with healthy individuals, in whom resistance fell by 90 ± 3% (P < 0.05 vs. both achalasia groups). The duration of EGJ resistance drop was also much shorter in achalasia with (0.7 ± 0.2 s) and without (0.2 ± 0.1 s) complete LES relaxation compared with healthy control values (6.6 ± 1.2 s). Our results reveal that the apparently complete LES relaxation observed manometrically in some patients with achalasia is functionally inadequate since it is not associated with the normal profound fall in EGJ resistance to flow.

MATERIALS AND METHODS

Participants

Healthy controls. Eight healthy volunteers (four women and four men, 20–24 years old) without gastrointestinal symptoms participated in the study. Standard esophageal manometry demonstrated normal esophageal body motility, normal resting LES pressure, and a >80% LES relaxation during wet swallowing.

Achalasia patients. Fifteen patients diagnosed with achalasia were also studied. The diagnosis of achalasia was substantiated by typical symptoms, absence of morphological lesions on radiological and endoscopic examination, and absolute esophageal body peristalsis on manometry. Seven patients showed complete (>80%) LES relaxation in response to swallowing measured by standard manometry, whereas eight showed incomplete relaxation (<40%). These patients were selected for study from a large pool of achalasia patients managed in our unit. Both groups of achalasia patients had similar demographic characteristics (Table 1).

All patients met the following entry criteria: 1) no history of diabetes mellitus, alcoholism, collagen vascular disorders, or neurological disease; 2) no previous history of esophageal, gastric, biliary, or oncologic surgery; and 3) no previous endoscopic or surgical treatment for achalasia.

Procedures

In each individual we first performed a standard esophageal manometry study and then performed the study with the

ACHALASIA IS AN ESOPHAGEAL motor disorder characterized by impaired esophageal transit and clearance. These are the functional consequences of a defective esophageal body propulsive capacity and an increased resistance to flow at the esophagogastric junction (EGJ). Thus the clinical diagnosis of achalasia has been conventionally verified by manometric tests showing absent peristalsis in response to swallowing and incomplete relaxation of a frequently hypertensive lower esophageal sphincter (LES) (7). However, in some patients with otherwise typical clinical and radiological features of achalasia, manometry shows peristalsis of the esophageal body but apparently complete or nearly complete LES relaxation (5, 8). Whether LES relaxation in such patients is functionally adequate or it represents a technical artifact has been difficult to elucidate. In fact, when LES relaxation is evaluated meticulously with appropriate recording techniques it is rarely complete. We reasoned that if a manometric LES relaxation in response to swallowing were functionally adequate it should be associated with a drop in the resistance to flow at the EGJ. Thus in the present study we quantified and compared changes in EGJ resistance to flow during wet swallowing in healthy controls and in achalasia patients with either apparently complete or incomplete manometric LES relaxation. Resistance to flow was quantified using a pneumatic resistometer, an instrument developed and previously validated in our laboratory (9–11).

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necessary to maintain a constant preselected pressure at the head of the cylinder. Under these conditions, the nitrogen flow inside the cylinder bears a constant inverse relationship to the resistance exerted by the gut encircling the cylinder. Therefore, an increase in nitrogen flow indicates a drop in resistance, and vice versa.

The volume of nitrogen expelled by the injection system is continuously measured and transmitted as electrical impulses to a polygraph (model 1600; MFE Instruments, Salem, NH). The pneumatic pump has a reserve volume of 600 ml. When the reserve is exhausted, an electronic mechanism opens a valve to a nitrogen supply and refills it automatically.

To evaluate motor activity in the esophageal body and EGJ resistance simultaneously, three open-tip manometric catheters were attached to the resistometer; their internal orifices were located 5, 10, and 15 cm from the midpoint of the measuring cylinder. A low-compliance pneumatic hydraulic perfusion system was connected to each of the catheters for pressure recording. These catheters served to record esophageal body motility during measurements of EGJ resistance as well as to confirm LES location using a stepwise pull-through technique.

The resistometry study was performed as follows. The measuring cylinder of the resistometer was swallowed through the intraluminal part (placed within the esophagogastric junction) and flow through cylinder maintain a constant inverse relationship. Therefore, an increase in nitrogen flow indicates a drop in EGJ resistance.

### Table 1. Demographic and laboratory data on achalasia patients

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Complete LES Relaxation</th>
<th>Incomplete LES Relaxation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Means (SE)</td>
<td>Means (SE)</td>
</tr>
<tr>
<td>Sex</td>
<td>F  F  F  F  M  M  M  M</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>66  19  65  22  48  37  68</td>
<td>46  18  19  71  54  69  71</td>
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<tr>
<td>Evolution, months</td>
<td>72  54  120  60  30  45  30</td>
<td>59  12</td>
</tr>
<tr>
<td>Dysphagia point scale, 1–5</td>
<td>5  5  4  4  5  3  4  4</td>
<td>4.3 (0.3)</td>
</tr>
<tr>
<td>Esophageal diameter, cm</td>
<td>3.4  4.1  5.7  2.5  5.4  3.5  2.6</td>
<td>3.9 (0.5)</td>
</tr>
<tr>
<td>Esophageal retention</td>
<td>98  90  89  72  88  85  94 np</td>
<td>3.9</td>
</tr>
<tr>
<td>LES pressure, mmHg</td>
<td>33  58  19  25  35  31  22  32</td>
<td>25</td>
</tr>
<tr>
<td>LES relaxation %</td>
<td>83  94  80  82  93  90  92  88</td>
<td>20</td>
</tr>
<tr>
<td>Wave amplitude, mmHg</td>
<td>5  58  20  12  10  14  56  25</td>
<td>12</td>
</tr>
</tbody>
</table>

For explanation of dysphagia points scale, see MATERIALS AND METHODS. Esophageal retention is expressed as % at 100 s. LES, lower esophageal sphincter; np, not performed.
the mouth and positioned intragastrically. The resistometer assembly was then withdrawn stepwise to locate the LES with the help of the manometric catheters. The midpoint of the LES was established by matching its distance from the incisors with that evidenced by the previous standard manometry. The pneumatic pump and the pressure sensor of the injection system were connected to the two lumens of the injection tube. The venting tube was left open to the air. Then the measuring cylinder was located sequentially at two different levels: intragastrically (midpoint of the cylinder 7 cm below the LES midpoint) and across the EGJ (midpoint of the cylinder at the LES midpoint). At each level (stomach and EGJ) the injection pressure was raised stepwise in increments of 2 mmHg from 0 to 20 mmHg or until the nitrogen flow exceeded 1,000 ml/min (this value corresponds to the pressure gradient at which resistance to flow becomes negligible and approaches the intrinsic resistance of the system). At each step, flow through the cylinder was recorded for 2 min, during which time the participant refrained from swallowing.

Thereafter, with the cylinder placed across the LES, changes in flow at injection pressures of 8–10 mmHg were recorded after a minimum of ten 5-ml water swallows. At the same time, esophageal pressure activity was constantly monitored by the manometric catheters mounted on the resistometry assembly.

Radiological evaluation of the esophageal diameter. An esophagogram using standard barium contrast radiology was obtained from every patient. The diameter of esophageal body 5 cm above the EGJ was measured in the anteroposterior projection, and the highest value was registered. A correction factor was used to obtain real esophageal diameter from the diameter measured by X-ray.

Radionuclide esophageal emptying studies. To evaluate esophageal emptying we used a standard radioisotope scintiscan technique (14). The patient was asked to drink, in a single swallow, a 5-ml water bolus containing 1 mCi of technetium sulfur colloid, which was introduced into the mouth by syringe. Some water deglutitions were practiced in advance. While the patient was standing erect with the back against a gamma camera, the field of view was adjusted to include both the mouth and the epigastrium. The gamma camera was connected to a computer that recorded the data for subsequent analysis on replay. Then the upper end of the esophagus was identified using a cricoid marker and the distal end was identified at the end of the study by locating the fundal pool of radioactivity. For analysis, 55 frames at frame rates of 1/0.2 s were used.

Data Analysis

Esophageal manometry. In each subject we recorded the resting LES pressure as the mean of the eight values obtained during two consecutive pullthroughs of the four-lumen manometric catheter. The magnitude of LES relaxation was calculated as the percent drop from mean resting LES pressure to gastric baseline pressure; relaxation was quantified by measuring LES pressure at end expiration after swallowing and referencing it to end-expiratory gastric pressure.

Duration of LES relaxation was defined as the time elapsed from the onset of relaxation to the point at which resting pressure was recorded; values for each subject were obtained as means of 10 wet swallows.

Pneumatic resistometry. In each individual we examined the dynamic correlation between injection pressure gradient and flow through the cylinder at the EGJ junction as well as in the stomach. Nitrogen flow inside the measuring cylinder was quantified at each pressure gradient during 2 min without swallowing and expressed in milliliters per minute. To overcome the possible influence of intragastric resistance on EGJ resistance, EGJ basal resistance was analyzed by subtracting flow at the EGJ from flow in the stomach at each injection pressure. With these values we constructed the curve of the EGJ-gastric resistance gradient. Basal EGJ resistance was evaluated as the cumulative resistance, that is, the sum of resistances exerted at each pressure level, calculated as the area under the curve of the EGJ-gastric resistance gradient.

Changes in EGJ resistance during swallowing were quantified as the percent increase in nitrogen flow, taking the basal period (30 s before deglutition) as 0% and 1,000 ml/min (approaching the maximal flow that could be obtained at the given injection pressure) as 100%. Relaxation time after swallowing was measured as the time elapsed from the onset of the fall in resting resistance to the time when it again reached the basal level.

Radionuclide esophageal emptying. Esophageal retention was quantified in achalasia patients as the percentage of the total radioisotope dose remaining in the esophageal area 100 s after deglutition.

Statistical analysis. We calculated the means ± SE of each parameter measured. Statistical comparisons were performed using Student’s t-test for normally distributed data, with a paired analysis for intragroup comparisons and unpaired analysis for intergroup comparisons. A nonparametric test (Mann-Whitney) was used for abnormally distributed data. Individual values were also subjected to ANOVA. P values < 0.05 were considered significant.

RESULTS

Demographic, clinical, and laboratory data for achalasia patients are shown in Table 1. All complained of severe dysphagia (grades 3 to 5). Evolution time from the onset of symptoms was not significantly different between patients with complete LES relaxation (59 ± 12 mo) and those with incomplete LES relaxation (49 ± 8 mo). Maximal esophageal diameter on the esophagogram was also similar in both groups of patients (3.5 ± 0.5 cm vs. 3.7 ± 0.2 cm), as was esophageal retention on radionuclide studies (isotope remaining at 100 s: 87 ± 4% vs. 83 ± 3%). Esophageal wave amplitude during swallowing was low in both groups of achalasia patients (25 ± 8 mmHg and 14 ± 3 mmHg).

LES basal pressure was similar in achalasia patients with complete LES relaxation (32 ± 5 mmHg) and with incomplete LES relaxation (30 ± 5 mmHg). Mean LES relaxation was 22 ± 4% and 88 ± 2%, respectively. Residual pressures in the seven achalasia patients with a relaxation percentage > 80% were as follows: 5.6 mmHg, 3.5 mmHg, 3.8 mmHg, 4.5 mmHg, 2.5 mmHg, 3.1 mmHg, and 1.8 mmHg (mean 3.5 mmHg). LES relaxation lasted significantly longer in patients with complete LES relaxation than in those with incomplete relaxation; in the former, duration of LES relaxation was shorter than in healthy volunteers, but the difference did not achieve statistical significance (Fig. 2).

Studies performed with the Dent sleeve in five achalasia patients with complete LES relaxation on stan-
standard manometry (relaxation >80%) confirmed that LES relaxation was complete; LES basal pressure was similar with both recording systems but mean duration of LES relaxation was shorter when measured with the Dent sleeve, although without reaching statistical significance (Table 2).

Resistometry studies showed that EGJ basal resistance in both groups of achalasia patients was greater than in healthy controls. However, analysis of the EGJ-gastric resistance gradient curve showed a different profile between the two groups: at low injection pressures the resistance curve was similar in both achalasia groups, whereas at high injection pressures resistance in the group of achalasia patients with complete LES relaxation was intermediate between the healthy patients and the achalasia patients with incomplete LES relaxation (Fig. 3).

In healthy volunteers, wet swallowing induced normal LES relaxation by manometry and a marked decrease in EGJ resistance (Fig. 4). Both groups of achalasia patients, those with incomplete LES relaxation on manometry and those with complete LES relaxation, showed only a minor decrease in EGJ resistance during wet swallowing compared with that observed in healthy patients (Figs. 5 and 6). This was also true for the duration of the fall in EGJ resistance that lasted only a short interval relative to that observed in healthy individuals (Fig. 7).

Table 2. Comparison of LES parameters using standard (open-tip) manometry vs. a Dent sleeve

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>LES Pressure, mmHg</th>
<th>Duration of LES Relaxation, s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard manometry</td>
<td>Dent sleeve</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>39</td>
</tr>
<tr>
<td>1</td>
<td>58</td>
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<td>6</td>
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<td>35</td>
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<tr>
<td>7</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>Means ± SE</td>
<td>33 ± 7</td>
<td>36 ± 0.4</td>
</tr>
</tbody>
</table>

DISCUSSION

The relaxatory function of gut sphincters is a major determinant of intraluminal motion. In the esophagus, if the LES does not relax completely during swallowing, esophageal emptying is impaired and, consequently, dysphagia and other clinical manifestations may develop. In patients with achalasia, the standard manometric criteria for diagnosis are incomplete LES relaxation associated with esophageal body aperistalsis (7). Nevertheless, in some patients with otherwise typical clinical manifestations of achalasia and compatible endoscopic and radiological findings, as well as esophageal aperistalsis, the LES relaxes >80% from basal pressure after swallowing during standard manometry. This apparently complete LES relaxation occurs in approximately 15–30% of patients with achalasia and has been the subject of some controversy in the medical literature (5, 8, 15). The issue is whether this manometrically recorded relaxation reflects a true fall in the resistance to intraluminal flow exerted by the LES or whether it is due to inadequate technique for evaluating the EGJ. Thus, when LES is examined with side-hole sensors, displacement of the manometric port due to esophageal shortening (3, 12) may be misinterpreted in the tracing as relaxation.

A substantial reduction in resistance would imply that such patients belong in a separate category of patients with achalasia, perhaps requiring different therapeutic approaches and with a different prognosis. On the other hand, Katz et al. (8) related this phenomenon, in part, to the size of the manometric catheter employed for the pull-through test. In healthy subjects these authors observed complete LES relaxation with catheters either 4.5, 7, or 11 mm in diameter, but in one patient with achalasia, LES relaxation was recorded as complete with the smaller catheters and as incomplete with the largest. One explanation for these findings is that in some patients with achalasia the LES relaxes enough to open up to a diameter larger than the measuring catheter (13).
To elucidate this interesting issue of apparently complete LES relaxation by manometry, we employed a different technical approach: the pneumatic resistometer. This device did not allow us to measure occlusive pressure (as in manometry) but measured changes in resistance to flow induced by LES contraction. Our results support the notion that the apparently complete relaxation observed manometrically in a subgroup of patients with achalasia is due to incomplete relaxations of the LES, enough to release the occluding snug over the catheter but far from the normal widening that produces a major fall in luminal resistance in healthy individuals. Such a drop in resistance to flow at the EGJ after deglutition is required to freely pass the bolus into the stomach. One advantage of pneumatic resistometry over manometry in the evaluation of EGJ relaxation is that resistance to flow depends not only on the pressure of the constricted segment but also on its diameter and length.

The physical factors that determine the changes in resistance quantified by the pneumatic resistometer have been previously established by us in vitro and in vivo, in animals as well as in humans (9, 11). The method is based on the fluid dynamic principle that resistance to flow (R) produced by a tubular segment, in this case the EGJ, can be calculated by measuring changes in flow (F) through the segment while maintaining a constant pressure gradient (∆P) between its extremes; under these conditions flow and resistance are related in a constant inverse fashion \[ R = k \cdot \frac{\Delta P}{F} \]. The pneumatic resistometer continuously measures the flow rate of injected nitrogen while maintaining a constant pressure gradient between the extremes of a flaccid polyurethane cylinder placed at the EGJ.

Fig. 4. Tracings obtained in a healthy volunteer. A: manometry showing presence of normal LES relaxation during swallowing (S). B: resistometry showing resistance fall (increase in flow) at EGJ during swallowing (S).
fore, changes in flow inside the cylinder reflect changes in resistance produced by the contractile action of the gut encircling the cylinder.

Whether the manometric finding of complete LES relaxation during swallowing represents a marker for a different type of achalasia has been the subject of some controversy. Katz et al. (8) concluded that the finding of complete LES relaxation by manometry might be a marker for a subgroup of patients with an early stage of achalasia. They compared the clinical and laboratory data obtained in seven achalasia patients with complete LES relaxation on manometry with data from 16 patients with incomplete relaxation. The former group of patients manifested a shorter symptomatic period and did not lose as much weight as the others. Furthermore, their esophagi were less dilated and isotope clearance during radionuclide studies showed intermediate values between normal subjects and classic achalasia patients. On the contrary, Garrigues et al. (5) did not find any significant functional or clinical difference between achalasia patients with or without complete LES relaxation on manometry. Baseline LES tone, esophageal diameter, symptom duration, and type or degree of symptoms, as well as therapeutic response, were all similar. In our clinical analysis we were also unable to find significant differences in clinical manifestations between the two groups of patients with achalasia. However, the resistometry studies showed that, although EGJ resistance to flow was increased in both groups of patients with achalasia, those with complete LES relaxation on manometry had intermediate values between classic achalasia and healthy controls. It is interesting to note that this occurred despite a similarly increased LES basal pressure in both groups of achalasia patients. Thus it is possible that impairment of LES function is somewhat milder in the subgroup of patients who exhibit complete LES relaxation on standard manometry.

With respect to the characteristics of LES relaxation in achalasia when measured manometrically, it has been reported that, although apparently complete in some patients, the duration of relaxation is consistently shorter than normal. In the present study we have observed that by standard manometry the duration of LES relaxation was significantly longer in patients
with complete LES relaxation than in those with incomplete relaxation. Nevertheless, in the resistometry studies the duration of the EGJ resistance drop during swallowing was quite short in both achalasia groups and much lower than in healthy individuals. Thus shortened duration of LES relaxation and absent esophageal peristalsis (in addition to incomplete LES relaxation) are factors contributing to the failure of the esophagus to empty.

Some of the discrepancies reported in the medical literature concerning the partial vs. complete LES relaxation in achalasia may relate to the criteria applied to define LES relaxation by manometry. Conventionally, LES relaxation is measured as the percent drop in LES pressure relative to gastric baseline pressure, but it would probably be better to use the residual pressure to assess LES relaxation (2). Holloway et al.
(6) have defined criteria for LES relaxation in healthy volunteers; in their study, mean nadir pressure was 1 mmHg, with an interquartile range of 0–2 mmHg and an upper limit of 7 mmHg. In fact, accepting 4 mmHg as the maximal residual pressure of a complete relaxation, the relaxation was assessed as complete in only five of our seven patients (1).

We conclude that the apparently complete LES relaxation observed manometrically in some patients with achalasia is functionally inadequate because it is not accompanied by the normal fall in EGJ resistance. It is possible that these patients suffer from a somewhat milder impairment of LES function than the bulk of patients with achalasia, but this manometric finding does not preclude the diagnosis of achalasia if established by other clinical and instrumental data.

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Received 30 March 1999; accepted in final form 25 October 1999.

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