Diminished mechanosensitivity and chemosensitivity in patients with achalasia

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Submitted 5 March 2003; accepted in final form 3 July 2003

Brackbill, Stephen, Guoxiang Shi, and Ikuo Hirano. Diminished mechanosensitivity and chemosensitivity in patients with achalasia. Am J Physiol Gastrointest Liver Physiol 285: G1198–G1203, 2003; 10.1152/ajpgi.00102.2003.—The pathogenesis of achalasia involves the degeneration of enteric and autonomic nervous systems with resultant effects on esophageal motility. The neural degeneration could affect visceral sensation in achalasia. The aim of this study was to examine mechanosensitivity and chemosensitivity in patients with achalasia. Perceptual responses to esophageal distension and acid perfusion were assessed in nine achalasia patients and nine healthy subjects. Mechanosensitivity was evaluated using a barostat with a double-random staircase distension protocol. Responses were graded as follows: 0, no sensation; 1, initial sensation; 2, mild discomfort; 3, moderate discomfort; and 4, pain. Mechanosensitivity was graded along a visual analog scale after perfusion of saline and 0.1 N HCl. Barostat pressure-volume relationships were used to report esophageal body compliance. Barostat pressures for initial sensation and mild discomfort were not significantly different for patients and controls. The pressures for moderate discomfort (37.9 ± 3.5 vs. 25.7 ± 2.4 mmHg; P < 0.05) and pain (47.8 ± 2.3 vs. 32.2 ± 3.5 mmHg; P = 0.002) were significantly higher in achalasias than controls. Seven of the eight achalasia patients never reached pain thresholds at the maximum distension pressure (50 mmHg). Sensation to acid perfusion was significantly lower in achalasias compared with controls (2.2 ± 1.2 vs. 6.7 ± 1.7 cm; P < 0.05). Compliance was significantly increased in patients with achalasia compared with controls. We conclude that both mechanosensitivity and chemosensitivity are significantly diminished in achalasia patients compared with controls. Also, initial sensation and pain sensation are differentially affected in achalasias. These findings suggest that neuropathic defects in achalasia may manifest themselves in visceral sensory and motor dysfunction.

motility; esophageal motility disorders; visceral sensitivity; noncardiac chest pain

ACHALASIA IS AN ESOPHAGEAL motility disorder characterized histopathologically by degeneration of ganglia of the myenteric plexus. The pathology may follow a continuum ranging from inflammation of the myenteric plexus with neuronal degeneration to complete ganglionosis (7). Loss of neurons within the dorsal motor nucleus and degenerative changes of vagal nerve fibers have also been described. The resulting motor deficits have been well characterized by manometry and include aperistalsis of the esophageal body and failure of the lower esophageal sphincter (LES) to relax with swallowing although manometric variability has been described (10). Functional obstruction of the LES leads to impaired esophageal emptying that is manifest clinically as progressive dysphagia, regurgitation, and weight loss. Serious complications of retained material in the esophagus exist, including stasis mucosal injury, chronic aspiration, and delayed transit of nutrients and medications.

In contrast to the pathophysiology of motor dysfunction, little is known about the integrity of esophageal sensory perception in patients with achalasia. Afferent innervation of the esophagus and conscious perception of sensation depends on vagal and spinal afferent fibers communicating with the central nervous system (6, 9). Although spinal afferents convey visceral pain perception, vagal afferents may modulate pain perception (3, 6). Degeneration of the autonomic and enteric nervous systems could lead to impaired visceral sensation in achalasia. Circumstantial evidence for such a functional impairment comes from the observation that patients with achalasia are often poorly cognizant of either retained food in the esophagus or esophageal distension. Furthermore, uncontrolled studies have reported that achalasia patients have diminished perception of acid reflux events both before and after treatment of their achalasia (20). In contrast, however, chest pain does occur in patients with achalasia with some frequency. It is most commonly found in patients of younger age and patients with shorter duration of disease, suggesting that esophageal visceral pain may be less common with increasing neurodegeneration (3).

A small number of studies has directly examined esophageal sensation in achalasia. Two previous studies have evaluated sensation using intraesophageal balloon distension (4, 16). Both studies found impairment of sensation in achalasia patients. However, these studies employed fixed-volume, latex balloons. As a result of the technique, the amount of pressure stimulus applied to the esophageal wall varies depending upon the degree of dilatation secondary to the underlying disease state. Therefore, this method is of limited validity in achalasia patients, where esophageal

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geal dilatation is common. The electronic barostat combined with an infinitely distensible polyethylene bag offers the ability to administer a constant pressure stimulus to the gastrointestinal tract independent of luminal diameter (5, 21). A study by Fass et al. used a modiﬁed acid-perfusion test as a means to test chemosensitivity in normal patients (5). This study also employed a modiﬁed acid-perfusion test as a means to test chemosensitivity in normal patients. Chemosensitivity in achalasia patients has not been studied previously.

Alterations in phasic contractile activity of the esophagus are a hallmark of achalasia where esophageal body contractions, if present at all, are usually of very low amplitude. Recent studies suggest that tonic activity is also abnormal in achalasia patients. The balance of myogenic and excitatory and inhibitory neurogenic inﬂuences on esophageal smooth muscle deﬁnes this tonic activity. Tonic activity may be indirectly determined by measurements of compliance. The barostat has been effectively used to measure esophageal tone and compliance, as it allows deﬁnition of pressure and volume relationships (14). A previous study by Gonzalez et al. (8, 11) using a barostat apparatus demonstrated increased esophageal compliance in untreated achalasia patients.

The present study was designed to evaluate esophageal mechanosensitivity and chemosensitivity in achalasia using a barostat. Both types of visceral sensitivity were diminished in patients compared with healthy subjects. In addition, compliance was notably increased in achalasia.

METHODS

Study population. Ten achalasia patients and 11 healthy controls were enrolled in the study. One achalasia patient and one control were unable to tolerate passage of the barostat catheter and could not be evaluated. One control study was terminated after successful placement of the catheter because of a software problem that prohibited running the protocol. One achalasia patient successfully completed the acid perfusion test but developed nausea during the study and could not complete the protocol. Nine achalasia patients were on antidepressant medications that might affect the low-elastance portion of the pressure-volume curve according to the recommendations of Whitehead and Delvaux (21). At volumes of <250 ml, the bag itself did not contribute signiﬁcantly to resistance to inﬂation and thus in vivo barostatic measurements in this range should reﬂect the mechanical properties of the surrounding tissues.

Acid perfusion test. After completion of the distension protocol, the barostat catheter was removed. A standard eight-channel manometry catheter with an infusion port was
results, with one achalasia patient unable to tolerate the barostat portion of the protocol. The median age of the achalasia patients was 50 (range 20–66 yr) compared with the control group where the median age was 37 (range 25–49 yr). The treated achalasics who were studied had a median esophageal diameter of 2.0 cm (range 1.2–3.7) at a point 10 cm above the gastroesophageal junction. The median elapsed time between the diagnosis of achalasia and entry in the study was 21 mo (range 5–43). The median time post-Heller myotomy for patients was 615 days (range 79–928).

Esophageal distension. Using the double-random staircase distension protocol, each subject underwent two full distension sequences. Each sensation threshold was determined by taking the average of the values for each sequence. No significant difference between achalasics and controls was found in mean bag pressures for initial sensation (16.9 ± 2.7 vs. 11.7 ± 0.8 mmHg) or at mild discomfort (23.6 ± 2.8 vs. 19.3 ± 1.6 mmHg), respectively (Fig. 2). The mean pressures for moderate discomfort (37.9 ± 3.5 vs. 25.7 ± 2.4 mmHg, \( P < 0.05 \)) and pain (47.8 ± 2.3 vs. 32.2 ± 3.5 mmHg, \( P = 0.002 \)) were significantly higher in achalasics than controls. Pain thresholds are likely underestimated, as seven of the eight achalasia patients failed to reach pain thresholds at the maximum distension pressure (50 mmHg). In addition, the entire pressure-sensation curve for the achalasia patients was compared with that for the controls using two-way ANOVA and found to be statistically significant (\( P < 0.01 \)). The maximum barostat volume used in any patient or control subject was 200 ml, which was within the low-elastance portion of the pressure-volume curve for the barostat bag measured ex vivo (Fig. 1).

Fig. 1. Barostat bag compliance measured ex vivo. The pressure-volume curve demonstrates operation in the low-elastance portion for operating volumes <250 ml. In this range, the bag was essentially infinitely compliant, assuring that barostat measurements reflect the mechanical characteristics of the surrounding tissue and not the bag itself.

Introduction transnasally. This catheter was advanced in the proximal stomach, and the LES was located again using the station pull-through technique. The infusion port was then situated 10 cm above the proximal extent of the LES. This port was used to instill 0.9 N saline at 10 ml/min for 2 min using a standard intravenous infusion pump. Without the patient’s knowledge, the saline was changed to 0.1 N HCl and infused at 10 ml/min for 10 min. This procedure has been described previously (18). Patients were asked to rate their sensation using a previously validated verbal descriptor scale (5). This scale is composed of a 20-cm line with 12 verbal descriptors spaced along the axis (no sensation, faint, very weak, weak, weak, very mild, mild, moderate, barely strong, strong, intense, very intense, extremely intense). Patients made a single mark along the line at the point corresponding to their sensation. The distance in centimeters from the “No sensation” point, in centimeters, was used as the sensation score.

Data analysis and statistics. For the double random staircase distension protocol, each subject underwent two full distension sequences. The pressure was determined for each sensatonal level (no sensation, initial sensation without discomfort, mild discomfort, moderate discomfort, and pain) in each of two distension sequences in every individual. In seven achalasics who failed to reach pain at maximal distension pressure (50 mmHg), 50 mmHg was used. The sensation threshold was the mean of the values of two sequences. Compliance was calculated by dividing volume by pressure. For the modified Bernstein test, statistical comparisons were made comparing the visual analog sensation scores (measured in cm) between the patient controls and achalasia patients. Data are presented as median with interquartile range or mean \( \pm \) SE, as specified. Patient and control data using means were compared with two-tailed, Student’s \( t \)-test. \( P \) values \(<0.05 \) were considered significant.

RESULTS

Patient characteristics. Nine achalasia patients (7 male) and nine controls (5 male) are included in the
Esophageal compliance and secondary esophageal contractions. Compliance was increased significantly in patients with achalasia compared with controls ($P < 0.05$; Fig. 3A). In addition, achalasia patients showed increased heterogeneity in compliance compared with controls (Fig. 3B). The frequency of secondary esophageal contractions both proximal and distal to the barostat bag did not differ significantly between the patients and controls.

Acid perfusion test. A significant difference in chemosensitivity was found between achalasia patients and controls using the modified acid perfusion test. Six of nine control subjects and four of eight achalasia subjects reported symptoms during the test. The symptom intensity score was based on subject responses to the verbal descriptor scale. There was a significant difference in mean intensity rating of symptoms for achalasia patients ($2.2 \pm 1.2$ cm) vs. controls ($6.7 \pm 1.7$ cm; $P < 0.05$; Fig. 4).

DISCUSSION

This study demonstrated significant differences in esophageal visceral sensitivity and compliance in achalasia patients compared with healthy controls. These findings have not been demonstrated previously using barostat methodology. Results from the present study suggest that patients with achalasia have higher thresholds for painful, distension-induced sensation than normal controls. Although the ability to sense mild stimuli was similar, achalasia patients reported moderate discomfort and pain much later than controls, with seven of the eight achalasic patients failing to reach pain thresholds at the maximum distension pressure.

Two earlier studies using latex balloons have suggested that achalasia patients may have decreased esophageal sensation to latex balloon distension (4, 15). Esophageal dilation in achalasia poses a significant technical limitation in the interpretation of protocols using such fixed-volume stimuli. The Barostat methodology used in the present study offers the ability to maintain a constant pressure stimulus that is independent of luminal diameter. This distinction of...
fers an important advantage in assessment of mech-
anosensitivity in achalasia. A recent study reported
diminished esophageal sensory responses to electrical
stimulation in a cohort of patients with varied esoph-
geal motility disorders that included achalasia (17).
This form of visceral stimulus should also be una-
fected by esophageal distension and supports the con-
cept of altered sensitivity in achalasia patients.

Although barostat modality is better suited for study-
ing variable esophageal diameters, marked esophageal
dilation would necessitate the utilization of a larger-
capacity Barostat bag. This presents a technical chal-
lenge in intubating the larger bag in the esophagus.
Post-surgical patients with mild degrees of esophageal
dilatation were therefore selected as the study popula-
 tion. An argument could be made that the surgical pro-
cedure may alter the sensation of the esophagus. This is
unlikely for several reasons. First, the laparoscopic ap-
proach minimizes effects on the thoracic esophagus and
is unlikely for several reasons. First, the laparoscopic ap-
proach minimizes effects on the thoracic esophagus and
is unlikely to directly affect the esophagus at the point of
study (i.e., 10 cm above the LES). All patients were
operated on by one of two surgeons, following a standard
study. Heterogeneity in visceral sensitivity in acha-
lasia patients that ranges from increased noncardiac
chest pain to diminished visceral sensitivity may be re-
lated to varying degrees of neurodegeneration.

A possible explanation of the observed decrease in
sensation in achalasia relates to central processing of
visceral stimuli. Conscious sensation of pain requires
sensory transmission from the esophagus to the central
nervous system. Visceral pain in the distal esophagus is
processed in different parts of the cerebral cortex than
somatic pain (1). It is possible that patients with achala-
sia have been conditioned by chronic esophageal disten-
sion and are therefore desensitized to otherwise noxious
stimuli. Additionally, anxiety or stress has in prior stud-
ies been demonstrated to increase sensitivity to visceral
stimuli (13). Because achalasia patients have undergone
a number of procedures, including esophageal manome-
try, before their involvement in the study, this may have
reduced their level of anxiety and therefore symptom
perception during the study protocol compared with
healthy controls. Finally, achalasia patients and controls
might perceive secondary esophageal contractions from
esophageal distension differently. However, no difference
in frequency of contractions was observed due to the high
frequency of spontaneous contractions present in the
achalasia patients. Nevertheless, in light of the complex-
ity of central processing of visceral sensation, further
investigation of responses to visceral and somatic stimuli
are warranted to determine the significance of the findings.

Table 1. Achalasia patient characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age, yr</th>
<th>Esophageal Diameter</th>
<th>Postoperative Day</th>
<th>Months Since Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>42</td>
<td>3.2</td>
<td>137</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>58</td>
<td>2.0</td>
<td>642</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>66</td>
<td>2.8</td>
<td>615</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>50</td>
<td>3.7</td>
<td>198</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>20</td>
<td>1.7</td>
<td>791</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>46</td>
<td>1.7</td>
<td>285</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>51</td>
<td>1.2</td>
<td>756</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>22</td>
<td>2.5</td>
<td>928</td>
<td>43</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>55</td>
<td>1.9</td>
<td>79</td>
<td>5</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td>2.0</td>
<td>615</td>
<td>21</td>
</tr>
</tbody>
</table>

M, male; F, female.
Previous studies in the opossum suggest that two distinct pathways mediate esophageal sensation. Physiological sensations are mediated largely by vagal afferents, whereas nociceptive sensations are primarily mediated by splanchnic afferents. In addition, different thresholds of stimuli appear to use disparate neural pathways. Low-intensity stimuli may activate different afferent pathways from noxious stimuli. In the opossum, studies have shown that splanchnic afferents demonstrate low- or high-threshold responses to balloon distension (19). The results from the present study suggest that these two systems may be differentially affected in patients with achalasia. With the small sample size investigated, however, a smaller but significant difference in sensation of low-intensity stimuli could have been missed.

Another important finding in this study is that esophageal compliance is increased significantly in patients with achalasia. This finding is similar to that reported in preoperative achalasia patients by Gonzalez et al. (8). One lingering question in that study is whether the observed difference in compliance was the result of the pathophysiology of achalasia itself or if it was a byproduct of the esophageal dilatation in the study population. An increase in the radius of the esophagus may lead to an increase in wall tension, independent of any substantive changes in muscle characteristics. Because the present study included only postmyotomy achalasia patients with mild esophageal dilatation, dilatation alone is unlikely to account for the observed differences in compliance. Interestingly, a recent study using endoscopic ultrasound to evaluate patients with achalasia has demonstrated that they have increased esophageal wall thickness compared with controls (12). Because thickness is inversely proportional to wall tension, this finding would tend to cause decreased tension. Muscle hypertrophy may represent a compensatory mechanism in an effort to maintain constant wall tension despite dilatation.

In summary, this study demonstrated significant differences in esophageal sensitivity and compliance in achalasia patients compared with controls. Deficits in sensitivity were demonstrated for both chemosensitivity and mechanosensitivity. Compliance of the esophagus was significantly higher for achalasia patients, although resting tone was similar. This is the first study using an electronic barostat to demonstrate these findings. The findings may explain the observations of poor perception of esophageal distension and retained esophageal contents and acid reflux events by achalasia patients. The poor visceral sensation in achalasia patients may lead to delayed presentations and thus place patients at greater risk for significant complications of aspiration or gastroesophageal reflux.

REFERENCES