Diminished mechanosensitivity and chemosensitivity in patients with achalasia

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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. Chemosensitivity 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 achalasics 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 achalasics 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 achalasics. These findings suggest that neuropathic defects in achalasia may manifest themselves in visceral sensory and motor dysfunction.

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 ganglioneuroma (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 deglutition 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 (5, 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...
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 the barostat to examine the effects of acid exposure on esophageal mechanosensitivity in normal subjects (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 and nine healthy controls were included in the final analysis. All achalasia patients had been treated surgically with laparoscopic Heller myotomy and Dor anterior fundoplication. After surgery, all patients underwent barium swallow to evaluate esophageal diameter. Patients were excluded who had an esophagus greater than three times the upper limit of normal (>3.9 cm). Other exclusion criteria included previous thoracic surgery, peptic ulcer disease, diabetes mellitus, or history of autonomic or peripheral neuropathy. Before study, patients and controls were instructed to fast at least 8 h and not to take any medications known to affect the muscle tone or gastric pH (e.g., nitrates, β-blockers, calcium channel blockers, nitrates, proton pump inhibitors, antacids). No patients were on antidepressant medications that might affect visceral sensitivity. The Institutional Review Board of Northwestern Memorial Hospital and Northwestern University approved the study protocol. Informed consent was obtained from all patients before enrollment in the study.

*Barostat protocol.* A polyethylene bag was constructed and attached to a custom-made 12-channel manometry catheter (Dent-Sleeve, Bowden, South Australia) using nylon suture. Once properly attached, the bag had a cylindrical shape and measured 6 cm long and 7 cm in maximum diameter, with a maximum volume of 250 ml. The catheter had a large central lumen for bag inflation, as well as standard water infusion ports to measure intraluminal pressure. Twelve infusion ports (5 ports distal to the bag and 7 ports proximal) were arranged 1–3 cm apart. Swallowing was monitored by a submental electromyelogram (EMG) recording obtained using two disc electrodes positioned under the chin and a grounding patch attached to the side of the subject’s neck. Manometry and swallowing EMG recording channels were connected to a 16-channel computerized polygraphy (Neomedix Systems; Warriewood, New South Wales, Australia) set at a sampling frequency of 40 Hz for pressure and 200 Hz for EMG. The infusion ports were connected to an external pressure transducer (Medex, Hillard, OH), and the analog signals from the transducer were amplified and recorded on a computer polygraph set. The transducer had a sampling frequency of 40 Hz, and signals were processed using Gas- tromac software (Neomedix Systems). With the bag fully distended, the catheter was placed transepithelially and advanced in the proximal stomach. The location of the LES was determined by station pull-through technique. The bag was positioned 10 cm above the proximal extent of the LES, and the catheter was fastened securely with tape, as previously described (2). All subjects were studied in the supine position.

A computer-controlled electronic barostat device (Dis- tender Series II; G&J Electronics, Toronto, Ontario) was used to rapidly inflate the bag to the desired pressure. The barostat was connected to an interactive, subject-operated device capable of recording patient responses. The device contains five buttons labeled as follows: 0, no sensation; 1, sensation without discomfort; 2, mild discomfort; 3, moderate discomfort; and 4, pain. This scale has been used for similar testing of esophageal sensation (5). An interactive computer program (Protocol Plus Deluxe for Windows 3.81R; G&J Electronics) executed a preprogrammed distension sequence. A “double random staircase” protocol for threshold tracking was chosen to minimize anticipation bias (21). Distensions lasted 30 s, followed by 30 s of rest. To minimize contact with the researcher, a signal on the control panel indicated the end of each distension period and prompted the subject to record a response. Distensions began with a pressure of 8 mmHg and increased by 2-mmHg increments to a maximum of 50 mmHg or the onset of pain. A “panic button” on the recording device allowed the subject to stop the distension and deflate the bag at any time. Frequency and amplitude of secondary esophageal peristalsis were determined. Secondary peristalsis was considered present if esophageal contraction activity >30 mmHg was detected in at least two channels proximal to the distending balloon. The barostat pressure and volume were also simultaneously recorded by the computerized polygraph (Neomedix Systems) set at a sampling frequency of 40 Hz.

The biomechanical properties of the bag were determined by pressure-volume measurements with the bag outside of a subject (ex vivo; Fig. 1). This was done to ensure operation in 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...
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result in lower residuals. The median compliance measured ex vivo was 200 ml, which was within 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.

introduced 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, 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. 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).

RESULTS

Patient characteristics. Nine achalasia patients (7 male) and nine controls (5 male) are included in the

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).
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-

Fig. 3. Pressure volume relationships for achalasia patients and controls during Barostat testing. A: higher volumes were required to achieve the same Barostat pressure in achalasia patients compared with controls. B: using the pressure/volume quotient as a measure for compliance, achalasia patients demonstrated higher compliance values compared with controls, although there was significant heterogeneity in the individual values. In B, each point represents the mean value with SE for an individual subject throughout the distension protocol.

Fig. 4. Chemosensitivity as determined by modified Bernstein testing, demonstrating significantly decreased sensitivity in achalasia patients compared with controls. The sensation score is based on a 20-point verbal descriptor visual analog scale that ranged from no sensation to extremely intense sensation ($^*P < 0.05$).
fers an important advantage in assessment of mechanosensitivity in achalasia. A recent study reported diminished esophageal sensory responses to electrical stimulation in a cohort of patients with varied esophageal motility disorders that included achalasia (17). This form of visceral stimulus should also be unaffected by esophageal distension and supports the concept of altered sensitivity in achalasia patients.

Although barostat modality is better suited for studying variable esophageal diameters, marked esophageal dilation would necessitate the utilization of a larger-capacity Barostat bag. This presents a technical challenge in intubating the larger bag in the esophagus. Postsurgical patients with mild degrees of esophageal dilatation were therefore selected as the study population. An argument could be made that the surgical procedure may alter the sensation of the esophagus. This is unlikely for several reasons. First, the laparoscopic approach 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 procedure for laparoscopic Heller myotomy and Dor fundoplication. In eight of the nine subjects studied, the myotomies extended <6 cm proximal to the squamocolumnar junction, and the vagal nerve was isolated and spared during each procedure. This information was obtained from operative reports for every patient. It should be noted, however, that in one of the achalasia patients the myotomy was extended 8 cm above the squamocolumnar junction for technical reasons. Further studies to compare achalasia patients before and after surgical intervention would be useful to determine whether decompression of functional obstruction or the surgical technique has an effect on esophageal sensation in achalasia.

This study also demonstrated significant impairment in esophageal chemosensitivity in achalasia. Achalasia patients were less likely than healthy controls to report symptoms on the modified acid perfusion test. When patients did report symptoms, they were less intense than those reported by control subjects. Overall, the percentage of patients reporting symptoms during the acid perfusion test was higher in both groups than the rates found in other studies. There are three possible explanations for this finding. First, it is possible that, in the control group, there were a disproportionate number of patients with gastroesophageal reflux disease. This is unlikely, however, as each patient was asked to report any reflux symptoms on a survey before participation, and none reported more than occasional reflux symptoms. Another explanation is that the test, as performed, was overly sensitive at the expense of specificity. Patients were asked to rate the intensity of any symptoms that they experienced, not strictly limited to substernal chest pain or burning. This may explain the finding of sensitivity to acid exposure in the controls. The increased responsiveness of the test, however, would apply equally to achalasia patients and controls and therefore would not affect the overall findings. A third possible explanation is that the preceding barostat distension sensitized the mucosa by inducing a mechanical disruption of the squamous epithelial barrier. Again, such an effect should have affected both the achalasia patients and controls, although it could account for the higher symptom reporting compared with prior studies of acid perfusion.

One potential source of bias in this study lies in the study population. In the cohorts studied, there was a 13-yr difference in median age between the two groups. It is possible that some of the observed difference in sensitivity is the result of the aging process, as esophageal sensation is thought to decrease with age. Unfortunately, the small sample size precludes any meaningful subgroup analysis. In addition, in the small achalasia patient group enrolled, none reported chest pain as a presenting symptom. Chest pain is a common symptom of patients with achalasia, although its etiology is unknown (3). Different results may have been observed if achalasia patients presenting with chest pain had been included in the study. Heterogeneity in visceral sensitivity in achalasia patients that ranges from increased noncardiac chest pain to diminished visceral sensitivity may be related 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 achalasia have been conditioned by chronic esophageal distension and are therefore desensitized to otherwise noxious stimuli. Additionally, anxiety or stress has in prior studies been demonstrated to increase sensitivity to visceral stimuli (13). Because achalasia patients have undergone a number of procedures, including esophageal manometry, 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 complexity 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>
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<tr>
<td>Median</td>
<td></td>
<td>50</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