Stimulus and site specific induction of hiccups in the oesophagus of normal subjects

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Abstract

Background—Hiccups that are induced by a large meal have been suggested to result from gastric overdistension. The role of the oesophagus in precipitating hiccups has never been defined.

Aims—To determine the involvement of oesophageal mechanoreceptors in the hiccup reflex.

Methods—Ten normal healthy subjects were prospectively evaluated at a university affiliated hospital. Controlled inflation of a polyethylene bag in the proximal and distal oesophagus was carried out using slow ramp and rapid phasic distensions, by an electronic distension device.

Results—Hiccups were induced in four subjects only during rapid phasic distensions and only in the proximal oesophagus. The mean (SEM) minimal volume threshold for the hiccup reflex was 32.5 (4.8) ml, which was above the perception threshold. Hiccups appeared during inflation and resolved after deflation.

Conclusions—Sudden rapid stretch of the mechanoreceptors in the proximal oesophagus can trigger the hiccup reflex in normal subjects. Only rapid distensions above a determined volume threshold will predictably induce hiccups in a given subject. This mechanism may play a role in the physiological induction of hiccups.

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A hiccup is a sudden, involuntary spasmodic contraction of the diaphragm and external intercostal muscles, that results in inspiration which abruptly ends with closure of the glottis.[1] Although the physiological role remains unknown, hiccups are usually short lived, uncomplicated, and affect healthy subjects on occasion.[1 2] Rarely, hiccups can become persistent, intractable and even refractory to a variety of therapeutic modalities.[1–6]

The hiccup reflex arc is comprised of afferent pathways—vagal, phrenic, and sympathetic (T6–T12) branches. The efferent pathways are composed of the phrenic nerve to the diaphragm and nerves to the glottis and the external intercostal muscles. The central connection is the spinal cord between segments C3 and C5, possibly controlled by supraspinal pathways.[1 2] Excessive food and alcohol consumption, ingestion of carbonated beverages, and aerophagia can trigger the hiccup reflex.[1 2 7] Several changes have been observed in the function of the oesophagus during hiccups: a complete disappearance of oesophageal body peristalsis, decreased lower oesophageal sphincter pressure, and a fluctuation in the oesophageal baseline, synchronous with hiccups activity.[8 9] These functional changes are transient and disappear after hiccup cessation.

Hiccups may be induced by rapid swallowing of a large bolus of food. Although gastric overdistension has been suggested as a possible aetiological mechanism, the role of the oesophagus in triggering the hiccup reflex remains to be elucidated.[1 2] The aim of our study was to characterise the stimulus and the oesophageal anatomical location which may be responsible for triggering the hiccup reflex. A better understanding of the physiological role of the oesophagus in inducing hiccups may improve the management of self limited or intractable hiccups of oesophageal origin.

Methods

Ten normal, healthy subjects (eight males and two females; age range 19–54 years, mean age 35.1 (12.2) years) were recruited. All subjects were interviewed to exclude a history of chronic hiccups, diaphragmatic irritation, central nervous system abnormality, gastro-oesophageal reflux disease, upper gastrointestinal tract surgery, active peptic ulcer disease, autonomic or peripheral neuropathy, myopathy, diabetes mellitus, and any other disorder or medication use that may induce hiccups or gastro-oesophageal reflux, or affect sensation. An essential inclusion criterion was normal 24 hour oesophageal pH monitoring to exclude asymptomatic gastro-oesophageal reflux disease. After an overnight fast, a pH probe was inserted via the nose into the stomach. The pH probe was connected to a digital portable recorder (Synectics Medical, Digitrapper Mark II). Using the pull through technique, the probe was placed 5 cm above the point of sudden rise in pH. A reference electrode was attached to the upper chest. The subjects were instructed to keep a diary, recording meal time and position changes. Subjects were encouraged to pursue their everyday activities and usual diet. At the beginning and the end of the study the electrode and the system were calibrated in standard solutions of pH 1 and pH 7. A study was considered abnormal when the percentage total time of pH<4 was greater than 4.2%.

The oesophageal distension protocol was carried out after an overnight fast, using a

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computer driven volume displacement device (electronic barostat, Synectics Visceral Stimulator; Synectics, Stockholm, Sweden) which was used to inflate a bag either continuously at a constant volume rate of 80 ml/min (ramp distension) or rapidly (870 ml/min) to constant volume plateaus (phasic distension). The distension device, which records pressures and volumes simultaneously (sampling rate of one per second) was connected to a subject operated marker device that logs the sensation of initial balloon inflation, discomfort, and pain onto the data file as bag inflation occurs. When a subject triggered the marker for pain during phasic or ramp distension, the device instantaneously deflated. There was a fixed pressure limit that also triggered bag deflation for pressures greater than 80 mm Hg.

A polyethylene bag was attached to a plastic probe (diameter 10F) and tied at both proximal and distal ends (MAK-LA, Los Angeles, California). The distance between the two attachment sites was 5.5 cm. Distension to a maximal volume of 150 ml and circumference of 27 cm resulted in a spherical bag shape. However, partial inflations resulted in a cylindrical shape in vivo. The bag was mounted over three ports used for inflation and intrabag pressure and volume measurements. The bag was inflated repeatedly before initial use and after completion of each experiment to ensure that there were no leaks.

Subjects were placed in the prone position on a padded table. The bag was inserted via the mouth and positioned initially in the distal (5 cm above lower oesophageal sphincter) and subsequently in the proximal (15 cm above lower oesophageal sphincter) oesophagus. The tube was secured each time in its proper position with tape. The location of the lower oesophageal sphincter was predetermined by oesophageal manometry. Patients were not informed about the nature of the distension protocols (ramp distension versus random phasic distension). During each protocol, subjects had full control and were able to terminate the test at any time of significant discomfort.

Initially, a slow ramp distension at a rate of 80 ml per minute was delivered until the subject pressed the pain button. The hiccups volume threshold, if precipitated, and the perception thresholds for initial sensation and discomfort were recorded. Perception threshold for initial sensation was defined as the lowest volume that induced oesophageal sensation. The slow ramp distension was repeated three times to determine reproducibility. Subsequently, a predetermined protocol of randomly delivered phasic distensions, at a rate of 870 ml per minute, was carried out in the proximal and distal oesophagus. Each stimulus lasted 30 seconds, followed by a 30 second resting interval. Five different volumes (20, 30, 40, 50, and 60 ml) were randomly delivered, such that each stimulus was given three times. During each phasic stimulus, subjects were requested to report their perception. Repetition of each protocol was carried out to ensure reproducibility of the hiccups, if precipitated. After completion of each protocol in the distal oesophagus, the balloon was withdrawn and placed 15 cm above the lower oesophageal sphincter (proximal oesophagus). Similar protocols were performed in the proximal oesophagus.

Data analysis was performed using Fisher's exact test and Student's t test. Results are presented as mean (SEM). All subjects gave informed consent and the study was approved by the Human Subject Committee of the West Los Angeles Veteran Administration Medical Center.

Results

Ten healthy subjects completed the study. Hiccups were not induced during slow ramp distension in the distal or the proximal oesophagus in any of the subjects. During rapid phasic distension, hiccups were induced in the proximal oesophagus of four subjects (40%). In contrast, hiccups were not induced by rapid phasic distension in the distal oesophagus of any subject, including those who developed hiccups in the proximal oesophagus.

There was no significant age difference between subjects who developed hiccups and those who did not (38.0 (9.0) and 34.0 (5.0) respectively). All four subjects who developed hiccups were males. The mean perception thresholds for initial sensation in the proximal and distal oesophagus were similar for all subjects (15.2 (1.7) and 19.8 (2.7) ml respectively). However, the mean threshold for discomfort was significantly higher in the distal than the proximal oesophagus for all subjects (31.3 (2.5) and 23.7 (2.1) ml respectively). During rapid phasic distension, the mean threshold for hiccups was 32.5 (4.8) ml, which was significantly above the threshold for initial perception ($p<0.05$) (fig 1). The mean intrabag pressure thresholds for hiccups did not differ from the intrabag pressures generated by similar volumes in subjects that did not develop hiccups (64.4 (7.2) and 62.1 (7.0) mm Hg, respectively). Only minimal contractile response to the different stimuli was recorded in
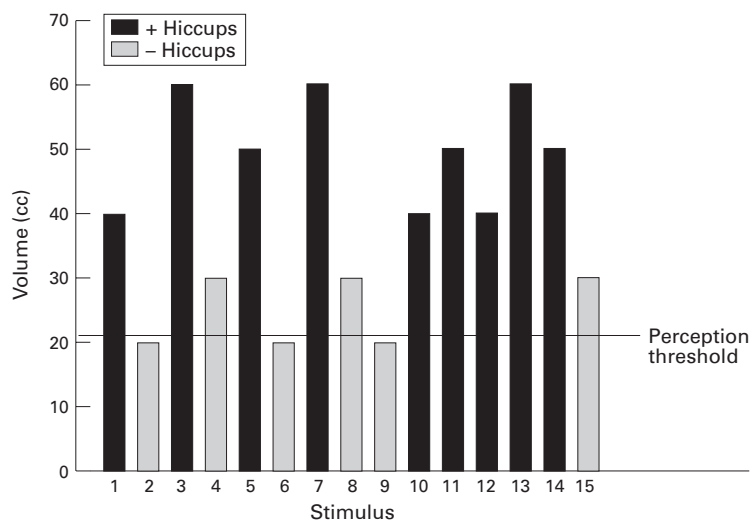

Figure 1: Stimulation of hiccups by rapid, phasic distensions in the proximal oesophagus of a single subject. The black bars represent phasic distensions that induced hiccups. The hiccup volume threshold is above the perception threshold.

the distal oesophagus of one subject out of the four that developed hiccups. In the proximal oesophagus, contractile response was recorded in 2/4 subjects, none of which had any detectable response in the distal oesophagus. Conclusions about contractile response to the different stimuli are thus hampered by the very small number of subjects. There was no significant difference in the mean perception thresholds for initial sensation and discomfort in the proximal oesophagus of the subjects who developed hiccups when compared with those who did not (18.2 (2.6) and 23.8 (2.9) versus 12.9 (2.2) and 24.3 (2.8) ml).

Phasic distensions greater than 40 ml induced hiccups in all four subjects in whom hiccups occurred. The hiccups were induced during the rising phase of inflation of the bag and immediately resolved after deflation. None of the participants who developed hiccups continued to experience them after completion of the protocols. Reproducibility of hiccups was achieved in all subjects who developed them initially, at the same location and after the same phasic stimulus. None of the subjects not experiencing hiccups during the initial set of slow or rapid distensions developed hiccups during any of the repeated protocols.

Discussion

The role of the oesophagus in precipitating hiccups has never been defined. The usual, brief, and transient hiccups that are induced by a large meal or carbonated beverages, have been suggested to result from overdistension of the stomach.[1 2] However, careful history of patients with hiccups, suggests that meal induced hiccups may be related to the size and the rapidity of a swallowed bolus rather than the overall amount of food that has been ingested. This study is the first to demonstrate a clear role for the proximal oesophagus in precipitating hiccups. Furthermore, the ability to induce hiccups by rapid phasic distension limited to the proximal oesophagus suggests that a sudden, rapid stimulation of oesophageal mechanoreceptors by either a large bolus of food or large amount of air, as in carbonated beverages, induces hiccups. Since we did not perform gastric distension in these subjects, we cannot rule out that hiccups in a given individual can be triggered by both oesophageal and gastric distension. However, in separate studies using the same protocols for gastric distension stimulation in healthy volunteers, we never observed the induction of hiccups.[11] In addition, it appears from our study that the mechanoreceptors responsible for triggering hiccups respond to a defined volume threshold which is above the perception threshold.

Even though compliance and perception thresholds are similar in both distal and proximal oesophagus in normal subjects, rapid balloon distension in the distal oesophagus did not induce hiccups.[10] A possible explanation is selective innervation of the proximal oesophagus by vagal or sympathetic afferents which participate in the hiccup reflex arc. The fact that hiccups were induced in only four of the volunteers may be related to a higher hiccup threshold in the non-responsive subjects.

Several reports have associated hiccups with gastro-oesophageal reflux disease (GORD).[12–16] Reproducibility of hiccups was demonstrated by stimulation of oesophageal chemoreceptors by acid perfusion in a patient with GORD who suffered from a persistent form of hiccups.[13] However, the association remains controversial as some authors hypothesised that hiccups themselves predispose to acid reflux, while others could not demonstrate improvement in hiccups with medical or surgical antireflux treatment.[12 14] In the current study, we have eliminated both symptomatic and asymptomatic GORD as a cause for the observed findings.

Achalasia, stricture, and malignant tumours confined to the oesophagus have been associated with intractable hiccups in sporadic case reports.[17–19] Dilatation of the oesophagus has been implicated as the underlying mechanism.[19] In these reports, patients developed hiccups after meals, suggesting an increased predisposition to sudden stretching of the proximal oesophagus due to oesophageal obstruction or lack of normal oesophageal peristalsis.

The physiological role of hiccups has never been determined. However, our study may suggest a protective mechanism, whereby hiccups possibly prevent very large boluses of food from entering the gastrointestinal tract. In summary, this is the first study to demonstrate the involvement of oesophageal mechanoreceptors in triggering hiccups. By understanding this physiological mechanism in patients with self limited or persistent hiccups of presumed oesophageal origin, one could suggest initial therapeutic measures in the form of chewing well and swallowing slowly small boluses of food. In cases of persistent symptoms, identification of possible underlying pathology remains mandatory.

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