Absence of a deglutitive inhibition equivalent with secondary peristalsis

John E. Pandolfino, Guoxiang Shi, Qing Zhang, and Peter J. Kahrilas

Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Submitted 27 August 2004; accepted in final form 1 November 2004

Absence of a deglutitive inhibition equivalent with secondary peristalsis. Am J Physiol Gastrointest Liver Physiol 288: G671–G676, 2005. First published December 16, 2004; doi:10.1152/ajpgi.00388.2004.—This study aimed to determine the interactions between closely paired swallow-induced primary peristalsis (PP) and air injection-induced secondary peristalsis (SP). Ten subjects (7 men, 18–42 yr) were studied using a catheter, including two sleeves (upper and lower esophageal sphincters), a midesophageal infusion port, and seven esophageal and two pharyngeal recording sites. Ten iterations of PP and SP were induced by 5-mL water swallows and 20-mL intraesophageal air injections, respectively. Thereafter, the interactions between PP and SP, separated by 1- to 12-s intervals, were studied in all four possible sequences: paired swallows, swallow preceded by air injection, air injection preceded by swallow, and paired air injections. Tracings were analyzed for lower esophageal sphincter relaxation, presence and integrity of peristalsis, and event interaction. Eight subjects with success rates of both ≥90% PP and ≥80% SP were analyzed (PP 97 ± 2%, SP 90 ± 3%). During paired PP interactions and SP followed by PP, the first sequence was inhibited by the second with intervals < 4–6 s. However, no inhibition of the first peristaltic sequence was found in either PP followed by SP trials or SP followed by air injection. In contrast to swallow-induced or proximal esophageal distention, air injection into the lumen of the midesophagus does not inhibit an ongoing peristaltic event. Being that the elicitation of SP in the smooth muscle esophagus is intramurally mediated, this suggests that deglutitive inhibition is a centrally mediated phenomenon rather than an intrinsic property of peristalsis.

Primary peristalsis affects esophageal bolus clearance after swallowing, whereas secondary peristalsis is initiated within the esophagus and functions to clear either residual bolus or refluxate. Early reports suggested that, despite having different stimuli for elicitation, these two modes of peristalsis may be mediated by similar neuromuscular control (4, 5). However, more recent data suggest that primary and secondary peristalsis may be quite different in terms of the central and peripheral neural control mechanisms (6, 9).

Deglutitive inhibition is a fundamental property of primary esophageal peristalsis and is evident as a wave of inhibition that precedes the sequenced peristaltic contraction. The physiological equivalent of deglutitive inhibition is hyperpolarization of the esophageal muscularis propria following the pharyngeal swallow. The period of hyperpolarization progressively increases in duration with increasingly distal esophageal loci, and this determines a latency period that defines both the direction and propagation of the subsequent peristaltic contraction. In addition, this latency period has been shown to affect the response to paired or multiple rapid swallows. Peristaltic activity resultant from a swallow is rapidly and completely inhibited by a second swallow if the interval between swallows is inadequate for the first contraction to traverse the striated muscle (proximal esophagus) (12). Once the peristaltic contraction associated with the first swallow reaches the distal esophagus, a second swallow cannot totally inhibit the contraction, but can abort its distal propagation. Peristalsis following paired swallows may also be affected by muscle refractoriness. If a second swallow follows the first by only a short interval, the peristaltic contraction associated with the second may be attenuated or incomplete as a result of muscle refractoriness consequent from the first swallow (1, 3, 10, 12). Thus, depending on the interswallow interval, a second swallow can have no effect, partially inhibit, or completely inhibit the peristaltic contraction associated with the first swallow on the basis of deglutitive inhibition. Conversely, the first swallow can attenuate the peristaltic contraction of the second by muscle refractoriness.

Whether there is a deglutitive inhibition equivalent that precedes secondary peristalsis is uncertain. To date, only one published study assessed the interaction between paired primary and secondary peristaltic waves (2). Using pharyngeal injection of water to induce primary peristalsis and air infusion 2 cm below an upper esophageal sphincter (UES) sleeve to induce secondary peristalsis, those authors concluded that both stimuli inhibited the propagation of both primary and secondary peristaltic waves. The aim of this study was to further explore this relationship, both by quantifying the effect of one type of peristalsis on the other when paired at a spectrum of intervals and by positioning the stimulus for secondary peristalsis where it is most likely to occur in a physiological setting, the midesophagus.

MATERIALS AND METHODS

Ten healthy volunteers (7 men), free of gastrointestinal symptoms and without a history of upper gastrointestinal 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. Smoking was not permitted on the day of the study.

Manometry. Manometric recording was performed with a custom-designed silicone catheter that incorporated two sleeves [for UES and lower esophageal sphincter (LES)], an air injection port located 11 cm above the center of the distal sleeve, an intragastric side port, seven intraesophageal side ports, and two pharyngeal recording sites (Fig. 1). The catheter was placed transnasally after an 8-h fast. Manometric recording channels were connected to a 16-channel computerized polygraph (Neomedix Systems Pty, Warriewood, New South Wales, Australia), set at a sampling frequency of 40 Hz. The catheter was

Address for reprint requests and other correspondence: J. E. Pandolfino, Division of Gastroenterology, Dept. of Medicine, Northwestern Univ. Feinberg School of Medicine, Suite 1400, 676 N St. Clair St., Chicago, IL 60611 (E-mail: j-pandolfino@northwestern.edu).

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positioned such that the distal sleeve sensor straddled the LES and was taped securely to the subject’s nose. Subjects were positioned 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. Thereafter, recording was continued during different combinations of primary peristalsis and secondary peristalsis. Primary peristalsis was induced by asking subjects to swallow 5 ml of water given with a syringe. Secondary peristalsis was induced by rapid intraesophageal injection (≤1 s) of 20 ml of air through an infusion port 11 cm above the LES center.

Study protocol. The study protocol began with 10 single swallows performed with swallows separated by at least 20 s. After completion of the single swallows, 10 single intraesophageal air injections were separated by at least 20 s were performed. Thereafter, four combinations of swallowing and intraesophageal air injection were performed, with each combination repeated 7–10 times: 1) double swallows at intervals from 1 to 12 s, 2) a swallow followed by an intraesophageal air injection at intervals ranging from 1 to 12 s, 3) an intraesophageal air injection followed by a swallow at ranging intervals from 1 to 12 s, and 4) double intraesophageal air injection at intervals ranging from 1 to 12 s. Manometric data were processed utilizing Gastromac software (version 3.5, Neomedix).

Data analysis. The data were analyzed to assess the presence and integrity of peristalsis and the interaction between the two events (swallowing, intraesophageal air injection). The amplitude of contrac-

**RESULTS**

**Contraction amplitude and relaxation duration during primary and secondary peristalsis.** Examples of manometric tracings for both primary and secondary peristalsis are shown in Fig. 2. The contraction amplitude of primary peristalsis and that of secondary peristalsis were not significantly different in the middle and distal esophagus. In contrast, the contraction amplitude in the proximal esophagus was lower with secondary peristalsis compared with primary peristalsis. The durations of LES relaxation associated with primary peristalsis and secondary peristalsis were not significantly different (Table 1).

**Pattern of interaction between primary and secondary peristalsis.** Manometric tracings from one subject are shown to illustrate the typical interactions between primary and secondary peristalsis during each experimental protocol (Figs. 3 and 4). When the second event was a swallow, the first event was totally or partially inhibited, regardless of whether it was a primary peristaltic waveform or air injection-induced secondary peristalsis (Fig. 3). If the interval between events was long enough, the first event was preserved, regardless of the type of peristalsis. By contrast, if the second event was an intraesophageal air injection, the first event remained intact, regardless of the interval between the two events (Fig. 4). The fate of the second intraesophageal air injection in a pair depended on the time interval between events and not the type of first-event stimulus (swallow vs. air injection). If the interval was short, no secondary peristalsis was induced by air injection after a swallow or after air injection-induced secondary peristalsis. If the interval was long, a propagated secondary peristaltic wave was induced by air injection and proceeded down the esophagus to completion.

**Inhibition of peristalsis.** The inhibition rate of the first event by the second is shown in Table 2. With short interevent intervals, swallows completely inhibited 88% of primary peristaltic events and 78% of secondary peristaltic events. With medium interevent intervals, swallow-induced primary peristalsis inhibited 68% of primary peristaltic events and 59% of secondary peristaltic events. In contrast, air injection did not inhibit any primary peristaltic events, regardless of time interval. Air injection did inhibit ~10% of air infusion-induced secondary peristaltic events during each time interval. This, however, was likely related to the inherent failure rate for air injection to induce secondary peristalsis and not a true inhibition caused by air injection.
DISCUSSION

This study examined the presence, integrity, and the interaction between primary peristalsis induced by swallowing and secondary peristalsis induced by midesophageal air injection. Paired peristaltic sequences were studied in each possible combination of primary and secondary and with a spectrum of intervals separating events ranging from brief (less than that required for the first event to traverse the proximal esophagus) to long (greater than the time required for the first peristaltic event to traverse the entire esophagus). Primary and secondary peristalsis were found to be quite similar, except for the slightly decreased amplitude of secondary peristalsis in the proximal esophagus. As expected, paired swallows exhibited deglutitive inhibition of the first peristaltic sequence that was dependent on the time interval separating the swallows. Similarly, a secondary peristaltic sequence was inhibited by a swallow if the time interval separating the events was brief enough. In contrast, neither the primary nor secondary peristaltic sequence was inhibited by midesophageal air injection. These results suggest that air injection in the midesophagus is incapable of eliciting deglutitive inhibition akin to that of primary peristalsis or distention of the proximal esophagus.

Physiologically, deglutitive inhibition results in relaxation of both the UES and LES, as well as inhibition of ongoing peristaltic activity, and is evident by hyperpolarization of the esophageal muscularis propria. Although the precise mechanism leading to this hyperpolarization is unclear, certain characteristics have been described. The inhibitory wave begins immediately after swallowing and is immediately evident along the entire length of the esophagus. Given that primary and secondary peristalsis share many similar features, it was theorized that secondary peristalsis may also be preceded by a wave of inhibition. Two previous studies explored this hypothesis, albeit each with unique methodology. Sifrim and Janssens (11) created an artificial high-pressure zone in the distal esophagus to ascertain whether or not air injection into the proximal esophagus could elicit relaxation of the high-pressure zone analogous to that seen during swallowing. They reported that relaxation did occur in the artificial high-pressure zone and thus concluded that a wave of inhibition did precede secondary peristalsis (11). However, they did not explore the effects of paired stimuli. In the second study, Bardan et al. (2) studied closely sequenced peristaltic contractions induced by instillation of water in the pharynx (primary peristalsis) and air injection into the proximal esophagus (secondary peristalsis) (2). They reported that air injection inhibited 70% of primary

Table 1. Contraction amplitude and LES relaxation duration associated with primary and secondary peristalsis

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<th>Amplitude, mmHg</th>
<th>LES Relaxation Duration, s</th>
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<tr>
<td>Proximal (18 cm)</td>
<td>43.8 ± 7.9</td>
<td>5.1 ± 0.7</td>
</tr>
<tr>
<td>Middle (12 cm)</td>
<td>68.1 ± 9.5</td>
<td>68.0 ± 9.1</td>
</tr>
<tr>
<td>Distal (6 cm)</td>
<td>65.4 ± 10.7</td>
<td>4.6 ± 0.7</td>
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Values are means ± SE. LES, lower esophageal sphincter. *p < 0.01 vs. primary peristalsis.
peristaltic events and 75% of secondary peristaltic events and concluded that air injection inhibited primary and secondary peristalsis via a neural control mechanism similar to deglutitive inhibition.

The results reported here are somewhat discrepant to the findings of Bardan et al. (2) described above. Although we found similar effects with regard to the effect of primary peristalsis on the inhibition of a previous peristaltic event, we could not demonstrate this with air injection into the midesophagus. We found that air injection 8–11 cm proximal to the LES (corresponding to the smooth muscle segment of the esophagus) applied during an ongoing peristaltic contraction did not inhibit either the primary or secondary peristaltic sequence. The reason for this discrepancy is likely a methodological issue, specifically the more distal location of air injection. We also used a larger volume of air injection, but this factor is unlikely to be responsible for the discrepant results as higher volumes would have been expected to be more effective at inducing inhibition of the previous peristaltic event. We chose the 20-ml volume based on the observations of Schoeman and Holloway (7, 8), who found this to be the most effective stimulus for inducing secondary peristalsis compared with 5-ml air, 10-ml air, 2-ml water, 5-ml water, or 10-ml water.

As detailed above, the most likely explanation for the contrasting effects of air injection into the proximal esophagus, as done by Bardan et al. (2), and into the midesophagus, as done in this study, pertains to the differences in the physiology.
of the striated as opposed to the smooth muscle esophagus. This suggests that secondary peristalsis induced by air distention in the striated muscle portion of the esophagus is centrally mediated via the vagus nerve and behaves similarly to primary peristalsis in that it can exhibit inhibition (analogous to deglutitive inhibition) of an ongoing peristaltic sequence. In contrast, secondary peristalsis induced by distention located in the smooth muscle esophagus is not mediated by a central vagal mechanism. Instead, the evidence suggests that distention in the smooth muscle esophagus elicits a peristaltic wave mediated via an intramural mechanism subject to deglutitive inhibition but without an analogous property itself.

Whether air injection into the midesophagus causes partial inhibition of the previous peristaltic event is unclear. LES relaxation was present with air injection into the midesophagus, and thus an inhibitory process is present. Unfortunately, we could not determine whether air injection into the midesophagus altered the contraction amplitude or duration of the previous peristaltic event. This limitation was due to the imprecise triggering and timing of air injection-induced secondary peristalsis. Thus it was difficult to quantify the effect of air injection on the manometric parameters of peristalsis.

Another interesting phenomenon illustrated in this study was that, in addition to not inhibiting a previous peristaltic event, air injection during ongoing peristalsis did not elicit any peristaltic event. This is in contrast to primary peristalsis, which clearly both inhibited the prior peristaltic event and elicited a propagated contraction. This suggests that the intramural mechanism responsible for the elicitation of secondary peristalsis is rendered inoperable by an ongoing peristaltic

Table 2. *The inhibition rate of the first event by the second, categorized by event combination and by the interval separating events*

<table>
<thead>
<tr>
<th>Event Sequence</th>
<th>Short interval</th>
<th>Medium interval</th>
<th>Long interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swallow-swallow</td>
<td>88</td>
<td>68</td>
<td>4</td>
</tr>
<tr>
<td>Swallow-air injection</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Air injection-swallow</td>
<td>78</td>
<td>59</td>
<td>0</td>
</tr>
<tr>
<td>Air injection-air injection</td>
<td>10</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

**Fig. 4.** Tracings illustrating the interaction between paired stimuli when the second event was air injection. *A* and *B*: swallows (vertical lines) followed by air injection (arrows). Primary peristalsis remained intact and propagated distally in both tracings. In addition, there was no evidence of secondary peristalsis after air injection when the time interval was short (*A*). *D* and *E*: pairs of air injections. Once again, air injection did not inhibit the preceding secondary peristaltic waveform from the first air injection. There was also no secondary peristaltic event noted with the second air injection, if the interval was short (*C*).
sequence. However, the second stimulus was not completely without effect, as evidenced by the prolongation of LES relaxation associated with the closely timed stimuli. Still, the absence of a subsequent contractile sequence suggests that the second stimulus was rendered subthreshold, possibly a consequence of a period of refractoriness accompanying the ongoing peristalsis. In conclusion, we found that, in contrast to what is observed with swallowing or with proximal esophageal distention, air injection into the lumen of the midesophagus does not inhibit an ongoing peristaltic event. Being that the elicitation of secondary peristalsis in the smooth muscle esophagus is intramurally mediated, this supports the contention that deglutitive inhibition is a centrally mediated phenomenon rather than an intrinsic property of peristalsis.

GRANTS

This work was supported by National Institute of Diabetes and Digestive and Kidney Diseases Grant RO1-DK-56033 (P. J. Kahrilas) from the Public Health Service.

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