Acid-induced esophageal shortening in humans: A cause of hiatus hernia?

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BACKGROUND: Hiatus hernia and gastroesophageal reflux disease commonly coexist, and there is pathophysiological evidence that the presence of a hiatus hernia contributes to abnormal acid reflux. However, the cause of hiatus hernia remains unclear. In an animal model, it has been shown that acute acid injury to the esophagus results in esophageal shortening, raising the possibility that reflux esophagitis per se can contribute to the formation of hiatus hernia by inducing esophageal shortening.

AIM: To determine whether luminal acid produces esophageal shortening in humans.

METHODS: Twelve volunteers were each studied on two occasions, one week apart, in a double-blind, crossover trial. The location of the lower esophageal sphincter (LES), as well as the LES resting pressure and axial length were determined at baseline and then again after 20 min of either acid or saline perfusion.

RESULTS: Acid perfusion did not induce significant changes in resting LES pressure but resulted in proximal migration of the LES (ie, esophageal shortening) by an average of 0.5 cm, with the largest proximal migration being 1.8 cm. In contrast, saline perfusion resulted in slight distal migration of the LES (ie, esophageal lengthening).

CONCLUSIONS: Intraluminal acid perfusion causes longitudinal axis shortening of the esophagus and suggests that gastroesophageal acid reflux may contribute to the cause of hiatus hernia.

Key Words: Acid perfusion; Esophagitis; Lower esophageal sphincter; Manometry

In the past decade, there has been renewed interest in the role of hiatus hernia in the pathogenesis of gastroesophageal reflux disease (GERD). Hiatus hernia and GERD commonly coexist (1,2), and the hernia sac can act as an acid reservoir that allows ready access of acidic juice into the esophagus whenever the lower esophageal sphincter (LES) relaxes, thus contributing to prolonged esophageal acid exposure (3,4). The crural fibres of the diaphragm are also thought to provide an external bolster to the LES, thereby contributing to the antireflux barrier (5,6). While there is
good evidence that a hiatus hernia contributes to the pathogenesis of GERD, little is known about how the hernia actually forms. The traditional explanation is that laxity of the ligamentous structures around the hiatus occurs, which allows the stomach to migrate upwards into the chest, particularly in the setting of increased abdominal pressure caused, for instance, by obesity (7). This hypothesis is not supported by experimental evidence. Furthermore, it does not explain the fundamental prerequisite for the development of hiatus hernia – esophageal shortening. Recent studies have demonstrated, in an animal model, that acute intraluminal acid perfusion induces esophageal shortening (8) that can be prevented by pretreatment with a mast cell stabilizer (9). This suggests that acid injury to the esophageal mucosa causes release of mast cell mediators, which in turn cause longitudinal muscle contraction and esophageal shortening. If this also occurs in humans, it would provide a mechanism whereby hiatus hernia could develop and enlarge in the setting of ongoing gastroesophageal reflux. The objective of the present study, therefore, was to determine whether acid-induced esophageal shortening also occurs in humans.

SUBJECTS AND METHODS

The study was approved by the Queen’s University Human Ethics Review Board, and all participants gave informed, written consent. Twelve healthy volunteers (seven females; age range 23 to 65 years), free of all esophageal symptoms, were each studied on two occasions, one week apart, in a randomized, double-blind crossover trial. Subjects were randomly allocated to receive intraluminal perfusion of 0.1 N hydrochloric acid or normal saline at a rate of 5 mL/min for 20 min. The catheter was then advanced so that all distal ports were once again located in the stomach, and the slow station pullthrough was repeated. The subject was not aware which infusate was being used. Recordings were made and analyzed using the PC Polygraf HR data acquisition system and Polygram Upper GI edition version 6.4 software, respectively (Synectics Medical, Sweden). Tracings were coded, stored on disk and subsequently analyzed by a blinded observer. The following three variables were measured.

- Resting LES pressure, which was taken as the end expiratory pressure at the highest pressure point in the LES where the baseline was stable. Regions of postrelaxation contraction were excluded.
- LES location relative to external nares (a measure of esophageal length), which was assessed by determining the point at which the LES was entered and exited during the slow station pullthrough. The gastric side of the LES was taken as the first point where a sustained elevation of baseline over gastric pressure was seen. The proximal margin of the LES was defined as the point where respiratory reversal had occurred and esophageal body pressures were recorded.
- The axial length of the LES, which was defined as the distance in centimeters from the distal to the proximal margin of the LES.

Data are expressed in terms of the change from baseline (ie, before and after infusion of either saline or acid), and statistical comparisons were made between the saline perfusion and acid perfusion days with the Mann-Whitney test. Linear regression analysis was used to determine the reproducibility of the pullthrough techniques in establishing the proximal margin of the LES. P<0.05 was considered significant. Data are expressed as mean ± SEM.

RESULTS

Reproducibility of manometric localization of LES: To determine the reproducibility of the LES mapping technique in establishing LES location relative to the nares (and hence...
esophageal length), the baseline pullthroughs performed on the two study days were compared. There was a highly significant correlation between the manometrically defined proximal margin of the LES in the same individual studied one week apart (r=0.95; P<0.0001) (Figure 1).

**Effect of acid perfusion on resting LES pressure:** Resting LES pressures remained stable before and after esophageal perfusion (Figure 2). There was no difference in resting LES pressure between the acid perfusion and saline perfusion days.

**Effect of acid perfusion on LES location and LES axial length:** Figure 3 shows the variable of primary interest – the change in LES position as a measure of esophageal length. With saline perfusion, the LES migrated slightly distally, indicating esophageal lengthening. Acid perfusion resulted in a significant (P=0.016) proximal migration of the LES that averaged 0.5±0.2 cm, with a shortening of 1.8 cm occurring in one subject.

The axial length of the LES itself also appeared to decrease in the acid-perfused group compared with the saline-perfused group (Figure 4), although this difference was not statistically significant (P=0.16).

**DISCUSSION**

These studies confirm that, in humans, intraluminal acid exposure of a duration similar to that which can occur in GERD (10), results in significant esophageal shortening, as measured by proximal migration of the LES. This result is similar to that seen in the opossum model (8,9) and raises the intriguing possibility that reflux esophagitis might contribute to the formation of a hiatus hernia.

A large, fixed hiatus hernia can make reflux worse by providing an acid reservoir with ready access to the LES (3,4). Also, if normally located, the crural fibres of the diaphragm may buttress the region of the LES, thereby contributing to the gastroesophageal pressure barrier (5,6). However, children with abnormal reflux usually do not have a hiatus hernia unless severe esophagitis is present (11). It is, therefore, conceivable that abnormal reflux, primarily triggered by pathological transient LES relaxations (12), may result in longitudinal axis shortening of the esophagus, which, in turn, may contribute to the formation of a hiatus hernia. Once formed, a vicious cycle may be established, whereby the hernia exacerbates reflux, which in turn induces more esophageal shortening and the production of a larger hernia.
The mechanism for this acid-induced esophageal shortening is unclear. In the opossum model, acute intraluminal acid perfusion causes esophageal shortening that appears to be caused by sustained contraction of the longitudinally oriented esophageal musculature. This is not affected by anticholinergic agents or bilateral cervical vagotomy (8). However, pretreatment of the animals with mast cell stabilizers can completely prevent the shortening (9). Luminal acid perfusion of short duration has been shown to result in mast cell degranulation in the opossum esophagus (13), and the histamine released from the mast cells mediates the augmentation of esophageal blood flow triggered by the luminal acid (14). Furthermore, the lamina propria of the human esophagus contains a large number of mast cells, similar to the number seen in the opossum model (15,16).

Although the degree of esophageal shortening induced in our experiments was relatively small (0.5 cm on average), there were three subjects in whom the shortening was more than 1.0 cm. Furthermore, with acid perfusion, one-half of the subjects had 0.5 cm or greater shortening recorded, whereas shortening of this magnitude was never recorded after saline perfusion. It is unclear why significant acid-induced shortening was confined to a subset of individuals studied. When subjects with significant acid-induced shortening were compared with those in whom acid did not induce significant shortening, no significant difference in resting LES pressure or length was revealed. This degree of shortening occurred after only a single, 20 min acid exposure and may have been considerably greater with repeated acid exposures. Shirazi et al (17) induced severe esophagitis in opossums by performing prolonged (4 h) acid perfusion and may have been considerably greater with repeated acid exposures. Clearly, our observations with short duration acid perfusion in healthy volunteers do not prove that reflux esophagitis contributes to hiatus hernia. However, this is the first human experimental study directed at the cause of hiatus hernia, and when taken in combination with the animal data, should make us revisit our thinking on the pathophysiological relationship between hiatus hernia and GERD.

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