Esophageal Body Motor Response to Reflux Events: Secondary Peristalsis

Richard H. Holloway, MD, FRACP

The esophageal body is a major component of the antireflux mechanism. Disruption of esophageal peristalsis affects both volume clearance and delivery of swallowed saliva to the distal esophageal body. The esophageal body responds to reflux by an increase in primary peristalsis through stimulation of swallowing and secondary peristalsis through esophageal distension. Primary peristalsis is the most common motor event after reflux and accounts for up to 90% of initial and subsequent motor activity. Secondary peristalsis is uncommon but may be important during sleep when swallowing is relatively suppressed. Some patients with reflux disease, particularly those with severe esophagitis, exhibit impaired esophageal responses to reflux. It is likely that this impairment prolongs acid clearance and may also influence the proximal extent of the refluxate within the esophageal body. *Am J Med.* 2000;108(4A): 20S–26S. © 2000 by Excerpta Medica, Inc.

From the Department of Gastrointestinal Medicine, Royal Adelaide Hospital, Adelaide, South Australia, Australia.

Reprints are not available.

Correspondence should be addressed to Richard H. Holloway, MD, FRACP, Department of Gastrointestinal Medicine, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia 5000, Australia.

Gastroesophageal reflux is a physiologic event and occurs in almost all individuals to some degree. Reflux disease in most patients, however, is characterized by an increased exposure of the esophageal mucosa to acid, resulting primarily from an increased rate of reflux episodes. Approximately 50% of patients exhibit abnormally slow clearance of the refluxed acid, and prolonged periods of esophageal acidification are believed to be more damaging to the esophageal mucosa than are frequent short periods. Acid refluxate also extends more proximally up the esophageal body in patients with reflux disease compared with controls,[1] and an important subset of patients with supraesophageal complications such as posterior laryngitis,[2,3] hoarseness,[4] or asthma[5] exhibits higher levels of acid exposure in the proximal esophagus than do those without such complications. Patients with chronic cough also have been reported to have defective esophageal acid clearance.[6]

The esophageal body is a major component of the antireflux mechanism. Once reflux has occurred, up to 90% of the refluxate volume can be cleared by one or two peristaltic sequences,[7] leaving just a small residue for neutralization by swallowed saliva. An intact peristaltic mechanism is essential for effective acid clearance; disruption of esophageal peristalsis affects not only volume clearance[8] but also delivery of swallowed saliva to the distal esophageal body.

PATTERNS OF ESOPHAGEAL BODY MOTILITY IN RESPONSE TO ACID REFLUX

Two major components of esophageal body motility should be considered: propagated activity, or peristalsis, and tone.

Esophageal Peristalsis

Initial motor response: In normal subjects, the initial response to acid reflux is usually primary peristalsis (**Figure 1**), which occurs in 41% to 57% of occasions.[9–11] This is probably because of the high rate of swallowing during the awake state, about once per minute, and the stimulation of swallowing by acid reflux.[9] Secondary peristalsis (**Figure 2**) is less common and occurs on only 27% to 57% of occasions.[9–11] However, secondary peristalsis may be more important when subjects are supine and asleep. During that period, secondary peristalsis has been reported to be the initial clearance event on 86% of occa-

0002-9343/00/$20.00
PII S0002-9343(99)00291-0

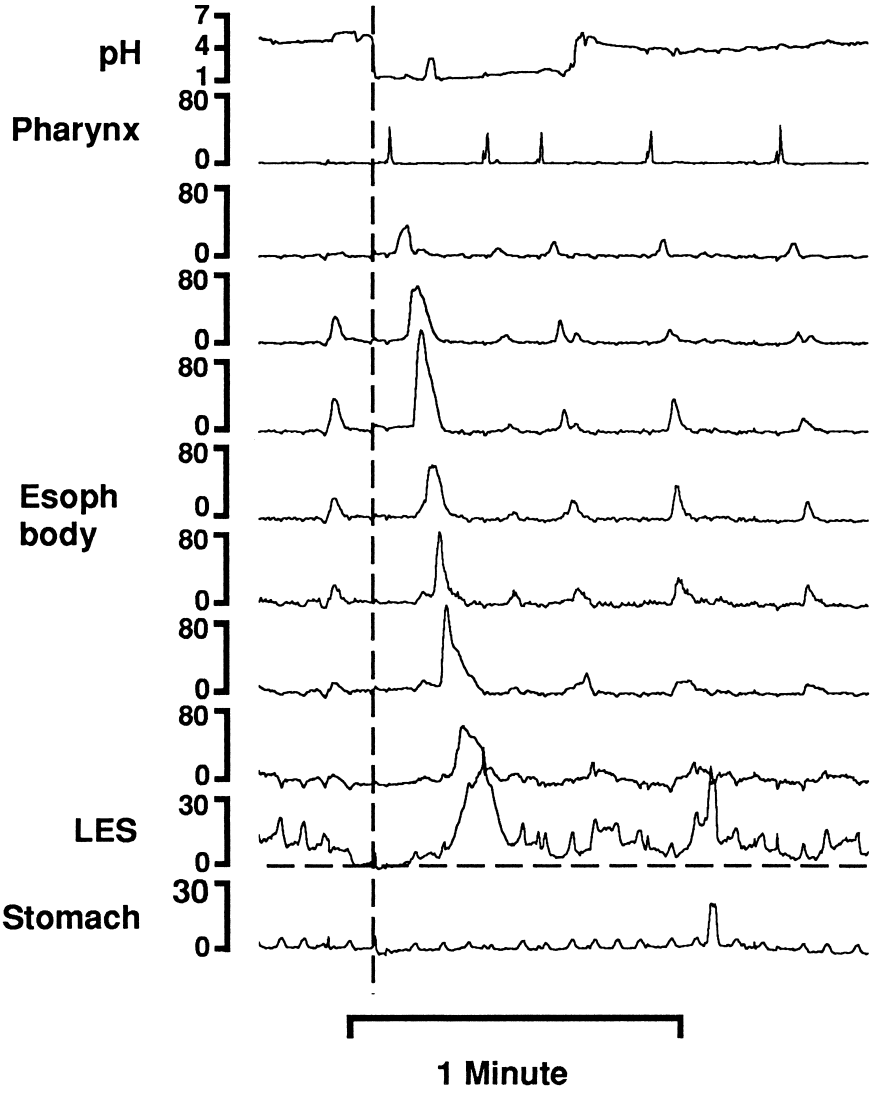

Figure 1. Gastroesophageal reflux occurring during a transient lower esophageal sphincter (LES) relaxation. The occurrence of reflux is indicated by the vertical dashed line. The first esophageal (Esoph) response after reflux is primary peristalsis that terminates the transient LES relaxation.

sions.[11] It is likely that suppression of salivation and swallowing by sleep[12] reduces the occurrence of primary peristalsis and thereby increases the relative frequency and importance of secondary peristalsis under those conditions.

In patients with reflux disease, primary peristalsis is also the most common initial response and has been reported to account for 80% to 90% of initial clearance events.[10,13,14] Secondary peristalsis accounts for only a minority (12% to 17%) of initial clearance events. It also occurs less frequently than in normal subjects,[10,13,14] probably because of defective triggering of secondary peristalsis (see below). Patients with reflux disease also exhibit a greater delay between the onset of reflux and the occurrence of the initial clearance event than do normal subjects. This time may be up to twice that in normal subjects[10,15] and even longer in patients with peptic strictures.[16]

Overall esophageal body motor activity during reflux episodes: Patterns of esophageal motility during acid reflux events mirror those of the initial events. Primary peristalsis remains the most prevalent activity when esophageal pH is below 4. In healthy subjects, it accounts for 70% to 90% of all activity and approximately 90% in patients with reflux disease (**Figure 3**).[9,10,14,17,18] Consequently, secondary peristalsis accounts for only a small proportion of esophageal body activity both in healthy subjects and in patients with reflux disease, ranging from 10% to 25% of all activity. Most studies also have shown

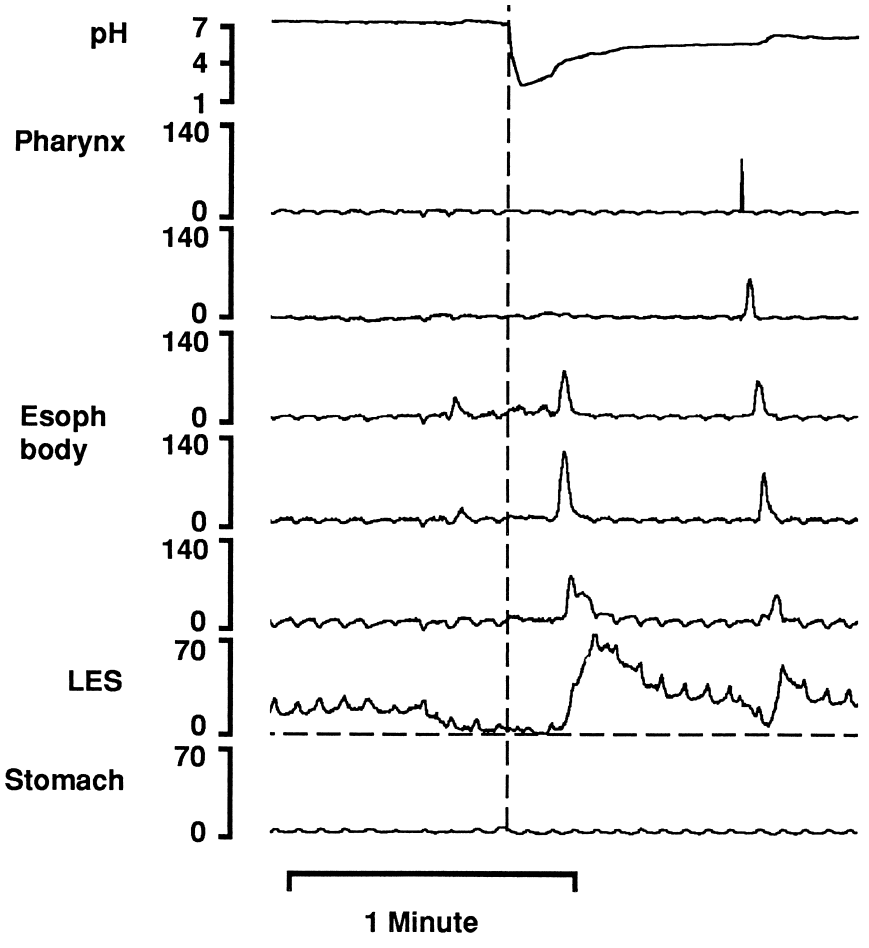

Figure 2. Gastroesophageal reflux occurring during a transient lower esophageal sphincter (LES) relaxation. The occurrence of reflux is indicated by the vertical dashed line. The first esophageal (Esoph) response after reflux is an abnormal secondary peristaltic sequence.

that patients with reflux disease have impaired esophageal motor responses to reflux, as evidenced by an increased time to the first peristaltic response, fewer responses in general and fewer peristaltic responses, an increased interval between peristaltic responses, and a lower proportion of complete peristaltic sequences than do healthy controls.[10,15,16,18] In contrast, one study found no evidence of impaired esophageal body motor response to reflux in patients with reflux disease.[19] This study, however, used a different analytical approach and limited the analysis to the first 2 minutes after the onset of reflux.

Esophageal Tone

As well as phasic propagated motor activity, the esophageal body also exhibits tone.[20] Esophageal tone has been postulated to help restrict the retrograde flow of material up the esophagus during reflux. The effect of reflux on esophageal tone has been measured using an intraesophageal balloon to create an artificial high-pressure zone. The majority of reflux episodes in normal subjects and in most patients with reflux disease occur during transient lower esophageal sphincter (LES) relaxations. Transient LES relaxations per se do not appear to be associated with any changes in tone.[21] In normal subjects, reflux associated with esophageal acidification without distension either causes no change in tone or provokes an increase in esophageal tone. However, reflux associated with abrupt distension of the esophageal body sufficient to produce a common cavity usually (78%) inhibits esophageal tone, as evidenced by relaxation of the artificial high-pressure zone. Subsequent observations in patients with reflux disease have shown that the increase in tone with acidification is significantly less common, and inhibition significantly more common than in healthy controls.[22] The importance of these responses to patterns of reflux remains undetermined. However, it is possible that these patterns of tonic change in response to reflux may contribute either to the more proximal extent of the refluxate and/or the higher prevalence of reflux during transient LES relaxations in patients with reflux disease.

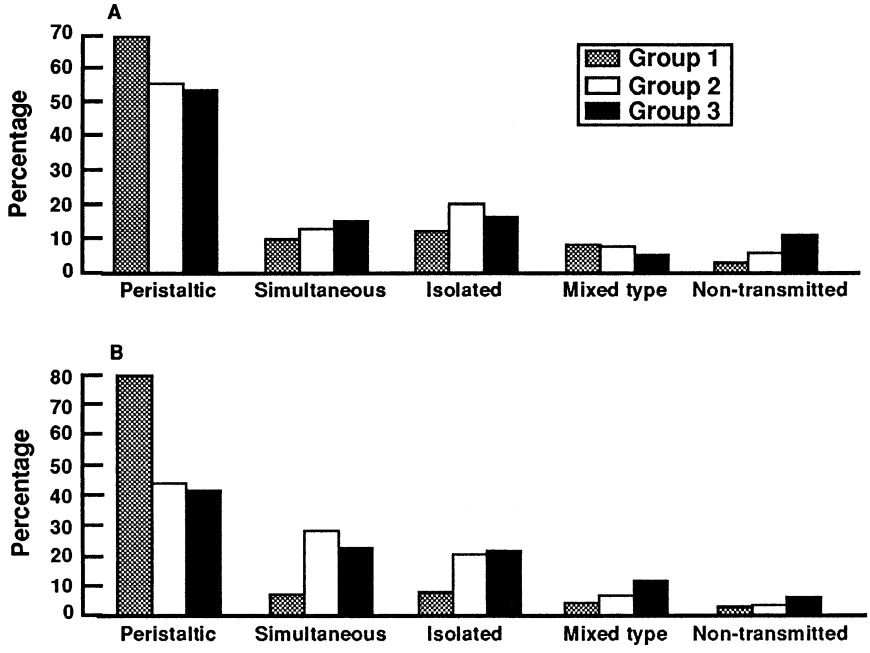

Figure 3. Percentages of different motor activities during gastroesophageal reflux in the upright (A) and supine (B) periods of 24-hour ambulatory monitoring. Group 1, healthy controls; Group 2, endoscopy-negative reflux disease; Group 3, patients with erosive or ulcerative esophagitis. (Reproduced with permission from *Gut.*[18])

RELATIONSHIP BETWEEN ESOPHAGEAL BODY RESPONSE TO REFLUX AND ACID CLEARANCE

Esophageal peristalsis has an integral and dual role in esophageal acid clearance: primarily in the initial clearance of the bulk of the refluxate volume but also in the transport of saliva for the subsequent neutralization of the residual acid. Therefore, one might expect an inverse relationship between the integrity of the esophageal body response to reflux and acid clearance time. Indirect support for this can be found in a number of studies. Overall, acid clearance in patients with reflux disease is two to three times longer than in controls.[23–25] Impaired acid clearance is found in approximately 50% of patients with reflux disease and is more common in patients with severe esophagitis. The two main patterns of peristaltic dysfunction commonly encountered in reflux disease, failed peristalsis, and hypotensive peristalsis[26] impair esophageal volume clearance[8] and are found in 20% of patients with mild esophagitis and in 50% of patients with severe esophagitis.[26] Certainly, defective peristalsis is the major factor underlying abnormal acid clearance in patients with severe esophageal motor disorders, such as scleroderma.[27]

Studies that have examined directly the relationship between esophageal body motility and clearance of spontaneous acid reflux episodes are relatively few. A static laboratory study done in recumbent normal subjects showed that peristaltic failure or incomplete peristaltic sequences were associated with prolongation of acid clearance and a smaller increment in esophageal pH than were complete peristaltic sequences.[9] Similar findings were noted in a comparable study in patients with reflux disease[10] (**Figure 4**). Subsequent studies using 24-hour ambulatory manometry and pH monitoring have tended to support these findings.[14,18,28] As a group, patients with reflux disease had more prolonged acid clearance. This was associated with a longer time from the onset of reflux to the first peristaltic sequence, less frequent motor activity while pH was below 4, and a smaller proportion of peristaltic sequences. Although this pattern of motor activity might be expected to prolong acid clearance, a direct correlation between motility and acid clearance in individual subjects was not performed. Moreover, compared with control subjects, patients with reflux disease required a greater number of peristaltic sequences to restore esophageal pH to above 4, and each sequence was associated with a smaller increment in esophageal pH. These differences suggest that other factors, perhaps defective salivary bicarbonate, were contributing significantly to impaired acid clearance[18] (**Figure 5**). Timmer et al were unable to demonstrate any impairment of esophageal body motility in reflux disease[19] despite similar findings with regard to acid clearance. A potential problem with all of these ambulatory studies is that superimposed reflux, that is, reflux that occurs when esophageal pH is below 4, was not taken into account. Superimposed reflux can artifactually prolong the measured clearance

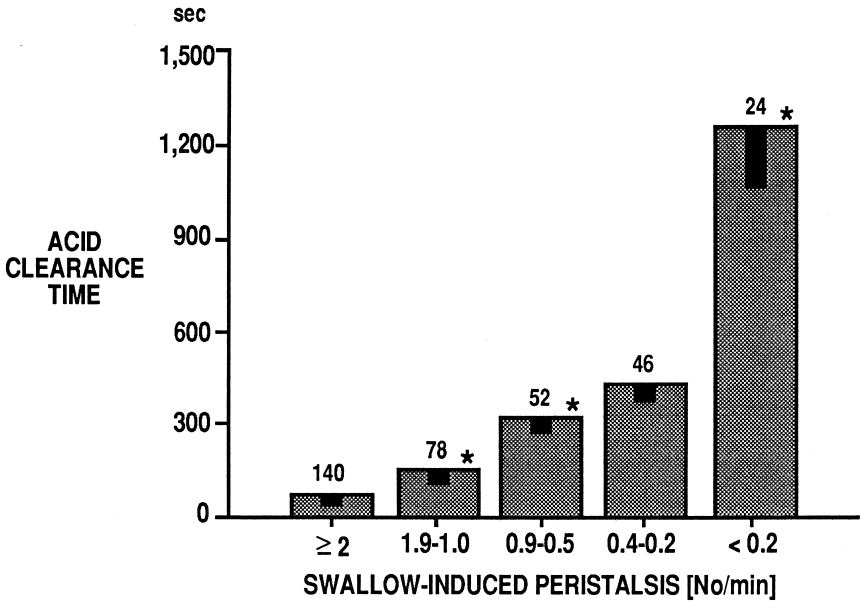

Figure 4. Relationship between the rate of swallow-induced intact primary peristalsis and acid clearance time for pH decreases to less than 3.0 in 20 patients with reflux esophagitis. Each bar represents the mean (SEM) acid clearance time for the number of reflux episodes listed above the bar. *$P < 0.05$ versus bar to immediate left. (Reproduced with permission from *J Gastrointest Motil.*[10])

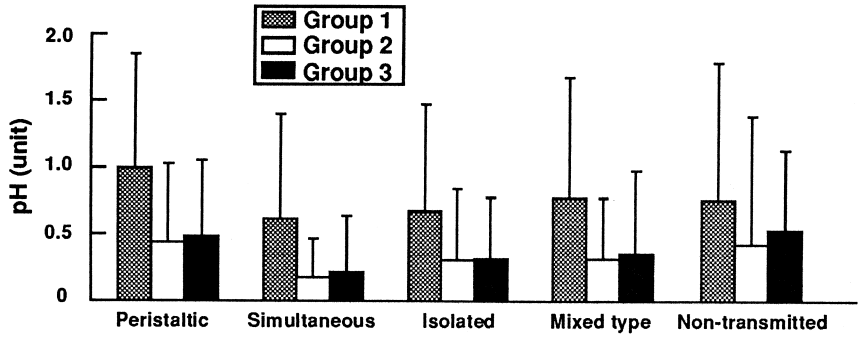

Figure 5. Mean (±SD) pH increment in response to each type of motor activity during 24-hour ambulatory esophageal manometry and pH monitoring. (Reproduced with permission from *Gut.*[18])

time of individual reflux episodes by combining separate reflux episodes. Much of this reflux probably occurs from a hiatus hernia.[29]

The contribution of esophageal body activity to the distribution and proximal extent of the refluxate within the esophageal body remains undetermined. As mentioned above, it has been postulated that esophageal tone may be important. However, there are no published studies that specifically have investigated this issue.

SECONDARY PERISTALSIS

The substantially lower frequency of secondary peristalsis after reflux in patients with reflux disease suggests that there may be a defect of the triggering of secondary peristalsis in this group. Initial studies using relatively slow infusions of liquids at both neutral and acidic pH found that in normal subjects, the volume of acidic (pH $\leq$4) liquid required to trigger a secondary peristaltic response was smaller than that of a neutral solution.[30] A subsequent study performed in patients with reflux disease found no difference between the responses to acidic and neutral solutions, and the responses were similar in patients with and without positive Bernstein or acid clearance tests.[31] These results suggested to the authors that patients with reflux disease had lost the ability to lower the threshold for triggering secondary peristalsis in response to an acid stimulus.

More recent studies using rapid and brief (5-second) distensions with air and water have found a substantial defect in the triggering of secondary peristalsis in patients

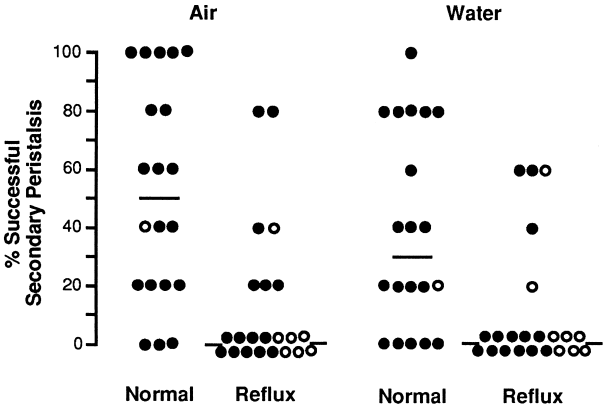

Figure 6. Percentage of secondary peristalsis in response to air and water bolus injections in patients with reflux esophagitis and age-matched healthy controls. Each point represents the proportion of normal secondary peristaltic responses for each subject. Subjects with normal primary peristalsis are represented by the filled circles and those with abnormal primary peristalsis by the open circles. The response rates in patients with reflux disease are significantly less than in the normal subjects . (Reproduced with permission from *Gut.*[32])

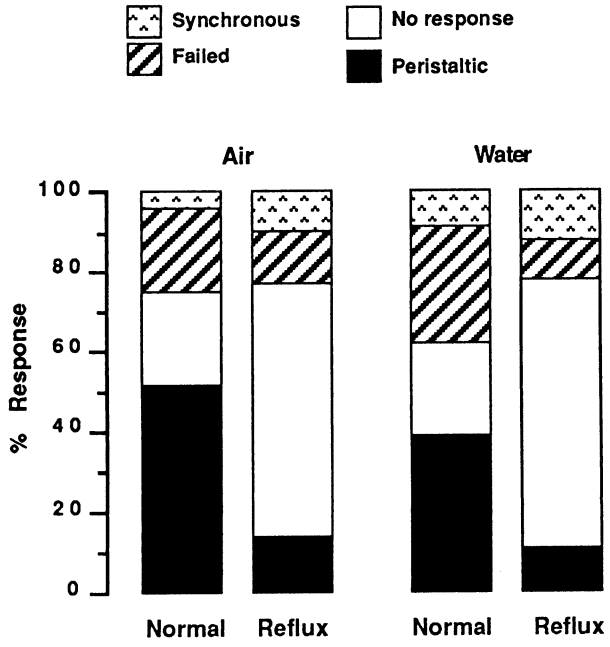

Figure 7. Patterns of manometric responses to 10-mL boluses of air and water in patients with reflux esophagitis and age-matched healthy controls. The most common pattern of failure of secondary peristalsis was no response. (Reproduced with permission from *Gut.*[32])

with reflux disease.[32] In comparison with those in age-matched controls, the secondary peristaltic response rates in patients with reflux disease were substantially lower with both stimuli, and most patients exhibited no response whatsoever (**Figures 6** and **7**). When present, however, the characteristics of secondary peristalsis (pressure wave amplitude and velocity) were similar to those in the controls. The secondary peristaltic response was not influenced by the presence or absence of macroscopic esophagitis. The frequency of secondary peristalsis was also unrelated to the integrity of primary peristalsis, suggesting that the defect may be in esophageal sensation rather than in the motor arm of the reflex arc. In support of this notion, triggering of secondary peristalsis remains abnormal, even when a larger stimulus is used (R. Holloway, unpublished observations).

EFFECT OF ACID ON THE ESOPHAGEAL BODY MOTOR ACTIVITY

Esophageal motor responses during reflux may be influenced not only by distension but also by the pH of the refluxate. As described above, the esophageal response to distension is characterized by secondary peristalsis. The effect of acidification, however, is less clear.

Several studies have addressed this issue by investigating the effects of experimental acidification on esophageal peristalsis. Some studies have reported an increase in peristaltic amplitude and duration,[33–35] an increase in the proportion of nonpropagated pressure waves,[33,34] and a slowing of peristaltic velocity.[33–36] Other studies, however, have failed to demonstrate any effect.[37–40] A consistent finding in the studies that have reported changes in motility during acid infusion has been an association with the production of pain, either heartburn or chest pain.[33,34,36] This suggests that esophageal acidification itself has little or no effect on esophageal motility and that the effects, if any, are the result of pain.

The question as to whether or not intraluminal acid influences triggering of secondary peristalsis remains somewhat unclear. Although the initial studies suggested that acidic liquids had a lower volume threshold for initiating a secondary peristaltic response, subsequent studies have been conflicting. Low pH has no effect on secondary responses to rapid infusion in healthy volunteers.[40] On the other hand, in opossums, intraluminal acid lowers significantly the threshold for initiating secondary peristalsis.[41]

CONCLUSION

The esophageal body responds to gastroesophageal reflux by increases in primary peristalsis through stimulation of swallowing and secondary peristalsis through esophageal distension. Primary peristalsis is the most prevalent activity, but secondary peristalsis may be important during sleep when swallowing is suppressed. Some patients with reflux disease, particularly those with severe esophagitis, exhibit impaired esophageal responses to reflux. It is likely that this impairment interferes with esophageal

acid clearance and also may influence the proximal extent of the refluxate within the esophageal body.

REFERENCES

1. Weusten BL, Akkermans LM, van Berge-Henegouwen GP, Smout AJ. Dynamic characteristic of gastro-oesophageal reflux in ambulatory patients with gastro-oesophageal reflux disease and normal control subjects. *Scand J Gastroenterol*. 1995;30:731–737.
2. Jacob P, Kahrilas PJ, Herzon G. Proximal esophageal pH-metry in patients with reflux laryngitis. *Gastroenterology*. 1991;100:305–310.
3. Shaker R, Milbrath M, Ren J, et al. Esophagopharyngeal distribution of refluxed gastric acid in patients with reflux laryngitis. *Gastroenterology*. 1995;109:1575–1582.
4. Wiener G, Koufman J, Wu W, et al. Chronic hoarseness secondary to gastroesophageal reflux disease: documentation with 24-H ambulatory pH monitoring. *Am J Gastroenterol*. 1989;84:1503–1508.
5. Harding SM, Richter JE, Guzzo MR, et al. Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. *Am J Med*. 1996;100:395–405.
6. Ing AJ, Ngu MC, Breslin AB. Chronic persistent cough and clearance of esophageal acid. *Chest*. 1992;102:1668–1671.
7. Helm JF, Dodds WJ, Pelc LR, et al. Effect of esophageal emptying and saliva on clearance of acid from the esophagus. *N Engl J Med*. 1984;310:284–288.
8. Kahrilas PJ, Dodds WJ, Hogan WJ. Effect of peristaltic dysfunction on esophageal volume clearance. *Gastroenterology*. 1988;94:73–80.
9. Dent J, Dodds WJ, Friedman RH, et al. Mechanism of gastroesophagal reflux in recumbent asymptomatic subjects. *J Clin Invest*. 1980;65:256–267.
10. Dodds WJ, Kahrilas PJ, Dent J, et al. Analysis of spontaneous gastroesophageal reflux and esophageal acid clearance in patients with reflux esophagitis. *J Gastrointest Motil*. 1990;2:79–89.
11. Schoeman MN, Tippett MD, Akkermans LM, et al. Mechanisms of gastroesophageal reflux in ambulant healthy human subjects. *Gastroenterology*. 1995;108:83–91.
12. Orr WC, Johnson LC, Robinson MG. Effect of sleep on swallowing, esophageal peristalsis and acid clearance. *Gastroenterology*. 1984;86:814–819.
13. Penagini R, Schoeman MN, Dent J, et al. Motor events underlying gastro-oesophageal reflux in ambulant patients with reflux oesophagitis. *J Neurogastroenterol Motil*. 1996;8:131–141.
14. Anggiansah A, Taylor G, Bright N, et al. Primary peristalsis is the major acid clearance mechanism in reflux patients. *Gut*. 1994;35:1536–1542.
15. Barham CP, Gotley DC, Miller R, et al. Ambulatory measurement of oesophageal function: clinical use of a new pH and motility recording system. *Br J Surg*. 1992;79:1056–1060.
16. Barham CP, Gotley DC, Mills A, Alderson D. Oesophageal acid clearance in patients with severe reflux oesophagitis. *Br J Surg*. 1995;82:333–337.
17. Bremner RM, Hoeft SF, Costantini M, et al. Pharyngeal swallowing. The major factor in clearance of esophageal reflux episodes. *Ann Surg*. 1993;218:364–369.
18. Anggiansah A, Taylor G, Marshall RE, et al. Oesophageal motor responses to gastro-oesophageal reflux in healthy controls and reflux patients. *Gut*. 1997;41:600–605.
19. Timmer R, Breumelhof R, Nadorp JHSM, Smout AJM. Oesophageal motor response to reflux is not impaired in reflux oesophagitis. *Gut*. 1993;34:317–320.
20. Mayrand S, Diamant NE. Measurement of human esophageal tone in vivo. *Gastroenterology*. 1993;105:1411–1420.
21. Sifrim D, Janssens J, Vantrappen G. Transient lower esophageal sphincter relaxations and esophageal body muscular contractile response in normal humans. *Gastroenterology*. 1996;110:659–668.
22. Sifrim D, Vantrappen G, Janssen J. Permissive role of the esophageal body during transient LES relaxations (TLESRs). A mechanism for increased reflux in patients with reflux esophagitis. *Neurogastroenterol Motil*. 1994;6:171. Abstract.
23. Booth DJ, Kemmerer WT, Skinner DB. Acid clearing from the distal esophagus. *Arch Surg*. 1968;96:731–734.
24. Stanciu C, Bennett JR. Oesophageal acid clearing: one factor in the production of reflux oesophagitis. *Gut*. 1974;15:852–857.
25. Johnson LF. 24-hour pH monitoring in the study of gastroesophageal reflux. *J Clin Gastroenterol*. 1980;2:378–399.
26. Kahrilas PJ, Dodds WJ, Hogan WJ, et al. Esophageal peristaltic dysfunction in peptic esophagitis. *Gastroenterology*. 1986;91:897–904.
27. Basilisco G, Barbera R, Molgora M, et al. Acid clearance and oesophageal sensitivity in patients with progressive systemic sclerosis. *Gut*. 1993;34:1487–1491.
28. Barham CP, Gotley DC, Mills A, Alderson D. Precipitating causes of acid reflux episodes in ambulant patients with gastro-oesophageal reflux disease. *Gut*. 1995;36:505–510.
29. Mittal RK, Lange RC, McCallum RW. Identification and mechanism of delayed esophageal acid clearance in subjects with hiatus hernia. *Gastroenterology*. 1987;92:130–135.
30. Corazziari E, Pozzessere C, Dani S, et al. Intraluminal pH and esophageal motility. *Gastroenterology*. 1978;75:275–277.
31. Corazziari E, Materia E, Pozzessere C, et al. Intraluminal pH and oesophageal motility in patients with gastro-oesophageal reflux. *Digestion*. 1986;35:151–157.
32. Schoeman MN, Holloway RH. Integrity and characteristics of secondary oesophageal peristalsis in patients with gastro-oesophageal reflux disease. *Gut*. 1995;36:499–504.
33. Siegel CI, Hendrix TR. Esophageal motor abnormalities induced by acid perfusion in patients with heartburn. *J Clin Invest*. 1963;42:686–695.
34. Kjellen G, Tibbling L. Oesophageal motility during acid-provoked heartburn and chest pain. *Scand J Gastroenterol*. 1985;20:937–940.
35. Bontempo I, Piretta L, Corazziari E, et al. Effects of intraluminal acidification on oesophageal motor activity. *Gut*. 1994;35:884–890.
36. Richter JE, Johns DN, Wu WC, Castell DO. Are esophageal motility abnormalities produced during the intraesophageal acid perfusion test? *JAMA*. 1985;253:1914–1917.
37. Tuttle SG, Rufin F, Bettarello A. The physiology of heartburn. *Ann Intern Med*. 1961;55:292–300.
38. Atkinson M, Bennett JR. Relationship between motor changes and pain during esophageal acid perfusion. *Am J Dig Dis*. 1968;18:346–350.
39. Burns TW, Venturatos SG. Esophageal motor function and response to acid perfusion in patients with symptomatic reflux esophagitis. *Dig Dis Sci*. 1985;30:529–535.
40. Thompson DG, Andreollo NA, McIntyre AS, Earlam RJ. Studies of the esophagus clearance responses to intraluminal acid. *Gut*. 1988;29:881–885.
41. Kusano M, Hogan WJ, Lang IM, et al. Initiation of esophageal secondary peristalsis by slow fluid infusion in the opossum: effect of hydrochloric acid. *Am J Physiol*. 1996;270:G927–G931.