

*Alimentary tract and pancreas*

## Studies of the oesophageal clearance responses to intraluminal acid

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**SUMMARY** Contraction of the upper oesophageal sphincter combined with secondary peristalsis clears the oesophagus of refluxed gastric contents and protects the trachea, but the nature of these reflex stimuli remains controversial. Secondary peristaltic and sphincteric responses were measured during intraluminal infusion of 0.1 N hydrochloric acid and equiosmolar saline solutions in seven normal volunteers. Responses to a single volume infused at varying sites in the oesophagus and to progressively increasing volumes of test solution were measured. In addition oesophageal responses to similar degrees of distension induced by inflation of an intraluminal balloon were also recorded. The sphincteric responses to both stimuli were similar, decreasing in value with distance from the sphincter from values of 70 (68-85) mmHg (median (range)) for HCl; and 70 (55-85) mmHg for NaCl at 5 cm below the sphincter to 40 (30-60) mmHg for both HCl and NaCl at 20 cm. As the volume of the solution infused into the proximal oesophagus was increased, the sphincter pressure also rose from a median basal value of 30 (25-50) mmHg to 40 (30-50) mmHg for HCl and NaCl after 1 ml, while after 7 ml infusion, the responses were greater, 65 (45-85) mmHg for HCl, and 60 (45-80) mmHg for NaCl. In the more distal oesophagus, responses were qualitatively similar but quantitatively smaller than proximally, being 30 (25-40) mmHg for HCl and 30 (25-50) mmHg for NaCl following 1 ml and 45 (40-55) mmHg for HCl and NaCl after 7 ml. Secondary peristalsis was also induced equally by both solutions and varied with volumes infused and site of infusion in a manner similar to the sphincter responses. After a 7 ml/min acid infusion 14 (1-40) secondary contractions/three min were recorded at 5 cm and eight (2-18)/three min were recorded at 20 cm. Values for saline were similar, 13 (1-38)/three min at 5 cm and eight (4-25)/three min at 20 cm. Oesophageal distension by a balloon positioned 10 cm below the sphincter induced identical clearance responses to those seen after similar volumes of either acid or saline infused at the same site. These results suggest that the principal stimulus for upper oesophageal clearance is intraluminal distension and do not support the idea that the oesophagus is pH sensitive.

Reflex motor responses of the oesophagus to intraluminal acid are important because of the pathophysiological relationship between gastric juice and reflux oesophagitis.

It is well known that refluxed gastric contents injure the oesophageal mucosa, the longer they stay there,<sup>1</sup> and that symptoms in patients with oesophagitis can be reproduced by acid.<sup>2</sup> Furthermore,

patients with severe oesophagitis are less able than normal subjects to clear refluxed intraluminal acid by swallowing<sup>3</sup> because of ineffective primary peristalsis,<sup>4</sup> although whether this abnormality is the cause or the result of the oesophagitis is uncertain.

In addition to swallow-induced primary peristalsis, intraluminal clearance is achieved by secondary peristalsis which is an intrinsically mediated process<sup>5</sup> induced by reflux from the stomach, independent of swallowing and closely linked with tonic contraction of the upper oesophageal sphincter.<sup>6,7</sup> Secondary peristaltic clearance is a major protective mechanism

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during sleep, when reflux is common,<sup>7,8</sup> swallowing infrequent,<sup>9</sup> and salivary flow diminished.<sup>10</sup>

The inter-relationships between intraoesophageal acid, secondary peristalsis and oesophagitis remain unclear and the mechanism by which intraluminal acid stimulates oesophageal clearance is controversial. Some reports have suggested the existence of acid specific motor responses<sup>11-13</sup> indicating the presence of hydrogen ion sensitive receptors in the oesophageal mucosa. Others have failed to show any significant effect.<sup>14,15</sup> Because of the undoubted sensitivity of the oesophagus to intraluminal distension which stimulates secondary peristalsis<sup>6</sup> and increases upper sphincteric tone,<sup>16</sup> it is important to distinguish between reflex responses induced by pH from those by distension. The purpose of this study was to examine this difference.

## Methods

### SUBJECTS

Seven healthy normal volunteers (median age 23 years, range 20-33) without gastrointestinal disease were studied according to protocols presented to and approved by The London Hospital Ethical Committee. Each gave written informed consent before study.

### RECORDING TUBE

A multilumenal oesophageal tube was constructed from three triple lumen polyvinyl chloride tubes (PVC) (id 0.5 mm, od 1.5 mm - Dural Plastics,

Australia) bonded with tetrahydrofuran around a central PVC tube (id 0.63 mm, od 1.4 mm - Portex Ltd, Hythe, Kent, England). Three ports 0.7 cm apart were sited in the upper sphincter itself, one was proximal in the pharynx 5 cm above the sphincter to identify initiation of swallowing, while distally four ports 5, 10, 15, and 20 cm below the sphincter detected peristaltic activity in the body of the oesophagus. In addition, a 5 cm inflatable balloon was attached to the tube assembly 10 cm below the middle of the three sphincteric ports. The tubes were continuously perfused at a rate of 0.3 ml/min using a standard pneumohydraulic infusion system. Pressure changes were measured at the proximal end of each lumen by strain gauge transducers (Gaeltec, SS8b, Skye, Scotland) the outputs of which were recorded on an eight channel chart recorder (Wantanabe Linear Corder, Mark VII, Tokyo, Japan) run at a paper speed of 50 mm/min.

### TEST SOLUTIONS

0.1 N hydrochloric acid was obtained from BDH Ltd (Chadwell Heath, Essex). The control saline solution was made by dissolving sodium chloride (Analar quality, BDH Ltd) in distilled water until the osmolality of the solution (measured using a vapour pressure osmometer) matched that of the acid solution.

### STUDY PROTOCOLS

After an overnight fast each subject was intubated, placed in the supine position and the height of the

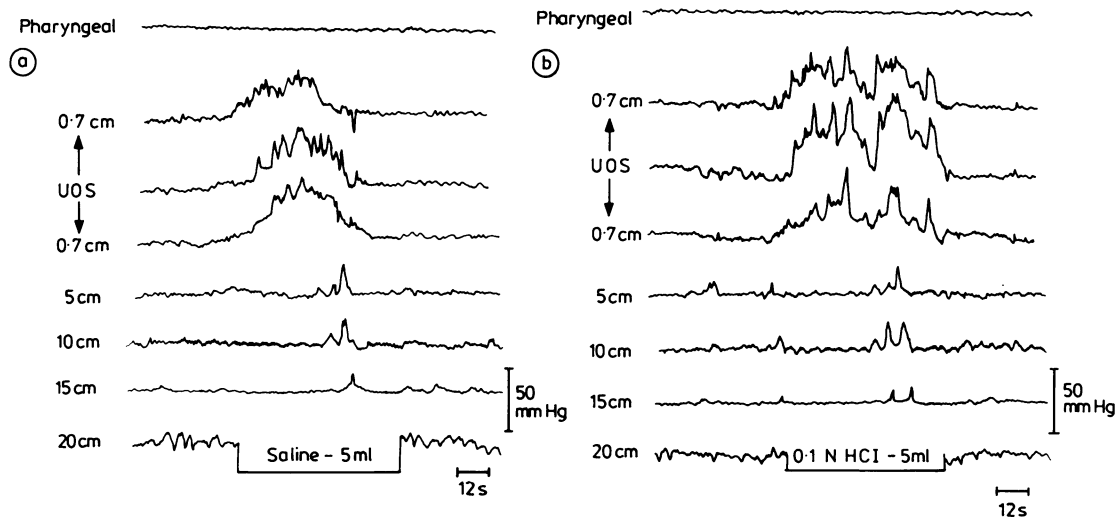


Fig. 1a, b Tracings of the intraluminal pressure responses to delivery of the two test solutions in one individual are shown. 1a shows the response to 5ml saline delivered 20cm below the upper oesophageal sphincter (UOS), figure b shows responses to 5ml hydrochloric acid (HCl). Values in cm denote distance of recording site from centre of UOS.

transducers adjusted until level with the midaxillary line. A standard oesophageal manometric study was first carried out to exclude abnormality and to identify the position of the sphincter. Then the recording tube was repositioned so that the three sphincteric ports were within the sphincter (recognised by the characteristic swallowing response).<sup>14</sup> Posterior orientation of the ports was then maintained by taping the tube in place at the angle of the mouth.

Each subject was studied twice, carrying out the two experiments on different days. During the infusion periods the solutions were delivered at a constant rate (7 ml/min)<sup>15</sup> down one of the capillary tubes, the choice depending upon the site of interest at that time. This method precluded measurement of motor activity from that channel during infusion but allowed the overall size of the tube to be kept as small as possible. To exclude swallowing related clearance effects, subjects refrained from swallowing during each period of study, but were allowed to swallow freely during the three to five minutes which elapsed between infusions.

#### EXPERIMENT 1

This experiment was designed to determine the response threshold of the upper sphincter and oesophageal body to varying volumes of saline and acid. All seven subjects received four volumes of both solutions (1, 3, 5, and 7 ml). Each solution was delivered either 5 cm or 20 cm below the upper sphincter; the overall order of study being randomised for each individual.

#### EXPERIMENT 2

This experiment was designed to determine the response of the oesophagus to acid and saline solutions at different anatomical levels, and to compare this with distension caused by balloon. Each of the seven subjects received both solutions in randomised order at 5, 10, 15, 20 cm below the sphincter, 20 ml of each solution being delivered to each site at a rate of 7 ml/minute. At the end of this study the oesophagus was distended by infusing 7 ml water over one minute into the attached balloon 10 cm below the middle sphincteric port and kept inflated for three minutes to simulate distension effects of the infusions.

#### DATA ANALYSIS

The upper sphincteric responses to infusion and balloon distension were determined to the nearest 5 mmHg by measuring the maximum deviation from the prestimulation baseline in the middle port. The median value and range for the grouped data were used to construct figures, because the data were not

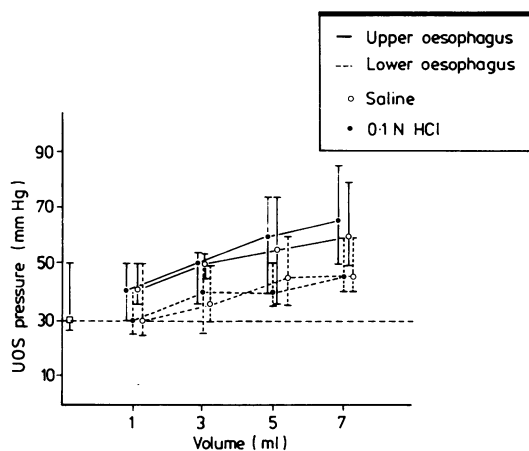


Fig. 2 This diagram shows the response of the upper oesophageal sphincter (UOS) to varying volumes of test solution delivered either 5 cm (upper oesophagus) or 20 cm (lower oesophagus) below the UOS. Values represent medians (range)  $n=7$ . The median (range) of the resting UOS pressure are represented by the  $\square$  on the left of the figure.

normally distributed. Peristaltic responses to the test solutions were determined by counting the number of secondary peristaltic waves recorded at each oesophageal port during the infusion. The Wilcoxon's rank-sum test<sup>17</sup> was used for statistical analyses. A  $p$  value of 0.05 or less was taken to indicate that observed differences were unlikely to have been due to chance.

#### Results

Figures 1a and 1b show the responses of the upper sphincter and body to saline and acid in one individual, recorded from seven channels.

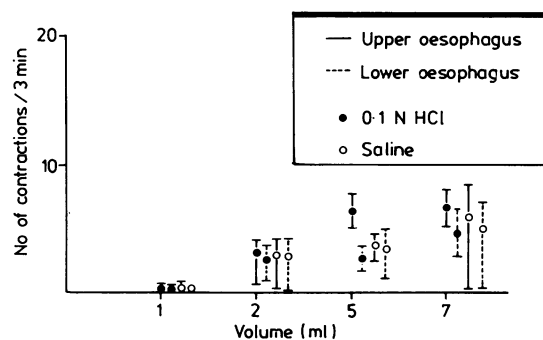


Fig. 3 This diagram shows the response of the oesophageal body to varying volumes of test solution delivered either 5 cm (upper oesophagus) or 20 cm (lower oesophagus) below the UOS. Values represent medians (range)  $n=7$ .

#### EXPERIMENT 1: RESPONSES TO DIFFERENT VOLUMES, AT 5 OR 20 CM BELOW THE UPPER SPHINCTER

Figures 2 and 3 show the results of these studies. For both solutions, responses of the upper sphincter and oesophageal body were similar, with a rise in sphincteric pressure response and an increase in peristaltic activity to increasing volumes at both infusion sites ( $p > 0.05$  for all comparisons).

A constant difference was seen between the two infusion sites, with the upper 5 cm site showing persistently higher sphincteric pressure and increased peristaltic activity in response to both solutions than the 20 cm site.

#### EXPERIMENT 2: RESPONSES TO THE SAME VOLUME AT DIFFERENT SITES, 5, 10, 15, AND 20 CM BELOW THE SPHINCTER

##### *Sphincteric response*

Within a few seconds after the onset of delivery of either solution, sphincteric pressures began to rise and remained raised for the duration of the infusion (Fig. 1). The solution difference itself did not cause any change in response at the various levels, but the sphincteric pressure increase fell proportional to the distance from the sphincter (Fig. 4).

##### *Secondary peristalsis*

Oesophageal motor responses to the two solutions were also similar; the effect being less with distance from the sphincter (Fig. 5). Over 90% of the secondary peristaltic waves induced by both infusions originated in the upper oesophagus and migrated aborally irrespective of the site of infusion.

Balloon distension 10 cm below the upper

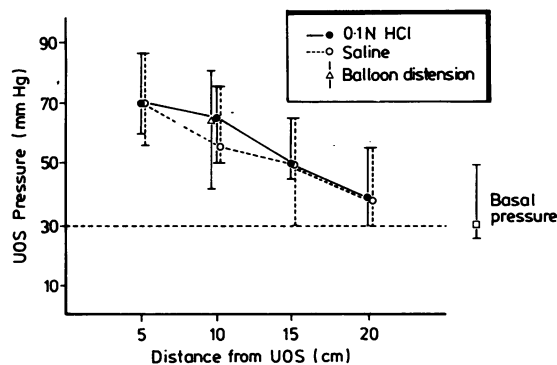


Fig. 4 This diagram shows the responses of the upper oesophageal sphincter (UOS) to instillation of 20ml test solution delivered at different sites in the oesophagus. Values represent median (range)  $n=7$ . Responses to balloon distension are also shown for comparison.

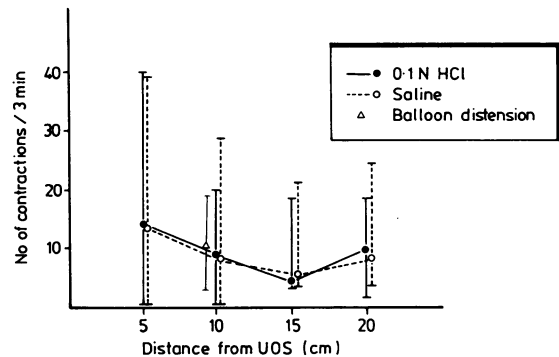


Fig. 5 This diagram shows the responses of the oesophageal body to 20ml test solution delivered at different sites in the oesophagus. Values represent median (range)  $n=7$ . The responses to balloon distension are also shown for comparison.

sphincter increased both sphincteric pressure and secondary peristalsis above the balloon in a similar manner to that induced by either of the test solutions ( $p > 0.05$  for either solution).

#### Discussion

The results of these studies in normal subjects under the experimental conditions used, indicate that the intrinsic oesophageal motor responses to intraluminal hydrochloric acid are indistinguishable from those to saline. Both solutions induced a prompt response in the upper sphincter and oesophageal body similar to those previously reported after intraluminal distension and which are known to be associated with oesophageal clearance. These findings suggest that distension is the principal factor responsible for the clearance response and this effect is not increased by increasing the hydrogen ion concentration.

It is difficult to make a direct comparison between this study and previous reports because of wide methodological differences. In general, studies are divisible into those in which acid has been perfused at a slow rate to avoid stimulating peristalsis and those in which it has been perfused more rapidly in order to observe peristaltic clearance responses. An additional difference is the level at which solutions are perfused.

In those studies using slow perfusion little or no difference has been found between acid and saline in normal subjects.<sup>14,15,18</sup> In patients with oesophagitis and reflux however, slow acid perfusions can produce pain<sup>2</sup> which in some cases, has been associated with an abnormality of oesophageal motility.<sup>19,20</sup> Whether this motility was the cause of the pain as suggested by

some authors, or was a consequence of the discomfort, cannot however, be determined from the data.

In the more rapid acid perfusion studies motor responses have been described in the sphincter and the oesophageal body<sup>8,14</sup> which resemble our data and indicate the need to exceed a minimum rate of delivery before any response is seen, possibly in order to exceed a distension threshold.<sup>6</sup> This finding does not necessarily exclude a pH effect because a certain volume of acid will be necessary to reduce mucosal pH below the threshold value for stimulation. The magnitude of responses attributable to hydrogen ion rather than volume raises questions about its biological significance. For example, Gerhardt *et al*<sup>14</sup> found an acid induced upper sphincter response which exceeded the saline control by only 8% whereas the effect of the control infusion over basal conditions was at least twice this value. This lack of specific responsiveness to acid is consistent with our current understanding of the oesophageal squamous epithelium. No evidence for specific hydrogen ion sensing receptors has been found, although distension and thermal receptors have been reported.<sup>21</sup>

A further possible explanation for the differences between our data and those of others may be the duration of acid infusion. In this study the maximum duration of infusion was three minutes and most infusions were one minute or less. Only one of our normal subjects reported any oesophageal discomfort suggesting that any epithelial damage attributable to acid was small. In our experience from other studies more prolonged infusions may induce retrosternal discomfort, resembling heartburn so that the apparent motor response to acid found during the more prolonged studies performed by others might be explained by the induction of pain due to mucosal injury.

In patients with oesophagitis it is clear that acid damage and poor clearance are linked, but which of the two is the primary factor still remains for future studies to determine.

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