Radionuclide Esophageal Transit Study in Detection of Esophageal Motor Dysfunction: Comparison with Motility Studies (Manometry)

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Radionuclide esophageal transit study (RETS) has been developed to assess motor function of the esophagus. The purpose of this study was to compare RETS to esophageal motility studies (EMS) in detection of motility disorders. A total of 109 consecutive patients without previous history of surgery on the esophagus underwent both RETS and EMS within one month of each other. Final diagnosis was divided into three categories: I—primary esophageal motor disorders (n = 39); II—reflux disease (n = 48); and III—non-cardiac chest pain and/or dysphagia (n = 22). Using EMS as the standard, the results of RETS were as follows: sensitivity for detection of motor dysfunction was 97%, 92%, and 77% for Groups I, II, and III, respectively, while specificity was 91% for Group II and 100% for Group III. Global sensitivity was 92% and specificity was 88%. No clinically significant motor disorders were missed by RETS. In conclusion, RETS is a useful noninvasive test for the screening of patients with symptoms thought to be of esophageal origin.

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Evaluation, diagnosis, and treatment of esophageal diseases are challenging because of the variety of symptoms and diversity of esophageal disorders. The development of quantitative radionuclide procedures for the assessment of esophagogastric function has been a significant advance in the investigation of upper digestive tract disease. Evaluation of esophageal emptying function using radionuclide esophageal transit study (RETS) was initially proposed by Kazem in 1972 (*1*). The introduction of more sophisticated computer-based analysis and displays and modifications of acquisition parameters improved the diagnostic accuracy and clinical utility of this relatively new test (*2–8*). RETS offers many advantages over the other standard clinical methods used in the investigation of esophageal disorders, including providing quantitative information on esophageal emptying, a unique feature unavailable from current esophageal investigation.

Despite these significant advantages, use of RETS as a clinical diagnostic test has not gained wide acceptance. Some discrepancies in the results obtained with RETS have been reported and questions have been raised on the clinical usefulness of this test in the evaluation of different types of esophageal disorders (*9*).

Since the primary purpose of RETS is to detect esophageal motility dysfunction, this study was undertaken to compare RETS to esophageal motility studies (EMS), used as a gold standard, in a patient population referred for the investigation of various esophageal diseases. The aim was to determine the sensitivity and specificity of this noninvasive test for the detection of esophageal motility disorders in a clinical context.

MATERIALS AND METHODS

Patient Population

One-hundred and nine consecutive patients without a previous history of surgery on the esophagus were prospectively studied with both RETS and EMS within one month of each other. There were 57 males and 52 females with an age range of 21 to 81 yr (mean of 52 yr). All patients were referred to the Esophageal Disorders Clinic of Hôtel-Dieu de Montréal for esophageal symptoms or non-cardiac chest pain. Following initial symptoms assessment, patients underwent a full esophageal investigation that included radiologic studies, 24-hr pH-metry, and upper digestive tract endoscopy and biopsy. The final diagnosis was based on global results of the esophageal investigation and divided into three categories: I—primary esophageal motor disorders; II—reflux disease; and III—non-cardiac chest pain.

Esophageal Motility Studies

After a 6–8-hr fast, a triple-lumen polyethylene tube was passed through the patient's nose and then swallowed. With

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the patient lying in the supine position, the three lumens were connected to external pressure transducers and an infusion pump. A triple-syringe Harvard infusion pump was used to slowly perfuse the three lumens at a rate of 3.8 ml/lumen/min when recording from the esophageal body and the lower esophageal sphincter. A higher infusion rate of 7.6 ml/lumen/min was used to perfuse the tube which recorded from the upper esophageal sphincter. The esophageal body was arbitrarily divided into two zones: the proximal and distal esophagus. To aid swallowing, patients were given a small bolus (2 ml) of water on each voluntary swallow. Ten such swallows were recorded in this position. Criteria for manometric interpretation used in our institution were previously described in details elsewhere (*10*). The following EMS parameters were determined:

1. Upper esophageal sphincter: resting and closing pressures, relaxation, relaxation time, and coordination.
2. Body of esophagus: proximal and distal resting pressure, peak contraction pressure, response to swallowing (primary and tertiary waves), and spontaneous activity (secondary and tertiary waves).
3. Lower esophageal sphincter: resting and closing pressures, relaxation, relaxation time, and coordination.

Radionuclide Esophageal Transit Studies

RETS was carried out after a 6–8-hr fast. RETS were interpreted without knowledge of patient history, symptoms, or the results of other diagnostic procedures. Patients had practice swallows (2 to 6) with unlabeled water before ingestion of the radioactive bolus. This preparation was performed in order to have a single-phase ingestion instead of a multiphasic ingestion, which is inadequate for data analysis. After the practice swallows, patients were placed in a supine position under a computer-interfaced, large field of view scintillation camera fitted with a low-energy, all-purpose, parallel-hole collimator. The anterior projection was used and patients were positioned so that the mouth, hypopharynx, entire esophagus, and, when possible, the proximal part of the gastric fundus could be clearly visualized in the same field of view. The patient's head was placed in a slight anterior oblique rotation. A bolus of 0.5–1.0 mCi (18–37 MBq) of technetium-99m-sulfur colloid diluted in 15–20 ml of water was then aspirated in the mouth through a plastic straw and patients were asked to retain the radioactive bolus in the mouth. On completion of the radionuclide oral administration, adequate positioning of the patient was improved if necessary and then, a 2-min analog and digital acquisition was immediately started. A few seconds after the beginning of data acquisition, patients were instructed to swallow the entire bolus in only one phase and not to move for 2 min. After 30 sec, patients were asked to have a dry swallow and additional dry swallows were allowed at 15-sec intervals for 2 min. Analog images were obtained at 2.0-sec intervals for 30 sec and then at 5-sec intervals for 90 sec. Computerized data were obtained at 0.5-sec intervals throughout the study. At the end of this dynamic part of the study, a static image (preset time of 60 sec) was obtained without moving the patient and a radioactive marker (cobalt-57 or technetium-99m) was placed over the cricoid cartilage to identify the level of the upper esophageal sphincter.

After data had been recorded, time-activity curves were generated for seven regions of interest (ROI): oral cavity, hypopharynx, proximal, middle, and distal esophageal segments, and gastric fundus. The last ROI was placed over the entire esophagus from the upper esophageal sphincter to the lower esophageal sphincter. Before tracing regions of interest, anatomic structures and morphologic lesions were recognized on either composite image from digital data or on the static analog image obtained at the end of the study with the cricoid marker. ROIs of the distal esophagus and the gastric fundus were separated by a few centimeters in order to avoid effects of the respiratory movement. Figure 1 is a schematic representation of objective parameters derived from RETS time-activity histograms. Segmental esophageal emptying time was defined as the time that it takes for 90% or more of the maximal activity in each ROI (hypopharynx, proximal, middle, and distal esophagus) to be cleared. Global esophageal emptying represented the time from entry of the bolus in the proximal esophagus to the clearance of more than 90% from the entire esophageal ROI.

Monitoring of oral and hypopharyngeal activity was mainly used to evaluate oropharyngeal dysphagia or hypopharyngeal emptying disorders. It was also used to detect the presence and the effects of an incomplete initial swallow, which can result in a fragmentation of the bolus in the esophagus (multiphasic ingestion). Data obtained from a fragmented ingestion are not suited to the quantitative procedure described below. When this effect was detected on the oral and hypopharyngeal time-activity curves, the study was repeated few days later. In many pharyngeal and esophageal disorders, a segmental or global emptying of 90% or more of the maximal ingested activity frequently can not be achieved at the end of the 2-min acquisition period. When this occurred, residual segmental and global activity for each ROI was assessed at 2 min after the ingestion. It was expressed as the percentage of the maximal activity detected for the given ROI at the end of the study.

The standard analysis of RETS includes the following:

1. Quality of ingestion (single or multiple swallows).
2. Hypopharyngeal, global and segmental esophageal emptying time and stasis at 2 min.

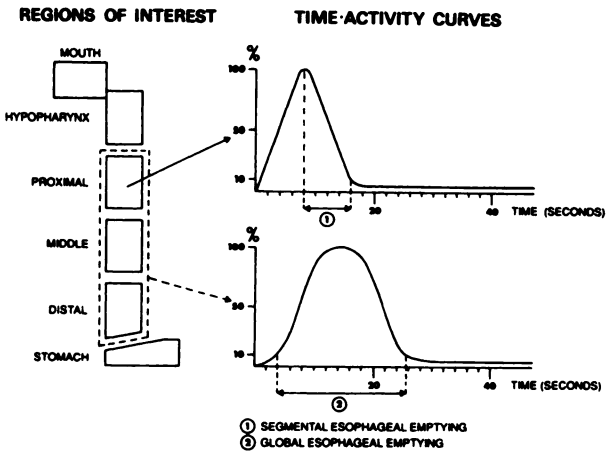

FIGURE 1
Schematic representation of objective parameters (segmental and global esophageal emptying times) derived from RETS time-activity curves.

3. Assessment of abnormal movement of the bolus (pharyngonasal, pharyngo-oral, esophagopharyngeal regurgitations, and esophagoesophageal and gastroesophageal reflux).
4. Evaluation of abnormal extraluminal focus of activity (bronchial aspiration, fistula).
5. Assessment of "anatomic" abnormalities (esophageal dilation, Zenker's diverticulum, epiphrenic diverticulum, paraesophageal hernia, hiatal hernia).

Control Group

In order to determine control values for both EMS and RETS, asymptomatic normal volunteers were studied using the same technical parameters described above. Forty normal volunteers (23 men and 17 women, with a mean age of 27 yr) and 30 normal subjects (20 men and 10 women with a mean age of 30 yr) without digestive symptoms or systemic illness and taking no medication were evaluated with EMS and RETS, respectively. All data obtained from both procedures were compared to the normal values derived from this group of normal subjects. Any deviations from these values were considered abnormal.

Statistical Analysis

The values in the text are expressed as arithmetic mean ± 1 s.d. Statistical terms were defined as follows: sensitivity: TP/(TP + FN) × 100; specificity: (TN/(TN + FP) × 100; predictive value of a negative result: TN/(TN + FN) × 100; and predictive value of a positive result: TP/(TP + FP) × 100, where TP = true-positive, TN = true-negative, FP = false-positive, and FN = false-negative.

RESULTS

Patient Population

According to their final diagnosis, the 109 patients were divided into three diagnostic groups: Group I: 39 patients with primary esophageal motor disorder; Group II: 48 patients with gastroesophageal reflux disease, and Group III: 22 patients with non-cardiac chest pain and/or dysphagia. Patients with gastroesophageal reflux disease had a diagnosis which was confirmed by a 24-hr pH-metry and esophagogastric endoscopy. Patients with non-cardiac chest pain had a negative cardiac work-up before their esophageal investigation.

Control Groups

In the group of normal volunteers, the esophageal emptying time was 1.5 ± 0.5 sec, 3.5 ± 1.0 sec, and 6.0 ± 2.5 sec for the upper, middle, and distal esophageal segments, respectively. For the entire esophageal ROI, the emptying time was 9.0 ± 2.5 sec. Residual radioactivity at 2 min after the initial swallow was always <10% of the maximal activity recorded in a given ROI. The upper limit of normality included 2 s.d. Data obtained from the 40 normal volunteers for each different manometric parameter were described in detail in a previous article (*11*). Criteria of interpretation were rigorous. Any deviation from these criteria for one or more parameters were considered to be abnormal.

TABLE 1
Comparison Between RETS and EMS in Patients with Primary Motor Dysfunction of the Esophagus (Group I)

		RETS	
		POSITIVE	NEGATIVE
EMS	POSITIVE	36	1
	NEGATIVE	2	0

n = 39.
Sensitivity = 97.3%.

Group I: Esophageal Motor Disorders

Thirty-nine patients had a final diagnosis of primary esophageal motor disorder. Distribution was as follows: achalasia (n = 7), diffuse esophageal spasm (n = 5), scleroderma (n = 4), oculopharyngeal muscular distrophy (n = 9), oropharyngeal dysphagia (n = 9), and Zenker's diverticulum (n = 5). Table 1 shows the correlation between RETS and EMS in this group of patients. Sensitivity of RETS was 97.3% and predictive value of a positive test was 94.7%. The number of normal cases was too low to determine the specificity. In one case, RETS was normal in a patient with oropharyngeal dysphagia while EMS demonstrated 80% of primary waves in response to swallowing in the proximal esophagus. Both endoscopy and 24-hr pH-metry were normal. EMS was normal in two cases while RETS showed esophageal motility dysfunction involving the proximal third of the esophageal lumen. One of these two patients had a Zenker's diverticulum and the other suffered from oropharyngeal dysphagia of central origin.

Characteristically, patients with achalasia (Fig. 2) had

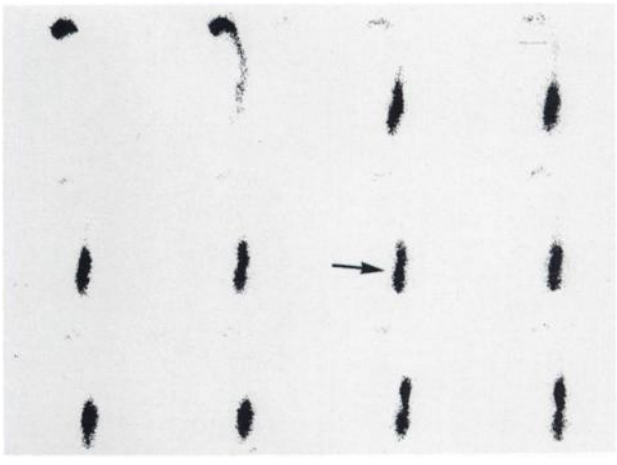

FIGURE 2
RETS in a patient with esophageal achalasia. Analog images are obtained in anterior projection at 2-sec intervals (beginning with the upper left image down to the bottom right image) following ingestion of 1.0 mCi of ^{99m}Tc-sulfur colloid. There is a significant radionuclide stasis (arrow) at the level of the distal esophageal lumen. More than 80% of the initially ingested activity remained in the esophagus at the end of the study.

a significant radionuclide esophageal stasis involving mainly the distal two-thirds of the esophageal body. The esophageal stasis at 2 min was more than 80% of the initially ingested activity in six out of the seven patients with this disease. Scleroderma gave a similar pattern on the RETS although radionuclide stasis was less significant. Oropharyngeal dysphagia and oculopharyngeal muscular dystrophy patients (Fig. 3) were characterized by significant hypopharyngeal stasis with delayed emptying mostly localized to the proximal third of the esophageal lumen. In severe cases, this stasis was accompanied by pharyngonasal regurgitation or tracheal aspiration. Patients with diffuse esophageal spasm (Fig. 4) showed slight to moderate esophageal stasis with bolus fragmentation and esophago-esophageal reflux or retrograde movement involving the distal two-thirds of the esophagus.

Group II: Gastroesophageal Reflux Disease

Forty-eight patients had gastroesophageal reflux disease established by 24-hr pH-metry. Table 2 shows the results of both RETS and EMS in detection of esophageal motility disorders related to a gastroesophageal reflux disease. Sensitivity and specificity of RETS were 92.3% and 90.9%, respectively. Predictive value of a negative test was 90.9% and 92.3% for a positive test. There were two false-negatives on RETS. One patient had a hypotensive lower esophageal sphincter and abnormal contractions in the proximal esophagus. The other patient had nonspecific abnormal contractions in the esophageal body. The two false-positive cases on RETS showed hiatal hernia and reflux disease on pH-metry. Abnormal RETS parameters were not related to gastroesophageal reflux episodes but rather to a dysmotility problem. Most of the patients of this group

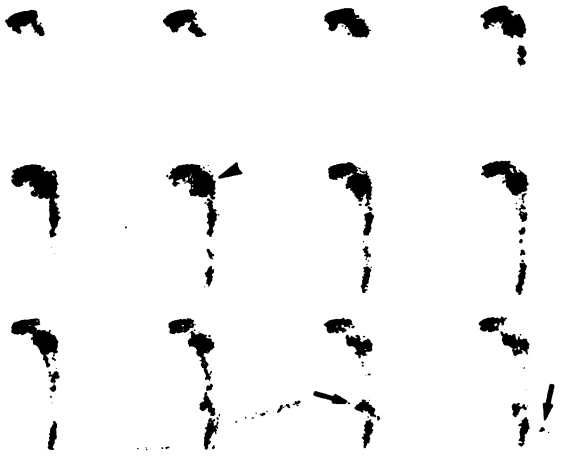

FIGURE 3
RETS in a patient with oculopharyngeal muscular dystrophy. There is a significant delay in the hypopharyngeal (arrowhead) and esophageal emptying. At 20 sec after the beginning of the acquisition, there are two slight paraesophageal foci of activity (arrows) corresponding to bronchial aspiration. This is a frequent complication of this disease.

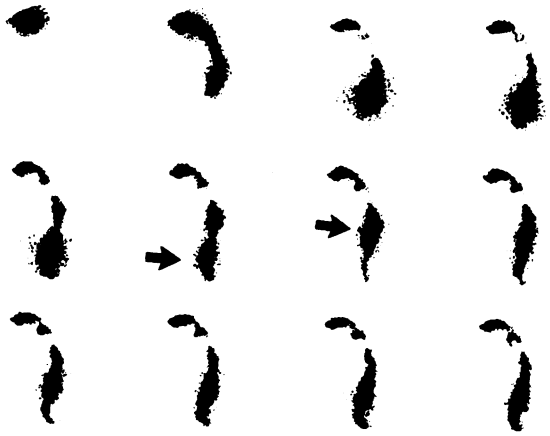

FIGURE 4
RETS in a patient with diffuse esophageal spasm. There is a decreased global and segmental esophageal emptying with incoordinate passage of the bolus through the esophageal lumen, accompanied by fragmentation and retrograde movement of the bolus (arrows).

with abnormal RETS showed segmental delayed emptying mainly involving the distal third of the esophagus. Eight patients also had a more proximal involvement. Although RETS is not designed to detect episodes of gastroesophageal reflux, three patients had such episodes during the 2-min acquisition.

Group III: Non-Cardiac Chest Pain

Twenty-two patients had a final diagnosis of non-cardiac chest pain. Table 3 shows results of both procedures in this group of patients. Sensitivity and specificity of RETS were 76.9% and 100%, respectively. The predictive value of a negative test was 75% and 100% for a positive test. In this group, RETS was normal in three patients in whom EMS detected slight nonspecific abnormalities: one patient had a hypertensive lower esophageal sphincter, one had a hypotensive lower esophageal sphincter, and another had 60% of primary waves in response to swallowing in the proximal esophagus. RETS did not show false-positive cases in this group of patients. Most of the RETS abnormalities found in this category of patients were slight or moderate (delayed segmental emptying involving distal two-

TABLE 2
Comparison Between RETS and EMS in Patients with Reflux Disease (Group II)

		RETS	
		POSITIVE	NEGATIVE
EMS	POSITIVE	24	2
	NEGATIVE	2	20

n = 48.
Sensitivity = 92.3%; specificity = 90.9%.

TABLE 3
Comparison Between RETS and EMS in Patients with Non-Cardiac Chest Pain (Group III)

		RETS	
		POSITIVE	NEGATIVE
EMS	POSITIVE	10	3
	NEGATIVE	0	9

n = 32.
Sensitivity = 76.9%; specificity = 100%.

thirds of esophagus) and without any specific characteristics. The same findings were seen on EMS.

Global Results

Table 4 summarizes the global results obtained in 109 patients. When compared to EMS, RETS had a sensitivity of 92.1% and a specificity of 87.9% in detecting a significant esophageal motor dysfunction. The predictive value of a positive test is 94.6% and 82.9% for a negative test. There were six false-negatives (5.5%) and four false-positives (3.7%).

DISCUSSION

Many modalities are currently available for the clinical evaluation of esophageal physiology and pathophysiology: motility studies, pH-metry, endoscopy, and barium contrast esophagogram. All these techniques provide useful information on the anatomy and some aspects of the esophageal function. However, each method has some limitations in the study of global esophageal motor function. They are all either semiquantitative or nonquantitative and they can alter the normal physiology of the esophagus. The barium esophagogram helps to clarify anatomic abnormalities of the esophagus and its sphincters. However, it is relatively insensitive to subtle motor disturbances, its interpretation is subjective (no quantitative data) and, because of radiation considerations, the function of the esophagus is studied for only a short period of time. Furthermore, barium is not a physiologic marker. Although considered the "gold standard" in the study of esophageal motility disorders, EMS requires intubation, itself an abnormal stimulant in the evaluation of esophageal physiology. Sometimes it is poorly accepted by patients because of the discomfort caused by the introduction of an endoluminal catheter. The resultant lack of patient compliance may be a significant concern in the follow-up of either medical or surgical treatment.

TABLE 4
Comparison Between RETS and EMS: Global Results (Groups I, II, and III)

		RETS	
		POSITIVE	NEGATIVE
EMS	POSITIVE	70	6
	NEGATIVE	4	29

n = 109.
Sensitivity = 92.1%; specificity = 87.9%.

Nuclear medicine, with computer data processing, offers advantages over other standard clinical methods used in the investigation of esophageal motility disorders. First introduced in 1972 (*1*) and subsequently modified to improve its accuracy, RETS fulfills the major criteria for evaluating esophageal emptying function: it is safe, noninvasive, very well accepted by patients, easy to perform, readily available to an average nuclear medicine laboratory, inexpensive, and has a low radiation burden. Most important, it uses physiologic markers and provides quantitative data on hypopharyngeal (*12*) and esophageal emptying functions.

Although different articles have been published on RETS in the investigation of esophageal disorders, there is no consensus on its role in clinical practice. This may be partially explained by the large number of different procedures that were used to perform this test. Many technical variants were reported including the radiopharmaceutical used, amount of ingested activity, patient positioning, single vs multiple swallows, duration of acquisition, type of computer analysis and interpretation criteria (*13–16*). This led to confusing reports and results obtained with RETS were variable.

Furthermore, RETS has been compared to other tests commonly used in clinical esophagology like endoscopy, radiologic studies, and pH-metry. RETS does not have the anatomic resolution of endoscopy or radiologic studies and it was not designed to detect gastroesophageal reflux like the 24-hr pH-metry. RETS has rather been developed to assess the motor function of the esophagus and the end result of its emptying capacity (*17*). In this study, RETS was compared to EMS used as a gold standard in the assessment of this motor function. The sensitivity and specificity of RETS in detection of esophageal motility disorders were 92.1% and 87.9%, respectively. It should be emphasized that these results were obtained using rigorous EMS criteria. All six (5.5%) false-negative cases on RETS had only minor "nonspecific" abnormalities on EMS. Thus, no significant motor disorder was missed by RETS. Furthermore, the four (3.9%) false-positive RETS studies had esophageal disorders demonstrated by endoscopy, pH-metry, or radiologic procedures.

In this study, EMS was used as the gold standard. However, the final diagnosis of an esophageal motor disorder is usually not based on the results of only one investigation procedure. Different tests looking at different aspects of esophageal pathophysiology and anatomy are generally required in order to make an adequate diagnosis and subsequent management. Although

most of the primary esophageal motor disorders show characteristic patterns on RETS, functional esophageal lesions related to either gastroesophageal reflux and chest pain may not be specific. In these cases, RETS, like EMS, showed significant abnormalities but without specific characteristics. The abnormalities usually seen are segmental delayed emptying mainly localized to the distal third of the esophageal lumen.

Different types of RETS acquisition protocols and analysis have been described in the literature. In this study, a uniform protocol was applied for both data acquisition and treatment. RETS can be performed either in upright or supine position. Although studies done in upright position provide a more physiologic evaluation as related to the normal position for swallowing, RETS was performed in the supine position in this study. By partially removing the effects of gravity, esophageal contractions alone become responsible for esophageal emptying. Esophageal motility disorders are easier to demonstrate in this position, particularly early in the disease when a study in erect position can be normal (*14*). Some studies advocate the posterior projection to provide a relatively uniform attenuation of radioactivity throughout the length of the esophagus, thereby avoiding the attenuation of the heart (*18*). Patients in this study were evaluated in the anterior projection because mouth and hypopharynx are closer to the detector surface. In addition, a higher dose (1.0 mCi of 99mTc-sulfur colloid) was used (instead of a 0.2–0.3 mCi dose) reducing the effect of heterogenous cervical and thoracic attenuation. Technetium-99m-sulfur colloid was selected as the radiopharmaceutical to improve both the quality of analog images and count rate. With a relatively high sensitivity and specificity for detection of esophageal motility dysfunction, RETS is a complementary procedure evaluating different parameters that would be unavailable by other means. While EMS measures the duration, velocity, and pressure of the esophagus and sphincters, RETS evaluates the combined effects of these factors on the segmental and global esophageal emptying. However, barium radiographic studies and/or endoscopy must also be performed in screening patients for esophageal dysmotility in order to rule out mechanical obstruction, stricture, or malignancy. These lesions cannot be distinguished from motor disorder by RETS alone.

In conclusion, RETS is a useful noninvasive test for the screening of patients with symptoms thought to be of esophageal origin and it can quantitate esophageal emptying abnormalities in patients with primary motor disorders, reflux disease, or other conditions affecting esophageal function.

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