Identification of the biomechanical factors associated with the perception of distension in the human esophagus

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The perception of distension in the human esophagus gives rise to both motor responses (secondary peristaltic activity) and sensation (8, 15), which becomes painful with increasing distension (3). Although the perception of distension is now being used to provide information about the integrity of the external neural pathways from the esophagus and its processing within the central nervous system (1, 2), the nature of the stimulus generating the sensation is still unclear. Distension of the esophageal lumen generates both circumferential stretch of the esophageal wall and increased intraluminal pressure that together serve to increase wall tension. In addition, the change in motor activity occurring in response to distension could itself influence sensation (11–13). Animal studies (7) have demonstrated a number of sensory receptor types in the esophagus. Some respond either to mucosal stroking or to distension, whereas others respond to both types of stimuli, suggesting that the development of either stretch or tension within the esophagus could be responsible for the generation of sensation.

So far it has not been possible to determine wall tension accurately in the intact human esophagus. Although the intraluminal pressure generated by a distending stimulus is easily measured, the degree of circumferential stretch is not, and so the volume of the distending stimulus has been used as a proxy (6). The use of volume, rather than cross-sectional area (CSA), however, introduces a number of problems. In particular, compliance of the esophagus varies along its length, being lower in the distal esophagus with a higher pressure being generated for a given degree of distension (5). Low esophageal compliance will induce greater longitudinal displacement of the distending bag or balloon for a given volume, thereby activating a larger sensory receptive field, and this could result in increased intensity of sensation (15).

Because of these technical limitations, the interpretation of data obtained from in vivo human studies has been difficult. It has been proposed nonetheless that the mechanism responsible for the perception of distension is a tension receptor (10). If this were true, then both the circumferential stretch and intramural pressure induced by a distending stimulus would be relevant factors in determining sensation intensity.

In has now become possible to make a more accurate assessment of the degree of stretch of a hollow viscus in vivo using impedance planimetry (4, 9, 14). This technique, combined with manometry, provides both an estimate of CSA and transmural pressure at the site of distension. Tension at the site of distension can then be calculated using the law of LaPlace, which allows the derivation of tension using the formula $tension = \frac{radius \times pressure}{radius}$, where the radius is calculated from the square root of CSA divided by $\pi$, and pressure is the transmural pressure recorded from within the distending bag.

We therefore used a combination of impedance planimetry and manometry to determine the role of...
played by tension and stretch on the generation of sensory responses to esophageal distension in the human esophagus.

MATERIALS AND METHODS

Subjects

Twenty-five healthy adult volunteers (18 males, 7 females) with a median age of 30 yr (range 18–56) took part in the studies. Informed, written consent was obtained from each of the subjects as required by the local ethics committee.

Methods

Intubation was performed with a combined manometry and impedance catheter (Cook, Bjaeverskov, Denmark) that was previously described in detail (4). Three manometry ports positioned at 6, 12, and 18 cm from the catheter tip were used to record pressure above, within, and below a 3-cm-long polyethylene distension bag, within which were housed a manometric channel, the distending channel, and two pairs of ring electrodes for impedance measurement. Each manometry channel was attached to a force transducer (model TTX, Viggo-Spectramed), and each was perfused at a constant rate of 0.5 mls/min using a low-compliance infusion system (Cook). Output signals from the transducers and impedance electrodes were connected to amplifiers housed within a polygraph system (model V3300 impedance planimeter; Gatehouse), which allowed display of both pressure and impedance data on line.

In vitro infusion of the distension bag was undertaken before the studies to ascertain the pressure-to-volume characteristics of the bag and so generate a pressure correction curve, the results of which are shown in Fig. 1. The bag had no effect on the intrabag pressure up to an infusion volume of 45 ml demonstrated by the pressure remaining at 0 mmHg. At infusion volumes >45 ml, the bag pressure showed a sharp rise to a mean pressure of 9.5 mmHg at a volume of 60 ml. The pressure/volume responses were highly reproducible over the three infusion series, confirming that no change in compliance of the bag material occurred as a result of repeated distension.

Subjects were in a supine position with the head slightly elevated on a pillow. Transducers used for detecting manometric information were positioned at the midthoracic level of each subject so that the recorded intrathoracic pressure at end expiration on the respiratory cycle was 0 mmHg, and all pressures were measured relative to this end-expiratory pressure. The subject remained in the same position throughout the study so that there was no change in the position of the manometric perfusion channels within the subject relative to the transducers that might have influenced the data measured. A station pull-through esophageal manometry was undertaken to ensure no manometric abnormality was present and to locate the position of the lower esophageal sphincter. The distension bag was secured in position 8 cm proximal to the lower esophageal sphincter to prevent migration of the catheter from the desired location. The distension bag was sited at the same level within the distal esophagus in all subjects. The position of the catheter was checked throughout the study via position markers on the catheter.

Measurements of CSA and intrabag pressure at sensory threshold and maximum tolerated sensation were made relative to the onset of the sensory responses described by the subject. The CSA and bag pressure at motor threshold were derived by extrapolation on the curves to the point at which motor activity was detected in the channel above the distension site. The relatively small variation in pressure due to respiration and its effect on the pressures at which these motor and sensory responses occurred was not compensated for. A respiratory artefact was not detectable on the CSA recording.

It was assumed that the esophagus in all subjects would be predominantly smooth muscle at the level of measurement and thus enable comparable responses among the subjects to be recorded. If the infused volume was ≥45 ml, then pressure compensation was made for the effect of resistance of the bag material on the intrabag pressure by subtracting the in vitro pressure from the in vivo pressure at the infused volume. For the volume step distension, the mean values of the CSA and pressure during distension were used for calculation of tension. The motility was measured as the area under the curve divided by the duration of the distension.

Definition of Terms

The CSA at baseline (mm²) was defined as the CSA of the bag at the point when the intrabag pressure began to increase above intrathoracic pressure. Motor threshold was defined as the onset of secondary motor activity in the channel proximal to the distension site. Sensation threshold was defined as the first awareness of sensation in the chest during the distension. Maximum tolerated sensation was defined as the sensation intensity at which the subjects requested the infusion be stopped because they had reached the maximum discomfort they could tolerate. This was indicated by a score of 100 on the visual analog scoring system.

Distension Protocols

After transnasal insertion of the catheter assembly into the esophagus, manometry was performed to establish the location of the lower and upper esophageal sphincters and to verify that the characteristics of esophageal function were normal. Distension of the esophagus was then performed by progressive filling of the bag, positioned 8 cm above the proximal border of the lower esophageal sphincter, with 0.009% sodium chloride solution warmed to 37°C. A continuous record of sensation intensity was made throughout each distension using an electronic visual analog scale, operated by the subject using a slider control over an unmarked 6-cm length, calibrated between 0 and 100, (0 represented no

Fig. 1. This figure illustrates the pressure-to-volume relationship of the distension bag used in the studies. The figure shows 3 consecutive distension series with from 0 to 60 ml fluid infusion.
sensation and 100 represented maximum tolerated sensation.

Protocol 1: ramp distension. To define the degree of circumferential stretch and tension that initiated sensation, a series of ramp distensions to sensory threshold was undertaken followed by ramp distension up to the maximum tolerated sensation. The esophagus was progressively distended at 1 ml/s in all 25 subjects, and the distension was terminated at the sensory threshold. Three consecutive distensions were undertaken in each of the 25 subjects to assess the reproducibility of the threshold responses. To define the parameters at the maximum tolerated sensation, the distension was repeated until the subject reported maximum tolerated sensation.

To investigate the influence of wall tension on sensation intensity, the distension protocol was repeated in 10 of the subjects (6 males, 4 females) after intravenous delivery of 20 mg of the muscarinic cholinergic receptor antagonist, hyoscine-N-butylbromide (HBB) (Boehringer Ingelheim, Bracknell, UK). A dose of 20 mg was chosen because this is the established dose routinely used for gastroenterological procedures to induce muscle relaxation, and it achieved the desired effect of measurable changes in motor activity and esophageal muscle tone that could be readily monitored using change in heart rate as an indicator of activity. The heart rate was monitored via surface chest electrodes using a LIFEPAK 7 electrocardiographic monitor (Physio-Control, Basingstoke, UK); the increase in heart rate, described as beats per minute, was used as a measure of the onset and duration of drug effect.

Measurements of the CSA and bag pressure were made to two predefined sensory end points: 1) the onset of sensation threshold as shown in Fig. 2A and 2) the point at which the subjects described maximum tolerated sensation as shown in Fig. 2B.

Protocol 2: volume step distension. To investigate the relationship between intensity of sensation and degree of distension, a volume step distension series was also undertaken in 20 of the subjects (13 males and 7 females, median age of 27.5 yr, range 18–56). Distension of the esophagus was conducted in 10-ml increments, each increment being maintained for 60 s, until the maximum tolerated sensation was reached. Between each distension step, the bag was fully emptied and a rest period of 30 s was allowed. Ten of the subjects were reinvestigated after HBB.

For each of the two distension protocols, the CSA, intrabag pressure, pressure activity above and below the distension site, and sensation intensity were measured.

Protocol 3: sensory responses to electrical stimulation of the esophagus. To determine whether any changes in esophageal sensory sensitivity associated with HBB could have resulted directly from an effect of the drug on sensory nerves, measurements of sensory threshold and maximum tolerated sensation to electrical stimulation were made in three of the subjects before and after 20 mg iv HBB. Because electrical stimulation activates neurons independently of mechanical distension, any HBB-induced change in neuronal sensitivity would have been expected to alter the sensory thresholds to electrical stimulation.

To perform the electrical stimulation, a catheter housing a pair of platinum ring electrodes (Gaeltec, Dunvegan, UK) was passed transnasally, and the electrode pair was positioned 6 cm above the lower esophageal sphincter. Direct electrical stimulation of the esophagus was then conducted using pulses of 0.5-Hz frequency and 200-μs duration and was undertaken in incremental steps of 1 mA to sensory threshold and to maximum tolerated sensation. Each incremental step was maintained for 5 s, and awareness of the sensation was immediate and not dependent on the length of time the stimulus was presented. The output current was generated by a constant current stimulator (model DST7A; Digitimer, Hertfordshire, UK). Intensity of stimulation (in mA) at sensation threshold and the maximum tolerated sensation described by the subjects, both before and after 20 mg iv HBB, were recorded. Stimulation was repeated three times, and the mean of the three values at each threshold level was used for comparison.

Data Analysis

Values for CSA, intrabag pressure, and tension for each subject are shown in the figures as individual plots together with the group median values for the results pre- and post-HBB. Because the data were not normally distributed, non-parametric statistical tests were applied.

Reproducibility of the series of ramp distension responses in the 25 subjects was assessed using ANOVA. The Wilcoxon signed-rank statistical test was used for the pre- versus post-HBB responses. To correct for minor differences in the duration of distension among subjects during the volume step distensions, averaged values for the CSA, intrabag pressure, and tension to the volume step distension were derived from the area under the curve divided by time (in seconds). The average values were then used to compare responses between the two conditions. Repeated-measures ANOVA was undertaken to compare the pre- versus post-HBB results.

RESULTS

In Vitro Measurements

Pressure volume curves generated from three consecutive distensions of the bag are shown in Fig. 1, illustrating the reproducibility of the pressure-to-volume relationship. As shown, the intrabag pressure remained at 0 mmHg up to a volume of 45 ml of fluid. Above 45 ml, the intrabag pressure increased with an intrabag pressure of 9.5 mmHg at 60 ml, which was the maximum capacity of the bag. Correction of the intrabag pressure was undertaken by deducting measured in vivo pressure from in vitro pressure for infusion volumes of ≥45 ml.

In Vivo Data Recording

An example of the data obtained from one subject during ramp distension is shown in Fig. 2A to illustrate the points of measurement used to derive the relevant values for analysis of the parameters at the onset of motor and sensory responses. An example of the ramp distension up to the onset of maximum tolerated sensation is shown in Fig. 2B and illustrates the relationship of CSA, bag pressure, motility, and sensation intensity. On Fig. 2, A and B, the infusion rate and the time scale are shown.

Reproducibility of the motor and sensory thresholds to ramp distension. Values for CSA, intrabag pressure, and tension at motor threshold and at sensation threshold, were similar for the three consecutive series (Table 1).

Responses to ramp distension. Individual data plots at the baseline, motor and sensation thresholds, and
maximum tolerated sensation before and after HBB are shown in Fig. 3.

CSA at baseline \((P = 0.1)\), sensation threshold \((P = 0.2)\), and maximum tolerated sensation \((P = 0.3)\) were unchanged by HBB, whereas, as might be expected, the CSA at the motor threshold was higher \((P = 0.02)\) after HBB, reflecting cholinergic inhibition. Results are illustrated in Fig. 3A. In contrast, pressure at both the sensation threshold and maximum tolerated sensation were lower after HBB \((P = 0.01)\) as illustrated in Fig. 3B. Results for tension are illustrated in Fig. 3C, showing tension was also lower after HBB due to reduction in intrabag pressure. Volume at sensory threshold and at maximum tolerated sensation is shown in Fig. 3D. There was no consistent change in volume required to initiate sensation threshold, but in six of the subjects,
a lower volume initiated maximum tolerated sensation after HBB compared with before HBB ($P = 0.05$). Because the CSA was unchanged, this implies that volume may be distributing in the circumferential plane rather than the longitudinal plane as would be expected with an increased compliance resulting from cholinergic inhibition generated by HBB. These results also indicate that CSA measurement, which provides a direct measure of stretch, was a more reproducible predictor of sensation intensity than volume, which showed a greater degree of variability in the volumes at which the maximum tolerated sensation was described.

The group median resting heart rate increased from 66 (range 54–84) to 109 (range 90–120) beats/min after HBB and remained elevated throughout the duration of investigation and was 86 (range 70–102) beats/min at the end of the study. A sustained increase of at least 10 beats/min over the original basal rate was present in all subjects throughout the investigation period and was taken as indicative of continued muscarinic blockade.

Response of HBB on sensory thresholds to electrical stimulation. Sensation thresholds were comparable before and after 20 mg HBB (sensation threshold $= 21.5$ vs. 28 mA, maximum tolerated sensation $= 53.7$ vs. 65 mA) indicating that the cholinergic blockade induced

### Table 1. Motor and sensation thresholds for three consecutive ramp distensions of the distal esophagus

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Distension 1</th>
<th>Distension 2</th>
<th>Distension 3</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor threshold</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSA, mm$^2$</td>
<td>286 (185–409)</td>
<td>307 (202–465)</td>
<td>255 (190–342)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>IBP, mmHg</td>
<td>18 (9–23)</td>
<td>13 (8–21)</td>
<td>16 (8–24)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>tension, mmHg/mm</td>
<td>174 (87–276)</td>
<td>118 (65–261)</td>
<td>142 (71–244)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Sensation threshold</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSA, mm$^2$</td>
<td>387 (272–482)</td>
<td>404 (301–609)</td>
<td>381 (255–516)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>IBP, mmHg</td>
<td>29 (18–47)</td>
<td>19 (12–44)</td>
<td>25 (17–40)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>tension, mmHg/mm</td>
<td>258 (168–530)</td>
<td>266 (100–579)</td>
<td>256 (162–458)</td>
<td>&gt;0.5</td>
</tr>
</tbody>
</table>

Values are median plus interquartile range. CSA, cross-sectional area; IBP, intrabag pressure. $P > 0.5$.

Responses to volume step distension. Volume step results are shown in Fig. 4, illustrating that a nonlinear increase in the CSA, intrabag pressure, tension, motility, and sensation intensity occurred with increasing infusion volume. Subjects with increasing infusion volume dropped out as they reached their maximum level of discomfort (20 subjects tolerated 10 ml distension, 18 tolerated 20 ml, and 12 tolerated 30 ml). For a given degree of distension, the sensory responses pre- and post-HBB were always comparable, whereas the intrabag pressure was lower at each distension step after HBB, indicating an overall reduction in tension. As expected, the motor activity induced above the distension site was reduced after HBB so that a larger volume was necessary to induce an equivalent motor response.

Fig. 3. The graphs illustrate the individual plots and group median (—) values for CSA (A), intrabag pressure (IBP) (B), and tension (C) at the BL, MT, ST, and MTS to ramp distension of the esophagus before and after hyoscine-N-butyl bromide (HBB). D: volume at which induced ST and MTS to ramp distension before and after HBB were described by the subjects. *Statistically significant differences at $P < 0.05$. 

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by this dose, exerted no direct inhibitory effect on esophageal sensation.

The relationship of CSA, volume, and length of distension bag. Because HBB could have increased esophageal compliance (as a result of muscle relaxation) and, in turn, altered the spatial characteristics of the distending bag, we compared the relationships between volume and CSA before and after HBB. CSA was unchanged after HBB both for ramp distension (Fig. 3A) and volume step distension for each given volume (Fig. 4A).

DISCUSSION

Our study shows that the degree of circumferential stretch at which sensation threshold and maximum tolerated sensation are reported remains unchanged despite a reduction in esophageal tone by HBB, strongly implicating circumferential stretch as the main factor influencing esophageal sensation. The degree of elongation of the distending bag was also unchanged after HBB because the volume and CSA parameters remained unchanged. It is still theoretically possible to explain our results by tension effect, in that in the presence of HBB any reduction in tension-induced sensation might be counterbalanced by an increase in sensation intensity resulting from a greater length of the esophagus being stimulated. However, the fact that the relationship between volume and CSA remained very similar both with and without HBB at sensation threshold level, makes any explanation that relies on altered length of esophageal stimulation highly unlikely. In addition, increased compliance secondary to HBB should increase the CSA to volume relationship and, therefore, decrease the length of stimulation, as shown by the decreased volume but sustained CSA at the maximum tolerated sensation.

The finding that motor responses always precede the onset of sensation indicates that the mechanism for initiating the motor responses has a lower threshold for activation than that initiating sensation, which is consistent with our earlier studies described by Williams (15). The fact that motor response after HBB requires a greater stimulus but sensation was induced at a comparable stimulus (both mechanical and electrical), implies that the HBB is selectively blocking motor, but not sensory, pathways.

HBB reduced but did not completely abolish the esophageal wall pressure generated by a given volume and CSA. This suggests that the intrabag pressure may be a function of at least two factors: an active neuromuscular component that can be altered by muscarinic receptor antagonism and a residual nonmuscarinic component unaffected by the HBB presumably related, in part, to the elastic components of the esophageal wall.

Two practical advantages of impedance planimetry to provide CSA measurements are that 1) it is possible to ascertain the spatial distribution of the infused volume and 2) it is possible to relate the sensation intensity to the degree of circumferential stretch. The CSA-to-volume graphs (see Fig. 4A) demonstrate that the relationship between volume and CSA is not linear.
and therefore, volume alone cannot easily be used as a proxy for CSA or stretch.

Responses to distension were shown to be highly reproducible within individuals, but the intersubject variability for the degree of circumferential stretch generated by a given volume makes it difficult to formulate a standard CSA-to-volume curve.

CSA measurement both before and after 20 mg iv HBB, provided relevant information relating circumferential stretch and sensory response thresholds and intensity. The change in bag pressure but comparable CSA after HBB indicated that an isometric change in esophageal muscle activity was generated by the cholinergic blockade.

This information will enable more useful assessment of the relationship between circumferential stretching of the esophagus and the induced sensory responses in patients with unexplained chest pain and hypersensitive gut disorders.

In conclusion, these results implicate a stretch responsive mechanism for transduction of luminal distension into sensation. Further studies are now required to determine whether stretch is similarly responsible for the sensory responses to distension elsewhere in the gastrointestinal tract and whether abnormalities of stretch rather than tension are responsible for the visceral hypersensitivity reported in many clinical gastrointestinal disorders.

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REFERENCES


