Esophageal Emptying and Acid Neutralization in Patients with Symptoms of Esophageal Reflux

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Clearance of refluxed acid from the distal esophagus is due to bolus emptying and salivary neutralization of acid. We compared results of 24-hour pH monitoring with acid clearance tests (ACT) and radioisotope swallows (RIS) in 26 symptomatic patients to determine which of the components of acid clearance is better correlated with gastroesophageal acid reflux (GER). Seven of eight patients with GER had delayed esophageal emptying on RIS. Abnormal salivary clearance of acid was present in nine of 18 patients without GER, accounting for a high false-positive rate of ACT. Delayed esophageal bolus emptying, not deficient acid neutralization by saliva, is the predominant component of abnormal acid clearance in patients with GER. RIS is superior to ACT as part of the evaluation of reflux symptoms, and may prove to be a valuable screening test for this condition.

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SYMPTOMATIC GASTROESOPHAGEAL ACID REFLUX remains an important clinical problem, necessitating more than 150 antireflux operations at The University of Chicago Hospitals in the last 5 years. Pathologic gastroesophageal reflux is characterized by several different abnormal features, including an increase in the frequency of reflux episodes, nonspecific motor disorders of the esophagus, and a delay in clearance of refluxed material from the distal esophagus.

For many years it was felt that the distal esophagus was emptied of refluxed acid solely by means of peristaltic waves. However, recent evidence implicates an additional factor in the disappearance of acid from the distal esophagus. While the major portion of an acid bolus is emptied rapidly from the esophagus by peristaltic waves, residual acid that coats the esophageal mucosa is neutralized in stepwise fashion by swallowed saliva.[1] Saliva has an acid neutralizing capacity related to its bicarbonate concentration,[2] and the return of pH to normal in the distal esophagus after intraesophageal instillation of acid is determined to a large degree by the quantity of saliva swallowed.[3]

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These studies of the ability of saliva to neutralize acid in the distal esophagus raise the question as to whether a defect in saliva production can interfere with the return of esophageal pH to normal following acid reflux. Failure of either mechanism for esophageal clearance of refluxed acid, bolus emptying or acid neutralization by saliva, may contribute to the pathologic consequences of gastroesophageal reflux. One of our current techniques for measuring distal esophageal function is the Acid Clearance Test (ACT). The ACT was developed initially to measure esophageal emptying[4] and has been used extensively to evaluate patients with symptoms of reflux.[5] This test is influenced by both components of esophageal acid clearance and may be abnormal when either is deficient.

A new technique, the radioisotope swallow (RIS), was introduced by Kazem et al.[6] and modified by subsequent workers[7–9] to provide a quantitative analysis of esophageal emptying separate from any effects of acid. This test can complement the ACT in defining abnormalities of acid clearance from the distal esophagus, and has been used prospectively by our group for several years. In this paper we review patients with symptoms of gastroesophageal acid reflux and compare ACT results with esophageal clearance as determined by RIS. This report attempts to identify which component of clearance predominates in the production of abnormal acid clearance, and which test (ACT or RIS) best correlates with abnormal gastroesophageal reflux as identified by 24-hour pH monitoring of the esophagus.

Methods

From January 1980 through December 1983, over 250 patients underwent evaluation in our Esophageal Function Laboratory for symptoms of gastroesophageal acid reflux. Of these, patients who did not have a

primary motor abnormality of the esophagus and had not undergone antireflux repair or other operations involving the fundus of the stomach or esophagus were reviewed. Twenty-six who also had RIS as part of their screening tests were selected for analysis.

Esophageal function studies were carried out as previously described.[10] Esophageal manometry was performed with the patient supine. A triple lumen catheter, with openings spaced 5 cm apart starting at the distal end of the catheter, was passed into the stomach. Each lumen was connected to a pressure transducer and was continuously perfused with saline at a rate of 0.5 cc per minute. The catheter was withdrawn at 0.5 to 1.0 cm increments, noting the length and resting pressure of the distal esophageal sphincter (DES), function of the body of the stomach with both dry and wet swallows, and function of the cricoid region. The ACT was performed by placing a pH electrode 5 cm above the DES, following which a 15 ml bolus of 0.1 N hydrocholoric acid was infused through the manometry catheter opening 10 cm proximal to the pH electrode. The patient was asked to swallow at 30-second intervals and the number of swallows required to raise the intraluminal esophageal pH to greater than 5.0 was recorded (normal is $\leq$10 swallows). The Standard Acid Reflux Test (SART) was performed by infusing 300 cc of 0.1N hydrochloric acid into the stomach and monitoring distal esophageal pH during a deep breath, a Muller maneuver, a Valsalva maneuver, and a cough in the right lateral, left lateral, supine, and upright positions. A fall in pH to less than 4.0 was considered positive, and the test was abnormal if more than two of a possible 16 maneuvers were positive. Twenty-four-hour pH monitoring was undertaken with the pH electrode located 5 cm above the DES and the patient maintained on a special pH diet without use of antacids, H_2-receptor antagonists, narcotics, or other drugs known to affect the function of the distal esophageal sphincter. The patient was asked to record episodes of heartburn, pain and dysphagia, and all changes in position.

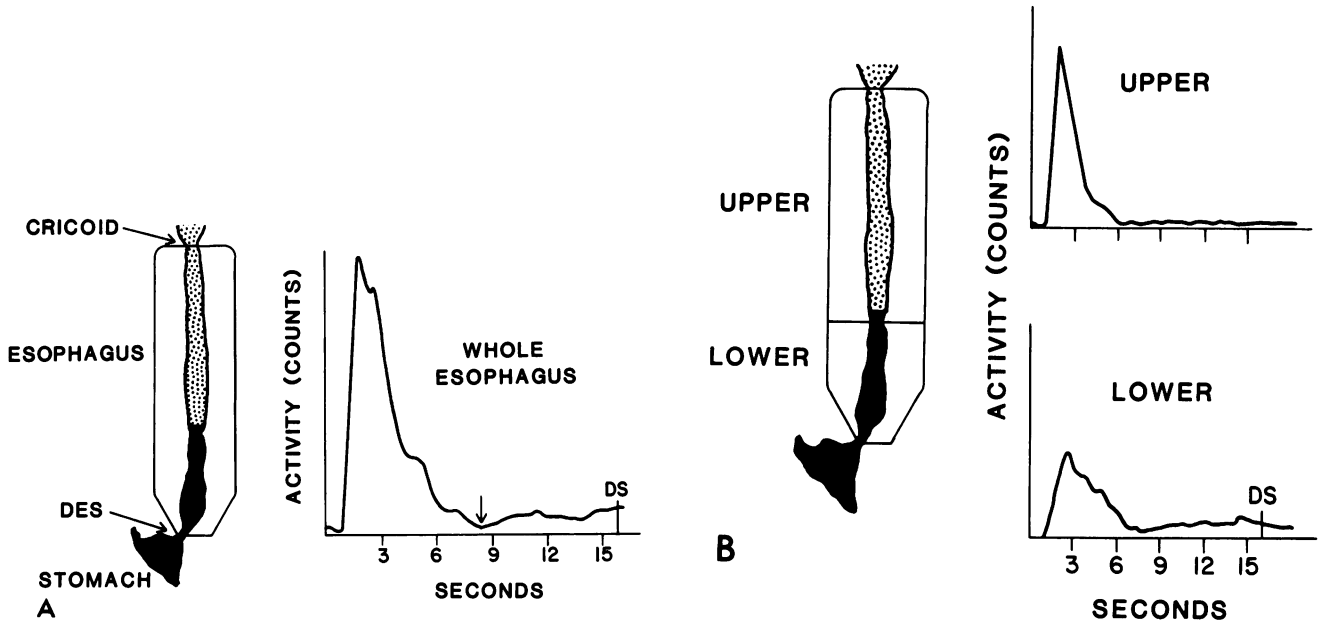
Radioisotope swallows were performed on a separate occasion. Patients were imaged from the posterior view upright or supine using a large-field-of-view gamma camera with a high sensitivity parallel hole collimator, and data was acquired into a computer or microprocessor. After an overnight fast, 15 cc of water containing 150–200 μCi of Tc-99m sulfur colloid were instilled into the patient's mouth with a syringe. The isotope swallow was initiated on command and dry swallows were then performed every 15 seconds for 60 seconds, unless clearance of isotope from the esophagus was demonstrated earlier on the monitor attached to the camera. Data were recorded at a frame rate of 0.15 seconds and displayed for viewing in cinematic mode. For analysis, frames were added together to form a single summed image of the swallow; regions of interest (ROIs) were drawn on this image and used to generate time activity curves (TACs) for 128 frames (19.2 seconds). The whole esophageal ROI extended from the cricoid to the distal esophageal sphincter (DES) (Fig. 1A). Intraesophageal bolus movement was analyzed by partitioning the esophagus into two ROIs at the site of bolus slowing noted near the level of the base of the heart on the summed image (Fig. 1B). This separated the upper (approximately two-thirds) and lower (approximately one-third) esophageal regions. In normal subjects, these regions had significantly different transit patterns, and subdividing the upper region did not contribute significant additional information about the swallow. The curves were smoothed once and displayed on film. Count rates for each 0.15-second frame interval were generated.

The onset of the swallow was the entry of the bolus into the esophagus, noted as the beginning of the upslope of the TAC of the whole esophagus. Prior to the arrival of the bolus in the esophagus, as determined from the cine display, there were usually a few counts detected in the whole esophageal and upper esophageal ROIs due to some scatter radiation from the activity in the mouth. In replicate swallows, scatter radiation from the activity in the stomach also contributed to the preswallow count rates in the esophagus. To correct the curves for these counts in the comparative analysis of swallows, "background" counts in the whole esophageal ROI in three frames prior to the onset of the swallow were averaged and then subtracted from the entire curve. The time for maximum isotope clearance and the per cent activity cleared in one swallow were obtained. Isotope clearance was defined as

$$IC_t = \frac{E\ max - E_t}{E\ max} \times 100$$

where IC_t represents per cent esophageal clearance of isotope at time "t," E max represents maximum count rate in the esophagus, and E_t represents esophageal count rate at time "t." The time of maximum isotope clearance was determined as the minimum point in the downsloping portion of the TAC from the whole esophageal ROI prior to the first dry swallow at 15 seconds (Fig. 1A). The transit time was the interval from the initial entry of the bolus into the esophagus to the maximum isotope clearance from the esophagus in one swallow.

Later in the study, we developed a functional image display of swallows for analysis and production of the TAC curves (Figs. 2A and B). This display was generated by a computer (Medical Data Systems), which com-



FIGS. 1A and B. *A*, Radioisotope swallow analysis. The region of interest (ROI) for the whole esophagus drawn on the computer-summed image is shown on the left and extends from the cricoid to the distal esophageal sphincter (DES). The time activity curve (TAC) generated from this ROI is shown on the right. This normal swallow shows maximum isotope clearance at the time indicated by the arrow. DS is the dry swallow performed 15 seconds after the onset of the isotope swallow. *B*, Regional analysis of radioisotope bolus transit. The whole esophageal ROI is divided into two separate ROIs, encompassing the proximal and distal portions of the esophagus. The corresponding TACs are shown on the right.

pressed the data in a 64 × 64 word format in each frame into a single column and displayed 128 columns serially to form a single image. Profiles were marked on the functional image from regions of interest and TACs were generated in a manner analogous to that obtained from the single-frame-summed-image display. In 10 patients, the swallowing data were analyzed by both techniques and there was no significant difference noted. Abnormal results were defined as any values two standard deviations beyond the transit times or per cent isotope clearances of normal subjects.

Patients had upper gastrointestinal series performed in a standard manner and underwent flexible esophagoastroscopy. Esophagitis was recorded as Grade 1 in the presence of mucosal erythema; Grade 2 when ulceration was found; Grade 3 with fibrosis or stiffening of the esophagus secondary to chronic ulceration; and Grade 4 in the presence of frank stricture. Results of biopsies were recorded when available.

Fifteen asymptomatic control subjects also underwent the entire battery of tests excluding esophagoscopy. The protocol for this evaluation was reviewed by the Clinical Investigation Committee of The University of Chicago and informed consents were obtained from all participants.

Results

There were 26 patients, 14 men and 12 women. Twenty-one were white, the other five were black. Mean age was 52.9 years, ranging from 27 to 75 years, with a median age of 56.5 years. Patients had been symptomatic for 1.5 months to 27 years, with a mean duration of symptoms of 6.1 years and a median duration of 2 years. Eighteen patients had symptoms of heartburn, 17 had regurgitation, and 13 patients had dysphagia. The predominant symptoms were heartburn in 11, regurgitation in eight, and dysphagia in five, while two patients complained primarily of chest pain.

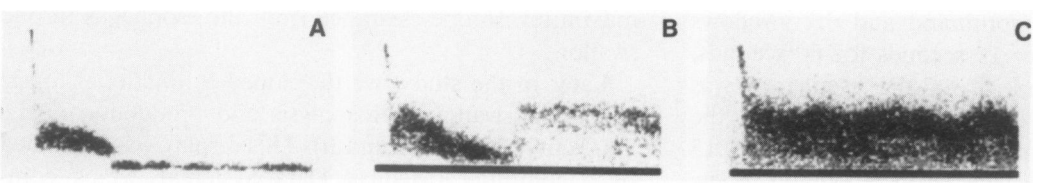


FIG. 2A. Functional images of radioisotope swallows. The upright swallow (A) is normal, while the two supine swallows (B and C) show abnormal bolus retention. The corresponding TACs derived from these images are shown in Figure 2B.

Manometry revealed normal motility patterns in 13 patients. Nonspecific manometric abnormalities included decreased amplitude of peristaltic waves in five, and occasional spontaneous, simultaneous, or repetitive contractions of normal amplitude in the remaining eight patients. No primary motor abnormalities were found. The ACT was abnormal in 17 patients, while the Standard Acid Reflux Test was abnormal in eight patients. Twenty-four-hour pH monitoring was abnormal for total score in eight patients. The UGI series revealed the presence of a hiatal hernia in 10, free gastroesophageal reflux of barium in four, and the presence of occasional distal tertiary contractions in seven. Endoscopy was performed in 24 patients and showed esophagitis (Grades 2 or 3) in two.

Twenty-three radioisotope swallows (12 upright, 11 supine) were examined in normal subjects, and of these three were replicated upright and two supine. Clearance was complete in one swallow in both upright and supine positions. For upright swallows in eight normals with normal ACT, the transit time was 7.2 ± 1.4 seconds (S.D.) and isotope clearance was 96.1 ± 2.4%. The transit time for supine swallows in nine normals with normal ACT was 9.9 ± 0.8 seconds, and isotope clearance was 96.2 ± 4.0%. No abnormal bolus movement within the esophagus was observed and no episode of reflux occurred.

Since all normal subjects cleared the bolus within the first swallow, we analyzed only the data from the initial isotope swallow for the symptomatic patient population to categorize their swallows as normal or abnormal in comparison with the normal subjects. When swallows were abnormal, data from the intraesophageal regions were used to identify episodic reflux of activity from the stomach (Figs. 2A and B). Abnormal swallows with reflux contributing to esophageal activity were excluded from analysis. However, if a swallow manifested both normal transit time and maximum clearance of tracer, it was classified as normal even if subsequent reflux episodes occurred. Seventy-one RIS were examined in symptomatic patients with 13 replicated upright and nine supine. In 18 (69%) patients the transit time and per cent isotope clearance cleared in one swallow were normal in both upright and supine positions. In eight (31%) patients there was significantly delayed bolus transit time and/or abnormal retention of tracer up to 15 seconds after the isotope swallow.

In patients with increased retention of isotope, the intraesophageal ROIs also depicted various patterns of abnormal bolus transit within the esophagus, but these were not further categorized in this analysis.

Results of UGI, manometry, SART, 24-hour pH monitoring, and RIS were normal in all controls. The ACT was abnormal in five and was normal in 10.

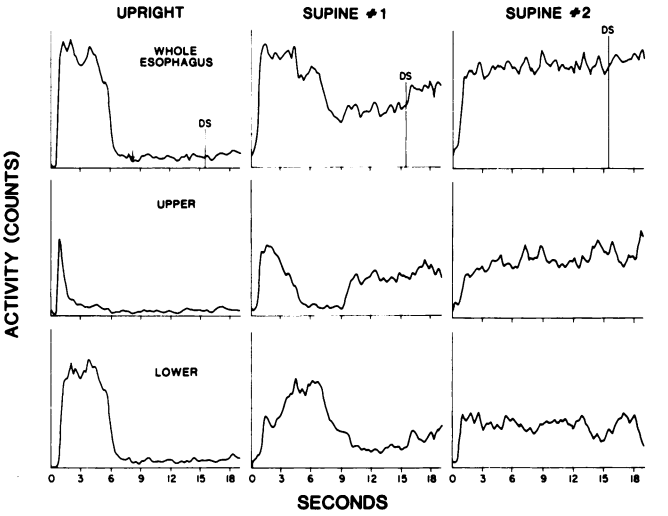


FIG. 2B. Time activity curves (TACs) from functional images. The upright swallow has a normal time of maximum isotope clearance (arrow). Supine representing an episode of reflux from the stomach activity with subsequent retention within the proximal esophagus. Supine swallow #2 shows abnormal esophageal retention without demonstrable reflux.

Using results of 24-hour pH monitoring as the reference standard for pathologic gastroesophageal reflux, we compared results of this test to those of the ACT and RIS to determine which had a greater predictive value of abnormal reflux in patients with symptoms of gastroesophageal reflux (Table 1). Sensitivity, specificity, positive predictive index, negative predictive index, and accuracy were calculated by the following formulas:[11]

$$\text{Sensitivity} = \frac{\text{true positive}}{\text{true positives} + \text{false negatives}} \times 100$$

$$\text{Specificity} = \frac{\text{true negatives}}{\text{true negatives} + \text{false positives}} \times 100$$

$$\text{Positive Predictive Index} = \frac{\text{true positives}}{\text{true positives} + \text{false positives}} \times 100$$

$$\text{Negative Predictive Index} = \frac{\text{true negatives}}{\text{true negatives} + \text{false negatives}} \times 100$$

$$\text{Accuracy} = \frac{\text{true positives} + \text{true negatives}}{\text{total instances}} \times 100$$

To determine which component of acid reflux, frequency or duration of reflux episodes, correlated most significantly with abnormal results of RIS and ACT, we compared both the frequency of individual reflux episodes and the number of reflux episodes that persisted for greater than 5 minutes to results of ACT and RIS using a chi square analysis with correction for continuity

TABLE 1. *Sensitivity, Specificity, Predictive Values, and Overall Accuracy of Acid Clearance Test and Radioisotope Swallow for the Presence of Pathologic Reflux as Determined by 24-Hour pH Monitoring*

	ACT (%)	RIS (%)
Sensitivity	100	87.5
Specificity	50	88.9
+ Predictive value	47	77.8
− Predictive value	100	94.1
Accuracy	65.4	88.5

(Tables 2 and 3). Only the analyses comparing RIS with the frequency of reflux or with the number of reflux episodes greater than 5 minutes in length were statistically significant ($p < 0.05$ and $p < 0.005$, respectively).

Patients and volunteers with a normal ACT had a definite step rise in their ACT pH tracings following most swallows (Fig. 3). Those patients and controls with abnormal ACT scores had occasional step rises but more often had a gradual sloping rise to their tracings (Fig. 4). The maximal per cent decrease in hydrogen ion concentration was calculated for each swallow as an estimate of the acid neutralization capacity of each person's swallowed saliva. The first two swallows in each test were omitted to allow for complete bolus emptying of the esophagus. The maximal per cent drop in [H+] for 42 swallows in seven controls with a normal ACT was 81.3 ± 23.5% (S.D.), while for 23 swallows in five controls with an abnormal ACT it was 48.3 ± 29.9% ($p < 0.0001$). Likewise, for 32 swallows in four symptomatic patients with a normal RIS and an abnormal ACT and whose tracings were available, maximal per cent drop in [H+] was 43.2 ± 40.7% ($p < 0.0001$ *vs.* seven controls). The distribution of maximal per cent decrease in [H+] for these three groups is illustrated in Figure 5.

TABLE 2. *Chi Square Analyses of Frequency of Reflux Episodes and Number of Reflux Episodes > 5 Minutes on 24-Hour pH Monitoring* Versus *Results of Acid Clearance Test in 26 Symptomatic Patients*

		Abnormal	Normal	Totals
Reflux Episode Frequency				
	Abnormal	10	7	17
ACT	Normal	3	6	9
	Totals	13	13	26
	Chi square = 1.53 (N.S.)			
Reflux Episodes > 5 min				
	Abnormal	8	9	17
ACT	Normal	1	8	9
	Totals	9	17	26
	Chi square = 3.36 (N.S.)			

TABLE 3. *Chi Squared Analysis of Frequency of Reflux Episodes and Number of Reflux Episodes > 5 Minutes on 24-Hour pH Monitoring* Versus *Results of Radioisotope Swallow in 26 Symptomatic Patients*

		Abnormal	Normal	Totals
Reflux Episode Frequency				
	Abnormal	7	2	9
RIS	Normal	6	11	17
	Totals	13	13	26
	Chi square = 4.25 ($p < 0.05$)			
Reflux Episodes > 5 min				
	Abnormal	7	2	9
RIS	Normal	2	15	17
	Totals	9	17	26
	Chi square = 11.33 ($p < 0.005$)			

Discussion

Our understanding of the pathophysiology of gastroesophageal reflux remains incomplete. For many years attention focused on the function of the distal esophagus and the sphincter as the main elements preventing pathologic reflux. Helm and his group have recently provided new insights into the physiology of acid clearance from the distal esophagus.[1,3] Based on their work, it is now known that a bolus of acid in the distal esophagus is emptied by a single esophageal stripping wave while the esophageal mucosa remains coated with acid. The production of saliva and its transport to the distal esophagus by a peristaltic wave neutralizes this remaining mucosal layer of acid and returns the pH of the distal esophagus to normal. The rapidity with which distal esophageal pH returns to normal is determined by the quantity of saliva produced, its bicarbonate concentration, and the rate of swallowing.

It is theorized that acid peptic disease of the distal esophagus may be a result not only of an increased

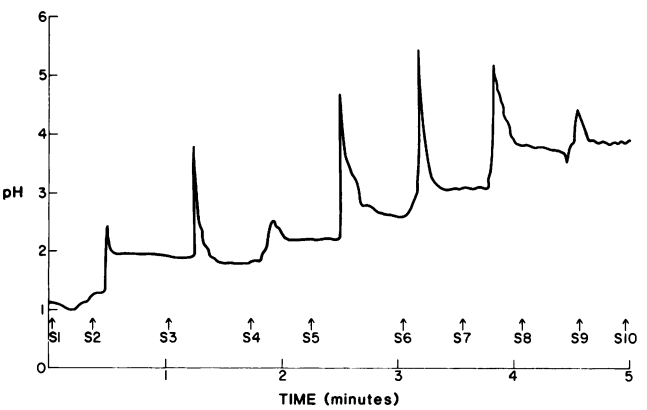


FIG. 3. Distal esophageal pH *versus* time during normal ACT, illustrating step rises in pH following each dry swallow (S1–S10).

frequency of acid reflux and/or a delay in emptying of refluxed acid from the distal esophagus, but also of a failure of salivary neutralization of acid in some patients. The actual role of salivary neutralization of acid has not yet been defined in a group of patients with symptoms of acid reflux. We previously used the Acid Clearance Test as a measure of esophageal emptying,[10] although we now understand it in light of these new findings to comprise elements of both bolus emptying of material in the distal esophagus and of salivary acid neutralization. The incidence of false-positive Acid Clearance Tests in this and other studies[4,5] is probably explained by variations in salivary neutralization of acid.

RIS has been used to evaluate esophageal function in a variety of diseases, and it has been shown to be a sensitive screening test for motor disorders of the esophagus.[12-15] It can provide quantitative data about bolus transit through the whole esophagus, and regions of the esophagus can be examined separately. Both the type of bolus and the position of the patient can be changed for additional evaluation of swallowing mechanisms. RIS is noninvasive and has a low radiation burden. It can also detect spontaneous episodes of gastroesophageal reflux in a fashion similar to that evidenced on upper gastrointestinal examination, but it is designed for evaluation of esophageal bolus transit. RIS is not yet available in community hospitals on a routine basis because of the expertise needed in technical performance, computer processing, and interpretation of the studies.

A number of different techniques have been employed in scintigraphic assessment of esophageal function. We have modified these techniques to achieve a reproducible and accurate method of assessing esophageal emptying.[16] One important modification is the use of the posterior view to obtain uniform attenuation of isotope activity throughout the length of the esophagus, thereby avoiding the focal, severe attenuation due to the heart in the anterior view. This allows us to assess accurately the activity in all regions of the esophagus and arrive at a more reliable end point for esophageal emptying than is obtained with studies performed from the anterior view.

Our data confirm the fact that the ACT does not correlate with the presence of abnormal acid reflux or 24-hour pH monitoring, as it had a high number of false-positive results in both symptomatic patients and asymptomatic controls. When comparing this test with results of radioisotope swallows in the same groups, it was evident that many people with abnormal ACT had normal esophageal emptying of a radioisotope bolus and no evidence for reflux on 24-hour monitoring. With normal esophageal emptying (normal RIS), the salivary neutralization capacity is low in people with an abnormal ACT compared to people with a normal ACT. These

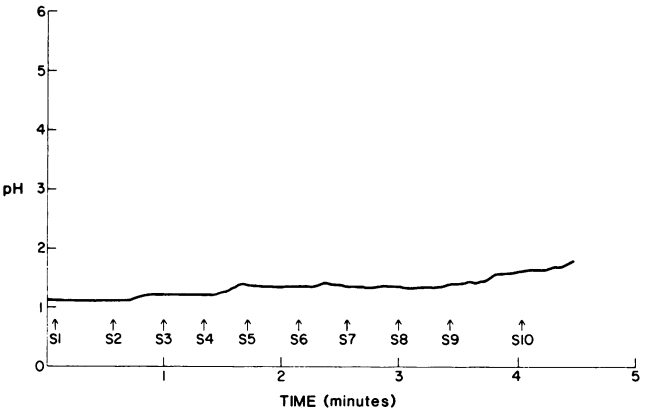


FIG. 4. Distal esophageal pH *versus* time during abnormal ACT, illustrating the relative lack of step rises in pH following dry swallows (S1-S10).

data indicate that an abnormal ACT in these people was due to deficiencies of salivary neutralization of acid, either from a low volume of saliva production or low salivary bicarbonate concentration.

The amount of acid which coats the esophagus following bolus emptying is estimated to be less than 1 cc.[2] It is not known whether this quantity of acid is capable of influencing the development of esophagitis, although the ability of even this small quantity to maintain a low distal esophageal pH certainly speaks in favor of the possibility. Because of the small number of patients in this study having documented esophagitis, we were unable to determine the relationship between abnormal salivary neutralization of acid and the development of esophagitis.

In seven of eight patients with evidence for pathologic reflux based on 24-hour pH monitoring, the RIS was abnormal, indicating delayed bolus emptying. This finding corresponds to the presence of nonspecific motor disorders of the distal esophagus previously described. Those with an abnormal RIS had a corresponding

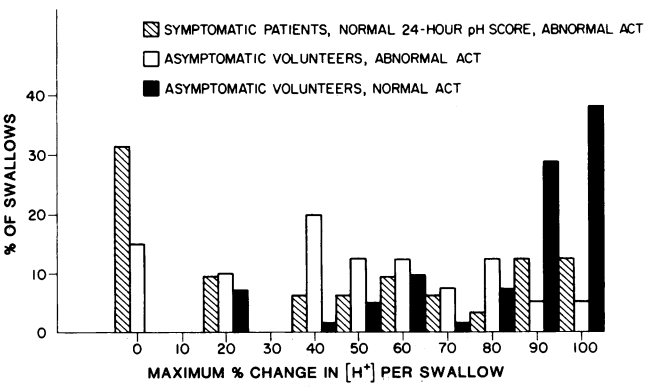


FIG. 5. Salivary neutralization of acid in patients and controls with normal esophageal emptying on RIS, expressed as relative frequency of maximal per cent decrease in [H+] per swallow.

maldistribution of both frequency of reflux episodes and number of prolonged reflux episodes. This suggests the probabilitiy of abnormalities in both peristalsis and DES function in these patients, and supports previous work from this institution.[18,19] We conclude that the failure of bolus emptying of acid is a more important contributor to the pathology of acid reflux than is a deficiency in salivary neutralization of acid.

RIS has been used to evaluate a series of symptomatic patients with GER by two groups. Tolin et al. found transit abnormalities in all 24 patients examined and isotope clearance was more abnormal when motor disorders were present on manometry.[7] None had endoscopic grading of esophagitis reported. Russell et al. studied 29 patients and detected transit abnormalities in 15 (52%).[20] Severe esophagitis or ulcer was present in 11 of 20 patients endoscoped, but the only abnormalities on manometry were nonspecific motor disorders of the esophagus in five of 28 (18%). After antireflux repair, the RIS abnormalities persisted despite improvement in symptoms. Neither group included ACT or 24-hour pH monitoring in their patient evaluation, and all patients were imaged in the supine position with an anterior view.

Our patients were selected from a large group undergoing extensive esophageal function evaluation for symptoms of GER and included only two of 24 with severe esophagitis on endoscopy. This may explain the lower incidence of abnormal RIS in our population. One beneficial sidelight of our investigation was that the RIS showed a high degree of correlation with results of 24-hour pH monitoring in patients with either normal or abnormal 24-hour pH monitoring. Because the performance of 24-hour pH monitoring is time-consuming, the RIS may prove to be a useful screening test in patients with symptoms of gastroesophageal reflux. As the radioisotope swallow has already been shown to be valuable in the detection of motor disorders of the esophagus, it may one day serve alongside endoscopy as the mainstay of confirmatory diagnosis of abnormal acid reflux in the evaluation of patients for possible antireflux surgery. It remains to be determined whether or not RIS will have a high degree of correlation with the presence or absence of esophagitis. Further investigation into this area is certainly warranted.

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Discussion

Dr. Robert E. Condon (Milwaukee, Wisconsin): I want to thank Drs. Skinner and Ferguson for providing me with an advance copy of their manuscript, and for their invitation to discuss their presentation. I think their work with this new measure of esophageal swallowing is going to prove to be an important advance in our understanding of the physiologic mechanisms that underlie the development of reflux esophagitis.

In patients who develop reflux esophagitis there is an interplay of two major factors, the frequency of reflux and the duration that the refluxed contents remain in the esophagus. The frequency of reflux is primarily reflected in manometric measurements of the tone and the length of the lower esophageal sphincter, and is also, obviously, importantly influenced by those factors that increase intra-abdominal pressure—body habitus, pregnancy, etc. We have had a reasonably good handle on those measures since Code first introduced esophageal manometry into clinical practice.