Deglutitive inhibition affects both esophageal peristaltic amplitude and shortening

Guoxiang Shi, John E. Pandolfino, Qing Zhang, Ikuo Hirano, Raymond J. Joehl, and Peter J. Kahrilas. Deglutitive inhibition affects both esophageal peristaltic amplitude and shortening. Am J Physiol Gastrointest Liver Physiol 284: G575–G582, 2003; 10.1152/ajpgi.00311.2002.—Deglutitive inhibition attenuates ongoing esophageal contractions if swallows are separated by short time intervals. This study aimed to determine whether esophageal shortening, mediated by longitudinal muscle, was similarly affected. Eight healthy subjects with two distal esophageal segments demarcated by mucosal clips and manometric recording sites positioned within those segments underwent concurrent manometry and fluoroscopy. Peristaltic amplitude and change in distal segment lengths were quantified during single swallows, paired swallows separated by progressively prolonged intervals, and a series of rapid repetitive swallows. During grouped swallows, deglutitive inhibition with complete attenuation of both the manometric contraction and segment shortening was evident with short-interval swallows and rapid-sequence swallows. No inhibition of either was evident with long-interval pairs. With intermediate interswallow intervals, the occurrence and degree of deglutitive inhibition between peristaltic amplitude and segment shortening were closely correlated. Deglutitive inhibition affects both the longitudinal and circular muscle layers of the esophageal wall, and the occurrence of inhibition evident in one layer is strongly correlated with the other.

METHODS

Eight healthy volunteers (3 males, 5 females) free of gastrointestinal symptoms and without a history of upper gas-
trointestinal surgery were studied. The mean age of participants was 26 ± 1 yr. The study protocol was approved by the Northwestern University Institutional Review Board and informed consent was obtained from each subject. No subjects were taking any medications that could affect esophageal motility. Tobacco use was not permitted on the day of the study.

**Endoscopic marking of the esophageal segments by mucosal clipping.** Subjects fasted overnight before undergoing an esophagoscopy under sedation with 1–3 mg of intravenous midazolam. During this procedure, three 11-mm stainless steel clips were attached to the esophageal mucosa using an endoscopic clip-fixing device (HX-3L, Olympus America, Lake Success, NY). *Clip 1* was fixed at the squamocolumnar junction (SCJ), and *clips 2* and *3* were placed ~3 and 6 cm proximal, respectively. *Clips 1* and 2 thus delineated the distal esophageal segment, whereas *clips 2* and 3 delineated the proximal esophageal segment in the subsequent analysis (Fig. 1). After completion of the clipping procedure, subjects were allowed to recover from sedation for at least 1 h before proceeding with the remainder of the experimental protocol. The esophagus was again imaged fluoroscopically 1 mo after the completion of the study, and mucosal clips that had not spontaneously dislodged were removed endoscopically.

**Manometric and fluoroscopic evaluation.** Manometric recording was performed with a 9-lumen silicone catheter, 3.5-mm outer diameter (Dentsleeve, Bowden, South Australia). A 6-cm sleeve was used to monitor the esophagogastric junction pressures. Side-hole recording sites were spaced 3 cm apart proximal to the sleeve center, with an additional site 27 cm above the sleeve center that was used as a swallow marker and another 4 cm distal to the sleeve center used to monitor intragastric pressure (Fig. 1). Manometric recording channels were connected to external pressure transducers that were, in turn, connected to a 16-channel computerized polygraph (Neomedix Systems, Warriewood, New South Wales, Australia) set at a sampling frequency of 40 Hz. The manometric assembly was passed transnasally, positioned such that the sleeve sensor straddled the lower esophageal sphincter, and taped securely to the subject’s nose. Subjects laid in a supine posture and were allowed to adapt to the recording apparatus for at least 15 min before experimentation. This was followed by a 15-min baseline recording period. Manometric data were processed using Gastromac software (Version 3.5, Neomedix).

The subject was then positioned under a fluoroscope centered on the lower chest and upper abdomen. Two swallow trials of 5 ml room-temperature water were imaged fluoroscopically. Thereafter, subjects were allowed to recover from sedation for at least 1 h before proceeding with the remainder of the experimental protocol.

The esophagus was again imaged fluoroscopically 1 mo after the completion of the study, and mucosal clips that had not spontaneously dislodged were removed endoscopically.

Fig. 1. Tracing of a fluoroscopic image of the lower esophagus illustrating the experimental setup. The distal clip (Clip 1) was attached at the squamocolumnar junction. Clip 2 was attached ~3 cm proximal, and Clip 3 was attached 6 cm proximal. Clip 1 and Clip 2 delineated the distal esophageal segment; Clip 2 and Clip 3 delineated the proximal esophageal segment. The sleeve sensor straddled the esophagogastric junction.
RESULTS

All subjects completed the protocol without unforeseen problems; clip attachment was easily accomplished, and the procedures were well tolerated. The clips and sites of mucosal attachment were readily identified fluoroscopically.

The intervals between two swallows measured from the pharyngeal recording site on the manometric tracing were 3.2 ± 0.2, 6.2 ± 0.3, and 9.3 ± 0.3 s for short-, intermediate-, and long-interval pairs, respectively. The interval between the first and second swallows during swallowing at maximal rate was 1.4 ± 0.1 s, and the number of swallows was 12 ± 2.

Interactions between swallows. Normally propagated peristalsis was observed in all subjects during the single swallow. In synchrony with the propagated contraction, the two esophageal segments exhibited an immediate initial lengthening (6–9% of baseline length) and subsequent shortening. The segments began to shorten 1–2 s before the arrival of the contractile wave within each segment. Maximal shortening ranged from 15 to 25%. After segment shortening, they regained their initial length before the termination of the propagated contraction within that segment.

With paired swallows, complex interactions were observed between the swallows. Figures 2 and 3 illustrate examples of manometric tracing and esophageal segment shortening from two of the subjects selected because of the clarity with which one exhibited deglutitive inhibition (Fig. 2) and the other exhibited muscle refractoriness (Fig. 3). Note that in both cases during the multiple swallow sequence, only the final swallow was associated with a propagated contractile sequence and an accompanying sequence of esophageal shortening. In Fig. 2, four paired swallows with different intervals are illustrated. When the interval between...
two swallows was very short (1.9 s), the first swallow was totally inhibited and the second was completely propagated, similar to a single swallow as evident by the manometrically recorded contraction and the sequenced esophageal shortening of both segments. When the interval between swallows was long (8.9 s), each resulted in a completely propagated manometrically recorded contraction and sequenced shortening, although the peristaltic amplitude was slightly lower than that of a single swallow. With paired swallows with intermediate intervals (4.3 and 4.6 s), the first contractile sequence was partially inhibited, evidenced by lower contraction amplitude and early termination of the manometrically recorded contraction in the distal segment. Analogous to this, only the proximal, not distal, segment exhibited slight shortening. On the other hand, the second swallow of the pairs appeared relatively normal, both manometrically and in terms of sequenced shortening.

Figure 3 illustrates a series of single, paired, and multiple swallows in another subject who best exhibited muscle refractoriness. The manometric and shortening activity associated with the single swallow, short-interval swallow, long-interval swallow, and multiple swallows is similar to those illustrated in Fig. 2. However, the intermediate interval swallows exhibited a distinct pattern. In the paired swallows separated by 4.8 s, the first swallow was relatively intact, whereas the second swallow was almost completely inhibited with only a low-amplitude simultaneous contraction evident in the two distal channels, and no significant esophageal shortening was observed. Similarly, in the paired swallows with an interval of 7.5 s, the first peristaltic sequence was relatively intact and, although the second was associated with a propagated contraction, this was of low amplitude. Similarly, the degree of shortening was minimal. Thus, rather than the second swallow attenuating the contractile activity...
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of the first, as illustrated in Fig. 2 (deglutitive inhibition), the first attenuated the second (muscle refractoriness). Of the eight subjects studied, five exhibited only deglutitive inhibition and three showed some degree of muscle refractoriness. Of the three, the example illustrated in Fig. 3 was by far the most illustrative.

**Duration of deglutitive inhibition.** Figure 4 summarizes the contraction amplitudes and the associated percentages of shortening observed during all single swallows; paired swallows of short, intermediate, and long intervals; and rapidly sequenced swallows for all subjects. The contraction amplitude and the extent of shortening observed for a single swallow, the second swallow of a pair, or the last of a series of multiple swallows was very similar within both esophageal segments. However, both peristaltic amplitude and the extent of segmental shortening were strongly influenced by the duration of the time interval between the paired swallows. With short intervals, there was nearly complete inhibition of the first peristaltic contraction both in terms of peristaltic amplitude and segmental shortening. Conversely, with long-interval swallows, there was no significant inhibition of peristaltic amplitude or segmental shortening within either esophageal segment. However, for paired swallows separated by intermediate time intervals, both segments exhibited significantly lower amplitude and a reduced extent of shortening (limited to the distal segment). Note that because deglutitive inhibition was by far the dominant pattern of interaction observed, the influence of muscle refractoriness is not evident in Fig. 4.

In Figs. 2 and 3, the intervals between the onset of the pharyngeal swallow and the onset of the manometric contraction are labeled L1, L2, and L3 for the channels 15, 6, and 3 cm proximal to the SCJ, respectively. These latencies approximate the period of inhibition before the onset of the manometric contraction at each esophageal locus. Thus, if deglutitive inhibition is simply a consequence of the normal period of inhibition associated with peristalsis, it should be evident at each esophageal location (SCJ + 15, SCJ + 6, and SCJ + 3 cm) for a period closely related to L1, L2, and L3 after the first swallow, respectively. Figure 5 tests this hypothesis for the manometrically recorded contractions 15 and 6 cm proximal to the SCJ. In the Fig. 5A, **time 0** for each pair of swallows is equal to L1 for the subject in question, and the contractile index is equal to the peristaltic amplitude of the first swallow divided by that of the single swallow for that subject. Thus, if there were no change in amplitude, the contractile index would be 1, and if there was complete inhibition of the first swallow, it was 0. Quite clearly, at 15 cm proximal to the SCJ, there was complete inhibition of the first swallow until **time −1.0** (s) and partial inhibition until **time 0**, after which no consistent effect was observed. Figure 5B illustrates the analogous analysis for the recording site 6 cm proximal to the SCJ; in this case, **time 0** was equal to L2 for each subject. Note that there is complete inhibition until −3.0 s, partial inhibition until 0.0 s, and no consistent inhibition of the first swallow after 0.0 s.

Figure 6 illustrates an analysis of the persistence of deglutitive inhibition of segment shortening that is analogous to that of inhibition of the manometric contraction illustrated in Fig. 5. Figure 5A pertains to the proximal segment, and Fig. 5B pertains to the distal segment. **Time 0** is equal to L2 in A and L3 in B for each subject. For both segments, significant inhibition is evident until −2.0 s and partial (although not statistically significant) inhibition is evident until −1.0 s. Thereafter, no consistent effect is seen in either segment.

**Correlation between manometric amplitude and the extent of segment shortening.** A case-by-case correlation of the contraction index with the shortening index for the first swallow of every pair is illustrated in Fig. 7. In every instance, the occurrence of a manometric contraction was accompanied by some degree of segment shortening. Quantitatively, a highly significant corre-
lation was found between the contraction index and the percentage of shortening during the first of the paired swallows ($r = 0.6, P \leq 0.001$ for the proximal segment, $r = 0.66, P \leq 0.001$ for the distal segment).

**DISCUSSION**

The major aims of this study were to determine whether or not deglutitive inhibition affected the longitudinal muscle of the esophageal muscularis propria in a similar manner to the circular muscle and, if so, to determine how the two correlated. Experiments were done using concurrent manometry and fluoroscopy after having demarcated two distal esophageal segments by placement of mucosal clips and situating side-hole recording sites within each segment. The major findings of the investigation were that longitudinal muscle does exhibit deglutitive inhibition, that the degree of attenuation of segment shortening observed strongly correlated with the degree of attenuation of peristaltic amplitude, and that the period of inhibition of segment shortening was 1–2 s less than the inhibition of contractile amplitude within that segment.

The manometric contractions associated with two closely spaced swallows observed in the current study closely parallel the earlier description of Vanek and Diamant (14): with short interswellow intervals (<4 s) or a rapid sequence of swallows, only the final swallow was associated with a propagated contraction; with interswellow intervals >8 s, there were two normally appearing propagated contractions; with interswellow intervals between 4 and 8 s, there was either significant or complete inhibition of the first propagated contraction. We also observed that in every case, complete inhibition of the manometric contraction was matched by inhibition of shortening in the corresponding segment, and in cases of partial inhibition, the...
degree of inhibition evident manometrically was closely correlated with the degree to which segment shortening was attenuated. These observations suggest that the property of deglutitive inhibition affects both the longitudinal and circular muscle contractile patterns that are integral to esophageal peristalsis and that if one component is subject to partial or complete deglutitive inhibition, the other is similarly affected.

An elegant investigation by Sifrim et al. (11) used an artificial high-pressure zone in the distal esophagus to demonstrate that normal peristalsis was comprised of a wave of inhibition followed by a sequenced contraction. That investigation uniquely focused on manometric recordings, presumably indicative of circular muscle contractility. In the current study, we tested the hypothesis that deglutitive inhibition is another manifestation of the initial wave of inhibition that precedes the sequenced esophageal contraction. We reasoned that if this were the case, the latency between swallowing and manometrically recorded contraction at a given esophageal locus would closely parallel the period of deglutitive inhibition operational at that locus. As evident by the analysis illustrated in Fig. 5, this relationship is highly significant; deglutitive inhibition persisted in both the proximal and distal esophagus for time periods equal to the respective latencies observed during normal peristalsis. We then tested the hypothesis that deglutitive inhibition of segment shortening, indicative of longitudinal muscle activity, should exhibit similar temporal characteristics. Figure 6 illustrates the findings from that analysis. Note that although there is a clear relationship between the degree of inhibition of shortening and the time reference, inhibition does not persist to time 0 as was the case with the manometric (circular muscle) contraction. In the case of shortening, deglutitive inhibition ends 1–2 s before the time references that were equal to the respective latencies of circular muscle contraction observed during peristalsis. In fact, owing to an inherent methodological limitation of our study, we probably somewhat underestimated the magnitude of the delay between the end of longitudinal and circular muscle inhibition. The methodological limitation in question is that segmental shortening was measured along a 3-cm segment of esophagus, whereas circular muscle contraction was measured at the proximal margin of that segment. Thus, if circular and longitudinal muscle contractions were simultaneous, the inherent error in our measurement would make it appear that the circular muscle contraction preceded the longitudinal muscle contraction, which is the opposite of what was observed. Intraluminal high-frequency ultrasound would overcome this limitation because it can quantify muscle thickness and hence contraction of both layers of esophageal muscle at a given location (7, 15). However, our observation is consistent with earlier observations relating to the relative timing of contraction of the longitudinal and circular muscle during peristalsis. Analysis using methods similar to the current investigation (4, 8, 9), external markers placed directly on the muscularis propria (2), or intraluminal high-frequency ultrasound (7) have all concluded that the onset of longitudinal muscle contraction precedes that of circular muscle contraction.

Swallow-evoked peristaltic sequences are mediated via vagal efferent nerves. Neurophysiological studies in animals support the hypothesis that peristalsis is comprised of active inhibition followed by a sequenced esophageal contraction and that both esophageal inhibition and contraction are centrally mediated (14). Vagal efferent fiber recordings have demonstrated populations of short- and long-latency neurons whose activity temporally corresponds with inhibition and contraction, respectively. Furthermore, the long-latency neurons to the striated and smooth muscles are sequentially activated. Peripheral mechanisms can also mediate sequential esophageal contractions as evidenced by the persistence of secondary peristalsis after thoracic vagotomy (5). No direct neurophysiological data exist regarding the mechanism of deglutitive inhibition of esophageal longitudinal muscle. However, on the basis of the similarities of deglutitive inhibition of the propagated contraction and segment shortening observed in the current investigation, we suspect that the mechanisms are similar, and both likely involve centrally mediated vagal inhibition. Furthermore, cen-
trally mediated vagal inhibition may be the only mechanism operational for longitudinal muscle, because the peripheral mechanism of sequential contraction was not demonstrated in longitudinal muscle (13).

In conclusion, esophageal shortening is affected by deglutitive inhibition in a similar manner to manometrically recorded esophageal contractions. The presence and degree of inhibition evident in peristaltic amplitude closely correlates with those observed in segmental shortening, indicative of longitudinal muscle activity. The deglutitive inhibition evident in both muscle layers is likely attributable to the same vagally mediated inhibition that is an integral component of normal peristalsis, with the caveat that just as the onset of longitudinal muscle contraction precedes circular muscle contraction, the period of deglutitive inhibition of the longitudinal muscle is 1–2 s shorter than that of circular muscle.

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REFERENCES