Esophageal tone in patients with total aperistalsis: gastroesophageal reflux disease versus achalasia

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Mearin, Férmin, Celia Vasconez, Natalia Zárate, and Juan R. Malagelada. Esophageal tone in patients with total aperistalsis: gastroesophageal reflux disease versus achalasia. Am J Physiol Gastrointest Liver Physiol 279: G374–G379, 2000.—We have evaluated esophageal tone in two different conditions that, in some cases, similarly impair phasic esophageal motility. Studies were performed in 14 healthy volunteers, 10 patients with total esophageal aperistalsis secondary to gastroesophageal reflux disease (GERD), and 25 untreated achalasia patients. We quantified esophageal compliance and relaxation induced by a nitric oxide donor using a barostat. Intraesophageal volume at a minimal distending pressure (2 mmHg) was not significantly different among all three groups (4.1 ± 0.7, 3.8 ± 0.7, and 4.2 ± 1.2 ml for healthy, GERD, and achalasia groups, respectively). Esophageal compliance was significantly increased (P < 0.05 vs. healthy group) in the two groups of patients with aperistalsis (1.9 ± 0.2, 3.0 ± 0.2, and 3.1 ± 0.3 ml/mmHg for healthy, GERD, and achalasia groups, respectively). Esophageal relaxation was decreased in GERD patients (Δ diameter: 0.4 ± 0.1 cm) and increased in achalasia patients (Δ diameter: 1.3 ± 0.4 cm relative to healthy subjects (Δ diameter: 0.9 ± 0.2 cm) (P < 0.05 for GERD vs. achalasia and healthy groups). Our results indicate that diseases that similarly impair phasic esophageal motility may affect esophageal tone differently.

COORDINATED ESOPHAGEAL MOTOR activity is a crucial element of normal deglutition. When esophageal motility is altered, either due to abnormal peristalsis or to decreased wave amplitude, bolus transport becomes impaired, resulting in symptoms such as dysphagia and regurgitation. Usually there is a good correlation between the intensity of the motor abnormality and symptom severity. Thus in patients with severe esophageal peristaltic dysfunction, primary or secondary, dysphagia constitutes a major disability (11, 26).

Severe dysfunction of the smooth muscle portion of the esophagus, including total aperistalsis on a standard manometry test, may be caused by various conditions, such as achalasia (7), scleroderma (19), or gastroesophageal reflux disease (GERD) (13). In most instances, clinical, laboratory, endoscopic, manometric, or pH metric data allow differential diagnosis among these various conditions. However, in some patients, the distinction is not readily apparent. For example, ~5% of patients with GERD have 100% failed primary peristalsis on esophageal manometry (13). Moreover, patients with GERD and severe dysmotility may lack a typical reflux history (23) and, conversely, patients with achalasia may complain of heartburn (24).

In patients with achalasia, we (10) have previously found that esophageal tonic activity, and not only phasic activity, is impaired. In the present study, our objective was to investigate esophageal wall tone in another group of patients with similarly impaired esophageal peristalsis on standard manometry: patients with aperistalsis secondary to severe GERD. Findings were compared for reference purposes to those obtained in patients with primary aperistalsis due to idiopathic achalasia and in healthy volunteers.

METHODS

Subjects

Patients with GERD. Ten patients with a chronic history of severe GERD, all with severe symptoms, erosive esophagitis, and increased gastroesophageal acid reflux on 24 h pH metry, were studied. All presented with esophageal aperistalsis, with low wave amplitude (~30 mmHg), in response to swallowing on standard manometry. There were nine men and one woman, with an age range of 31–71 years.

Patients with achalasia. Twenty-five symptomatic patients with achalasia (14 women and 11 men; 21–71 years of age) were also studied, with results obtained in 14 of these patients as previously reported (10). Symptom duration ranged from 5 to 144 mo (mean 42 mo). The diagnosis of achalasia was substantiated by radiological, endoscopic, and manometric criteria, including impaired relaxation of the lower esophageal sphincter (LES) (7, 26).

All patients met the following entry criteria: 1) no history of diabetes mellitus, alcoholism, collagen vascular disorders (scleroderma was excluded according to the criteria of the American Rheumatological Association (14)), or neurological disease; 2) no previous history of esophageal, gastric, biliary, or oncologic surgery; and 3) no previous endoscopic or surgical treatment for either GERD or achalasia.

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Table 1. Demographic and laboratory data

<table>
<thead>
<tr>
<th></th>
<th>Healthy Volunteers</th>
<th>Achalasia Patients</th>
<th>GERD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>14</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Male/female</td>
<td>9/5</td>
<td>11/14</td>
<td>1/9</td>
</tr>
<tr>
<td>Age, years (mean and range)</td>
<td>23(20–28)</td>
<td>47(21–71)</td>
<td>54(31–71)</td>
</tr>
<tr>
<td>Subjects with dysphagia (mean grade when present, 1–5)</td>
<td>0</td>
<td>25(3.9)</td>
<td>2(3)</td>
</tr>
<tr>
<td>Subjects with heartburn (mean grade when present 1–5)</td>
<td>0</td>
<td>3(1.3)</td>
<td>10(3.9)</td>
</tr>
<tr>
<td>Esophageal diameter, cm</td>
<td>n.p.</td>
<td>4.1 ± 0.3</td>
<td>2.5 ± 0.2</td>
</tr>
<tr>
<td>Esophageal pressure, mmHg</td>
<td>18 ± 2</td>
<td>29 ± 2</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>Wave amplitude, mmHg</td>
<td>64 ± 8</td>
<td>21 ± 4</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>Peristaltic waves, %</td>
<td>96 ± 2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>pH &lt;4/24 h (%)</td>
<td>n.p.</td>
<td>n.p.</td>
<td>31 ± 6</td>
</tr>
</tbody>
</table>

Esophageal diameter and pressure, wave amplitude, and peristaltic wave values are means ± SE. Normal values in our laboratory for esophageal diameter and pH are <2 cm and 5.2, respectively. GERD, gastroesophageal reflux disease; n.p., not performed.

Healthy controls. Fourteen volunteers (9 women and 5 men; 20–28 years of age) without esophageal symptoms served as the control group. Demographic and laboratory data of patients and controls are shown in Table 1. The research protocol was approved by the Vall d’Hebron Hospital Institutional Review Board (Comité de Ensayos Clínicos), and written informed consent was obtained from all participants before study.

Procedure

On separate days we performed a standard esophageal manometry test and assessment of esophageal tone in every patient. In patients with GERD, esophageal phasic and tonic activities were evaluated after treatment for at least 2 mo with 20–40 mg of omeprazole, with disappearance of active esophagitis lesions at endoscopy. Studies began in the morning after an overnight fast, and patients were without medications for at least 48 h previously.

Clinical assessment. All patients underwent complete history and physical examination. Special attention was paid to esophageal symptoms. Dysphagia and heartburn were assessed according to the frequency of occurrence using the following scores: 0, never; 1, less than once a month; 2, monthly; 3, weekly; 4, daily; and 5, with every meal or more than three times a day.

Radiological evaluation of the esophageal diameter. An esophagogram using a standard radiological method with barium contrast was obtained in every patient. The diameter of esophageal body 5 cm above the gastroesophageal junction was measured in the anteroposterior projection, and the highest value was recorded. A correction factor to obtain real esophageal diameter values from the diameter measured on the X ray films was used. We placed a radiopaque marker of known size (a coin) at the same distance from the X ray as the esophagus; then, by a simple equation, we calculated real esophageal diameter.

Esophageal manometry. Esophageal intraluminal pressures were measured using a four-lumen polyvinyl tube (0.9-mm ID each lumen), with its orifices spaced at 5-cm intervals along the distal portion of the tube. The lateral-opening manometric catheters were radially oriented and perfused continuously via a pneumohydraulic system. Respiration and swallowing were monitored using flexible bellows around the chest and neck, respectively. Studies were performed in the supine position after oral passage of the manometric tube.

Quantification of esophageal tone. To measure esophageal tone we used an electronic barostat that measures the volume of air within a bag maintained at a constant preselected pressure level, as previously described (1). The barostat was connected by a double-lumen polyvinyl tube (French no. 12, Argyle, Sherwood Medical, St. Louis, MO) to an ultrathin polyethylene bag, 5 cm in length, with a maximum diameter of 12 cm and 120-ml capacity. Three manometric catheters (placed at 5, 10, and 15 cm proximal to the middle point of the barostat bag) were attached to the connecting tube and served to record esophageal phasic activity (Fig. 1). To quantify esophageal tone, the barostat bag was inserted orally and positioned 5 cm above the LES (previously located by manometry). Participants were placed in a 30% recumbent position, and esophageal tone and phasic activities were recorded graphically on paper polygraph (model 1600, MFE, Salem, NH).

The specific procedure to measure esophageal basal tone and compliance was as follows. Using the pressure-selection dial of the barostat, we gradually increased intrabag pressure by 2-mmHg stepwise increments every 2 min up to 20 mmHg (or whenever participants experienced discomfort). Simultaneously, intrabag volume was continuously monitored. Esophageal tone in response to a nitric oxide (NO) donor was also evaluated as follows. Intrabag pressure was maintained with the barostat at 7 mmHg, and amyl nitrite (0.5 ml) was inhaled for 45 s to assess the effect of a smooth muscle relaxant on esophageal tone. Simultaneously, changes in intraesophageal balloon volume were recorded. Pulse rate was measured before and at the end of amyl nitrite inhalation.

Data Analysis

Esophageal manometry. Resting LES pressure was determined by the station pull-through technique using intragastric pressure as the zero reference. The means ± SE of the eight values obtained during two consecutive pull-throughs of the four-lumen catheters were calculated. Esophageal peristalsis was assessed after a minimum of ten 5-ml water swallows.

![Fig. 1. Diagram of the esophageal barostat and attached manometric catheters allowing simultaneous recording of tonic and phasic esophageal motor activity.](http://ajpgi.physiology.org/DownloadedFrom)
Esophageal tone at a minimal distending pressure. Esophageal tone was quantified at rest as the intraballoon volume obtained at the lowest distending pressure (2 mmHg). This value represents the resistance of the esophageal wall to initial stretch by a minimal intraluminal distending pressure.

Esophageal compliance. A compliance curve (volume vs. pressure) was constructed. Intrabag volume during each pressure step was averaged. Volumes at each pressure level were corrected for air compressibility using Boyle’s law \((P_1V_1 = P_2V_2)\).

Esophageal tone in response to amyl nitrite. In this test we measured the maximal intrasophageal volume for 1 min immediately after amyl nitrite inhalation. The change was calculated as the difference between this value and the basal value (average of intrasophageal volume during the 5-min period preceding the stimulus). It was expressed as the change in esophageal diameter induced by the stimulus. The esophageal diameter was calculated assuming a cylindrical shape for the intrasophageal balloon and knowing in each case the intraballoon volume \((v)\) and the balloon length \((l)\) (constant: 5 cm). Thus the formula is as follows

\[
\text{esophageal diameter} = \frac{v}{\sqrt{\frac{1}{\pi} \times 2}}
\]

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. To establish possible correlations we performed linear regression analysis. \(P < 0.05\) was considered significant.

RESULTS

Demographic and Laboratory Data

Demographic and laboratory data for study participants are shown in Table 1. All GERD patients complained of heartburn, but only two manifested dysphagia. In contrast, all achalasia patients complained of dysphagia and only three had mild heartburn. The esophageal diameter on the esophagram was significantly larger in achalasia patients (4.1 ± 0.3 cm) than in GERD patients (2.5 ± 0.2 cm). All but one achalasia patient had an esophageal diameter >2 cm. As expected, esophageal manometry showed that resting LES pressure was significantly lower in GERD (7 ± 1 mmHg) and higher in achalasia (29 ± 2 mmHg) compared with healthy control values (18 ± 2 mmHg, \(P < 0.05\)). Esophageal wave amplitude during swallowing was markedly lower for both groups of patients (10 ± 2 and 21 ± 4 mmHg for GERD and achalasia patients, respectively) compared with healthy controls (64 ± 8 mmHg, \(P < 0.05\)). Esophageal peristaltic activity during swallowing was observed in none of the patients (GERD and achalasia).

Esophageal Tone at a Minimal Distending Pressure

Esophageal tone at a minimal distending pressure (intrasophageal volume at 2 mmHg distending pressure) was similar in all three groups of subjects (4.1 ± 0.7, 3.8 ± 0.7, and 4.2 ± 1.2 ml for healthy, GERD, and achalasia groups, respectively).

Esophageal Compliance

Esophageal compliance was increased to a similar extent in patients with GERD-related aperistalsis and achalasia. Thus, compared with healthy control values, larger volumes were obtained at similar distending pressures, as shown by Fig. 2. Esophageal extension ratio was significantly increased (\(P < 0.05\) vs. healthy volunteers) in the two groups of patients with aperistalsis (1.9 ± 0.2, 3.0 ± 0.2, and 3.1 ± 0.3 for healthy, GERD, and achalasia groups, respectively). In achalasia patients, as well as in GERD-aperistalsis patients, compliance (volume/pressure relation) did not show the plateau observed in healthy controls, suggesting that even greater volumes could be obtained by increasing pressure above the tested values.

Esophageal Tone in Response to an NO Donor

In GERD patients, amyl nitrite inhalation induced a smaller esophageal relaxation than in normal subjects. The opposite reaction occurred in patients with achalasia; esophageal relaxation tended to be greater, although considerable variations were observed, and no statistical differences were achieved compared with healthy control values. Calculated esophageal diameter increased significantly less in the GERD group (0.4 ± 0.1 cm) than in the healthy (0.9 ± 0.2 cm) or achalasia groups (1.3 ± 0.4 cm) \((P < 0.05)\) (Fig. 3). Drug inhalation induced a similar increase in heart rate in the healthy and achalasia groups [26 ± 3 and 30 ± 6 beats/min (bpm), respectively] and a smaller increase in the GERD group (14 ± 2 bpm). Both the esophageal relaxation response and the tachycardia in response to amyl nitrite lasted <100 s.

![Graph showing esophageal compliance](http://ajpgi.physiology.org/)

Fig. 2. Esophageal compliance was similarly increased in patients with gastroesophageal reflux disease (GERD)-related aperistalsis or achalasia. Compared with healthy volunteers, higher volumes were obtained at similar distending pressures in GERD and achalasia patients. Values are means ± SE. \(P < 0.05\) vs. healthy group for cumulative values and slope.
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Fig. 3. Esophageal diameter increase (in cm) measured by the barostat in response to amyl nitrite inhalation. Values are means ± SE. *P < 0.05.

Relationship Between Esophageal Diameter, Esophageal Compliance, and Esophageal Relaxation Induced by Amyl Nitrite Inhalation

In patients with achalasia, esophageal diameter (measured on the esophagogram) was directly related to esophageal compliance whether expressed as the extension ratio \( r = 0.58; P = 0.02 \) or as the maximal intrabag volume obtained in each patient at the maximal distending pressure \( r = 0.71; P = 0.003 \). However, in patients with GERD-related aperistalsis no significant correlation was identified.

The esophageal relaxation induced by amyl nitrite in both GERD-related aperistalsis and achalasia was not directly related to the diameter of the esophagus measured on the swallow esophagogram. There was also no correlation between the magnitude of the relaxatory response and esophageal compliance (calculated as the extension ratio).

DISCUSSION

Motor disturbances of the esophagus are customarily evaluated and classified according to the manometric pattern of phasic pressure activity of the esophageal body. Tonic activity of the esophageal wall has been largely ignored probably on account of the absence of an appropriate methodology for quantifying esophageal tone. Adaptation of the barostat technology to the esophagus (10, 15, 16, 20, 22) makes it possible to quantify esophageal tone. Thus Mayrand and Diamant (15) were first to demonstrate “in vivo” that active tone is exerted by the muscular wall of the human esophagus and that tonic activity can be inhibited by smooth muscle relaxants. Later, the same group (5) as well as our own (10) demonstrated that esophageal tonic activity is abnormal in patients with achalasia.

In the present study, we examined esophageal tonic activity in two groups of patients with esophageal aperistalsis of different origin, GERD-related aperistalsis and achalasia, hypothesizing that tonic activity, unlike phasic activity, might differ between these two conditions. In fact, our findings show normal esophageal tone at a minimal distending pressure (2 mmHg) with similarly increased esophageal compliance in both groups of patients when compared with healthy control values. We also confirmed the findings (5, 10) that some patients with achalasia have an exaggerated relaxatory response of the esophageal tone to amyl nitrite inhalation, although in the present study achalasia patients as a group did not show a statistically significant increase of esophageal diameter in response to the nitrite. In contrast, patients with GERD-related aperistalsis show a relaxatory response to amyl nitrite even smaller than that of healthy volunteers. It is somewhat remarkable that intrabarostat volumes obtained in achalasia patients at the minimal distending pressure were rather small for the existing esophageal diameters; this could be explained by the presence of intraesophageal positive pressure in most cases, as well as the necessity of greater pressures to expand an enlarged esophageal wall. At this point, we have to remember that the achalasia population we studied was quite heterogeneous and that esophageal diameters varied greatly among them. Thus esophageal tone (mainly esophageal compliance) could be different depending on whether the esophagus is dilated or not.

Thus the different responses to amyl nitrite between achalasia and GERD-related aperistalsis support that the mechanism underlying disappearance of phasic contractile activity in the esophagus is different between these two conditions. In fact, why two such different diseases such as GERD (at its end stage) and achalasia lead, in some cases, to a similar disappearance of peristalsis at manometry is enigmatic. In most cases, there is no difficulty in distinguishing achalasia from severe esophageal motor derangement caused by GERD, but also it is true that in ~5% of the patients with GERD 100% failed primary peristalsis is observed on esophageal manometry (13). It has been suggested that the key pathogenetic mechanism in achalasia is the absence of inhibitory input, which could explain both the presence of a hypertonic LES and esophageal body dysmotility. Thus Sifrim et al. (21), by creating an artificial high-pressure zone, demonstrated that deglutitive inhibition normally observed in the esophageal body of healthy subjects is absent in achalasia patients. Moreover, because NO is crucial in motor esophageal inhibition and NO synthase is lacking in the achalasic esophagus (17), this could be related to the heightened relaxatory response to an NO donor observed in our study. The ability of NO donors to decrease LES pressure and to improve symptoms in achalasia patients has been known for many years, and drugs such as isosorbide dinitrate have been used for therapeutic purposes (4). Radiological observations (9) that amyl nitrite inhalation increases LES diameter in idiopathic achalasia but not in pseudoachalasia due to...
tumor infiltration of the esophagus may be even more useful in differential diagnosis.

On the other hand, absence of excitatory input in GERD could explain LES hypotonicity and esophageal body hypomotility (12). Biancani et al. (3) have demonstrated that induction of experimental esophagitis in the cat by esophageal perfusion of 0.1 HCl results in a significant reduction of the active component of LES tone; it has been also suggested (2) that either the intracellular calcium stores or the release mechanisms that mediate maintenance of tone and contraction response to acetylcholine may be damaged. Either way, absent peristalsis or extreme hypomotility, the manometric picture of aperistalsis would be similar. Whether end-stage GERD in its aperistaltic form behaves physiologically like an achalasia or whether some cases of achalasia are related pathogenically to GERD remains speculative, but it has been considered that in some cases achalasia may develop in the setting of underlying GERD (24).

Esophageal compliance seems to depend on three important mechanisms: active contractility, an “in-parallel” elastic component, and an “in-series” elastic component (18). We speculate that the similar alteration in compliance observed in both GERD-related and achalasia aperistalsis could result from alterations of the same or different compliance mechanisms. Thus it is conceivable that in achalasia compliance increase results from alteration of the in-parallel elastic component because of progressive esophageal dilatation; this hypothesis is supported by the fact that in our achalasia patients esophageal diameter was increased and correlated with esophageal compliance. In GERD patients, compliance could be increased because of alteration in the active contractile component, which matches with our findings of normal esophageal diameter on X-rays, and absent correlation between esophageal diameter and compliance. Another plausible hypothesis could be that esophageal peristaltic dysfunction in our GERD patients was due to fibrosis resulting from chronic inflammation, but then esophageal compliance should be decreased rather than increased. Thus esophageal compliance behavior does not necessarily depend on the thickness of the esophageal wall, which may be increased in both achalasia and GERD (6, 8).

The increased esophageal relaxation in response to amyl nitrite observed in some achalasia patients could have at least two possible explanations, a normal response in a more compliant esophagus or a hypersensitive response to exogenous NO. With regard to the first possibility, increased relaxation does not appear to be simply related to the mechanical properties of the esophagus, because esophageal relaxation was significantly different between achalasia and GERD-related aperistalsis even though esophageal compliance was similarly increased. However, in achalasia patients the magnitude of esophageal relaxation could be increased due to their larger esophageal diameter. With regard to the second possibility, it is known that NO is a major inhibitory neurotransmitter participating in the control of esophageal motility (25). We have previously demonstrated that NO synthase is absent in the gastrolesophageal junction of patients with achalasia and, furthermore, that esophageal muscle strips obtained from achalasia patients relax in response to sodium nitroprusside (another NO donor) (17). Therefore, it is possible that the increased relaxation in response to amyl nitrite is due to the basal absence of NO-related inhibition.

Regarding the decreased relaxatory response to NO in GERD, this might be secondary to an absence of inhibition of calcium release from intracellular stores in response to increased cGMP caused by acid-induced damage of calcium-handling mechanisms (2).

In summary, esophageal compliance is similarly impaired in GERD-related aperistalsis and in achalasia but relaxatory responses to an NO donor are different. Relaxation is decreased in GERD-related aperistalsis and normal, or even increased, in achalasia. These pharmacological responses reflect the different pathogenesis of the manometric finding of aperistalsis in these two conditions.

Part of this work was presented at the annual meeting of the American Gastroenterology Association, May 1996, in San Francisco, CA.

REFERENCES