Diagnosing gastroesophageal reflux disease
Szarka, Lawrence A; DeVault, Kenneth R; Murray, Joseph A. **Mayo Clinic Proceedings** 76. 1 (Jan 2001): 97-101.

Abstract (summary)
Gastroesophageal reflux disease (GERD) is a common condition with a variety of clinical manifestations and potentially serious complications. This article reviews available methods for diagnosing GERD. A clinical history of the classic symptoms of GERD, heartburn or acid regurgitation, is sensitive enough to establish the diagnosis in patients without other complications. Esophagogastroduodenoscopy is the best way to evaluate suspected complications of GERD, but endoscopic findings are insensitive for the presence of pathological reflux, and therefore they cannot reliably exclude GERD. The "gold standard" study for confirming or excluding the presence of abnormal gastroesophageal reflux is the 24-hour ambulatory esophageal pH monitoring test, and this study should be used for the evaluation of refractory symptoms and extraesophageal manifestations of GERD. A formal acid-suppression test is helpful in the evaluation of the atypical GERD symptom of noncardiac chest pain. Optimal use of currently available tests for GERD may allow for more efficient diagnosis and better characterization of the pathological manifestations associated with GERD.

Headnote
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EGD = esophagogastroduodenoscopy; GERD = gastroesophageal reflux disease; GI = gastrointestinal; LES = lower esophageal sphincter
Gastroesophageal reflux disease (GERD) describes the pathological movement of acid gastric contents into the esophagus. The classic symptoms of GERD, heartburn and acid regurgitation, are common in the general population. Approximately 18% of the adult population in the United States reports heartburn at least once a week.1 GERD is associated with impairment in quality of life2 and is an important risk factor for Barrett esophagus, and ultimately for adenocarcinoma of the esophagus, which is the most rapidly increasing cancer in the developed world.3 Unfortunately, the diagnosis of GERD is not always straightforward because of the wide range of typical, atypical, and extraesophageal symptoms in patients. There is also no single "gold standard" study to assess all the manifestations of GERD. We aim to review the available diagnostic techniques and to suggest the most efficient use of these tests.

DIAGNOSIS BY CLINICAL HISTORY
Despite the proliferation of laboratory and technical means of diagnosis, a well-taken patient history is still of paramount importance. The most typical symptoms described for GERD are heartburn (retrosternal burning or a tight sensation

radiating toward the neck) and acid regurgitation (the unpleasant return of sour or bitter gastric contents to the pharynx). Less common typical symptoms include water brash (hypersalivation associated with an episode of esophageal acid exposure), dysphagia (difficulty in swallowing), and globus sensation (a sensation of a lump in the throat). The common typical symptoms of heartburn and acid regurgitation often occur after eating, especially after large meals. These symptoms are exacerbated by recumbency, straining, and bending over and are usually improved by antacids. The diagnostic value of these typical symptoms has been examined in a large group of patients undergoing 24-hour ambulatory esophageal pH monitoring.4 Only the symptoms of heartburn and acid regurgitation helped to differentiate patients from nonpatients. When heartburn or acid regurgitation is the dominant symptom, the specificity is sufficiently high (89% and 95%, respectively) to establish the diagnosis of GERD. If there is no additional indication for further evaluation, then these patients may be confidently treated for GERD without undergoing confirmatory tests.

WHO NEEDS A DIAGNOSTIC TEST?

The patients who require further diagnostic evaluation are those who have initial symptoms of unclear etiology, lack a substantial response to adequate acid suppression therapy, have a history of symptoms suggestive of GERD complications, have atypical or extraesophageal symptoms that are possibly related to GERD, or have typical symptoms but need objective confirmation of the diagnosis before antireflux surgery is performed.

Patients with unclear symptoms require testing to establish a diagnosis. In patients with typical symptoms but without substantial improvement while on conventional therapy, diagnostic testing is needed because there is a strong suggestion of either alternative or additional pathology. Conditions such as cardiac disease, achalasia, scleroderma, infectious esophagitis, medication-induced esophagitis, Zollinger-Ellison syndrome, rumination, and visceral hypersensitivity all need to be considered.

Esophageal complications of GERD include erosive esophagitis, esophageal ulceration and stricture, Barrett esophagus, and esophageal adenocarcinoma.5 Symptoms that suggest these complications include long duration (>10 years) of typical symptoms, dysphagia, hematemesis or melena, and weight loss. The presence of these symptoms is a strong indication for diagnostic testing. New onset of symptoms of any functional gastrointestinal disorder, including GERD, in patients older than 65 years also requires investigation.

Atypical symptoms such as noncardiac chest pain and epigastric pain might be related to GERD. Extraesophageal symptoms or diseases that have also been described as possibly related to GERD include hoarseness, sore throat, ear pain, chronic cough, sinusitis, dental erosions, vocal cord ulcer, vocal cord granuloma, subglottic stenosis, asthma, and chronic idiopathic pneumonitis.6 The relationship between these conditions and GERD in an individual patient can only be confirmed if pathological reflux is diagnosed and its treatment alleviates the atypical or extraesophageal symptom.

WHICH TEST IS NEEDED?

A number of tests are available in clinical practice to facilitate the diagnosis of GERD. These include barium upper gastrointestinal (GI) tract radiography with or without air contrast, esophagogastroduodenoscopy (EGD) with or without esophageal mucosal biopsy, the acid suppression test, 24-hour ambulatory esophageal pH monitoring with or without symptom index, gastroesophageal scintigraphy, and the Bernstein test (an intraesophageal acid infusion test). Unfortunately, no single test provides all the information that may be needed to completely evaluate the symptoms. The choice of initial diagnostic test depends entirely on what question needs to be answered.

Is Abnormal Gastroesophageal Reflux Present When Esophagitis Is Not Seen?

Often patients with suspected GERD do not have erosive esophagitis either because of previous treatment or less severe reflux. Has the patient had

abnormal esophageal acid exposure? This is the critical question asked when the diagnosis of GERD, in the absence of erosive esophagitis, needs to be confirmed or excluded in the following situations: consideration for antireflux surgery, typical symptoms without response to appropriate therapy, and the presence of atypical or extraesophageal symptoms. A variety of tests are used to address this question, including barium upper GI tract radiography, prolonged ambulatory esophageal pH monitoring, and gastroesophageal scintigraphy.

Barium upper GI tract radiography is a frequently ordered initial test used to evaluate patients with possible reflux. Radiographic reflux is the movement of barium from the stomach into the esophagus, either spontaneously or induced by provocative maneuvers such as abdominal compression, Valsalva maneuver, and cough. When present, radiographic reflux indicates incompetence of the antireflux mechanism at the gastroesophageal junction at that particular moment. However, the majority of patients with GERD have normal lower esophageal sphincter (LES) tone, and reflux occurs due to random transient LES relaxations over time.7 A comparison between the presence of radiographic reflux and prolonged ambulatory esophageal pH monitoring for the diagnosis of GERD found that presence of spontaneous reflux had a sensitivity of only 26%, and the addition of a provocative maneuver (water-siphon test) resulted in a positive predictive value of only 60%.8 Barium upper GI tract radiography remains a useful study in the evaluation of patients with dysphagia, but it cannot reliably confirm or exclude reflux. In clinical practice, upper GI tract radiography has been essentially replaced by ambulatory 24-hour esophageal pH monitoring in the investigation of GERD.

The preferred method for detecting abnormal reflux is currently 24-hour ambulatory esophageal pH monitoring. The test is performed by transnasally placing a probe with a pH electrode at the tip to a level 5 cm above the proximal border of the LES. Accurate location of the LES is critical because normative values for acid exposure apply only if the distance between the pH probe and the LES is 5 cm. The LES position is usually determined manometrically, either by a standard stationary esophageal manometry study or via a combined single solid-state pressure transducer with a pH probe that can accurately locate the proximal LES border and requires only a single intubation.9 A lightweight, portable recorder is then attached to the patient's belt or a shoulder strap. The patient is instructed to maintain usual diet, activity, and habits during the study to allow assessment of findings relative to the patient's normal lifestyle. The recorder has event buttons on it for the patient to indicate when meals, sleep, and symptom events begin and end. The standard duration of 24 hours reflects the length of a complete circadian cycle. Reflux of acid is defined as a drop in intraesophageal pH of less than 4.0. There are a variety of ways to express the measured esophageal exposure to gastric acid. In 1974, Johnson and Demeester10 defined a 24-hour composite score to distinguish pathological from physiological acid reflux on the basis of the following 6 criteria: (1) percentage of total time when pH is less than 4.0; (2) percentage of upright time when pH is less than 4.0; (3) percentage of recumbent time when pH is less than 4.0; (4) total number of reflux events; (5) number of reflux episodes lasting more than 5 minutes; and (6) the longest episode of reflux (in minutes). In everyday practice, the first 3 measurements of acid exposure are used most frequently and have a reported sensitivity of 85% and specificity of more than 95% for diagnosing GERD as defined by esophagitis.11 Abnormal acid reflux is therefore most widely defined in terms of the reflux time (percentage of time that the distal esophageal pH is less than 4.0). A reflux time greater than 4% is considered abnormal, based on the value exceeding the mean and 2 SDs for healthy volunteers.

Although 24-hour ambulatory esophageal pH monitoring is generally accepted as the gold standard, it is important to appreciate its limitations. A computer program usually provides the composite reflux score, but it remains essential to review carefully each tracing for signs of probe malfunction or migration that

could lead to false-positive or false-negative findings. It is certainly possible that pH monitoring may result in false-negative results. One study reported that up to 17% of patients with endoscopically documented erosive esophagitis had a negative 24-hour pH study.12 An explanation for this phenomenon may be the variability in the amount of daily acid reflux in patients. The patients may be less active or may eat less during the study. Misplacement of the probe relative to the LES may adversely affect either sensitivity (too high) or specificity (too low). When the reproducibility of prolonged esophageal pH testing is measured on 2 separate days in patients with GERD symptoms or with esophagitis, the results change the diagnosis (normal or abnormal based on the percentage of patients with pH <4.0) in 11% of the cases.13 Another explanation for false-negative results is the possibility that the pH probe may become buried in the distal esophageal mucosal folds and actually fail to detect the acid that is adjacent to it. This was demonstrated in a study of patients who had 2 pH probes placed in the distal esophagus simultaneously. The differences in readings between the 2 probes would have changed the diagnosis (normal vs abnormal on the basis of pH <4.0) in 20% of the patients.14 Other disadvantages of esophageal pH monitoring include lack of availability at some centers, expense, labor intensity, and the mildly invasive nature of the test, which a small proportion of patients cannot tolerate. Additionally, pH monitoring of the esophagus does not identify esophageal injury due to GERD.

There is often much uncertainty regarding esophageal pH monitoring in patients taking acid-suppressing medications. If the diagnosis of reflux is under question, the study should be performed while the patient is off acid-suppression therapy. Conversely, if the question concerns the adequacy of acid suppression, the test is best performed when the patient is receiving therapy. For example, in patients whose symptoms are improved by acid suppression but who require objective documentation of GERD for antireflux surgery, the medication should be stopped approximately a week before the operation to minimize the possibility of a false-negative result. Patients who have refractory daily symptoms despite seemingly adequate treatment should be studied while they are on their current treatment regimen, either to exclude acid reflux as the cause of their symptoms or to document therapeutic failure. In the latter group, it is helpful to perform a dual pH probe study with an electrode placed in the stomach and another at the usual 5 cm above the LES. This configuration permits evaluation of gastric acid suppression over a 24-hour period in addition to documenting any esophageal acid reflux.ls

Gastroesophageal scintigraphy is a test used infrequently to demonstrate gastroesophageal reflux, aspiration, or both. The technique involves feeding the patient a technetium99m sulfur colloid-labeled meal and obtaining postprandial images with a gamma camera. Delayed images obtained the following day may reveal scintigraphic activity within the lung fields, thus demonstrating aspiration. Currently, gastroesophageal scintigraphy lacks adequate normal standards in adults, and therefore its clinical use is limited.

Are the Symptoms Due to GERD?

The question of whether certain symptoms are attributable to GERD arises when the symptoms are atypical (eg, noncardiac chest pain) or extraesophageal (eg, hoarseness or cough). Tests to determine the relationship between these symptoms and GERD include the Bernstein test, 24hour ambulatory esophageal pH monitoring, and the acidsuppression test.

The Bernstein test is performed by infusing the esophagus with either dilute hydrochloric acid or saline in a single-blinded manner. If the symptom in question is induced by acid and clears with saline, then it is appropriate to conclude that GERD is the cause of the spontaneously occurring symptoms. It has been reported that this test has a sensitivity and specificity of about 80% in. diagnosing GERD as a cause of the symptoms in patients with reflux esophagitis.16 Unfortunately, this test suffers from poor standardization and a

lack of appropriate confirmatory studies. In addition, the attitude of the person performing the test may induce bias. Many centers no longer offer this test.
Twenty-four-hour ambulatory esophageal monitoring with a symptom index is essentially a prolonged physiologic Bernstein test that allows temporal correlation between the patient's symptoms and actual reflux episodes. During the study, the patient presses the appropriate marker indicating the presence of a specific symptom. In a study of patients with typical GERD symptoms, the majority of symptoms occurred within 5 minutes of an esophageal pH decline to less than 4.0.17 A symptom index can be calculated by dividing the total number of symptoms that are temporally related to reflux events (symptoms occurring within 5 minutes of a pH decline to less than 4.0) by the total number of reflux events. A symptom index of greater than 0.75 is considered to be clinically important, although this may be too strict a standard, and a symptom index of greater than 0.50 may have greater sensitivity and specificity in patients with GERD.18
Recent studies also suggest that the response to a short course of empiric treatment with a high dose of acidsuppression medications (eg, 40 mg of omeprazole in the morning and 20 mg in the evening for 7 days) is helpful in diagnosing GERD in patients with typical symptoms.19 The sensitivity of this omeprazole test is 80%, and specificity is 56% when compared with the combination of prolonged esophageal pH monitoring and the presence of erosive esophagitis found via endoscopy.16 Of course, patients with typical symptoms already have a high likelihood of having GERD, and confirmatory testing is not usually indicated. The real value of the acid-suppression test is in diagnosing patients with the atypical symptom of noncardiac chest pain. In these patients, response to the omeprazole test was found to have a sensitivity of 78% and a specificity of 85% for diagnosing GERD as the cause of their symptoms.20 Advantages to such an acid-suppression test include its ease of availability, noninvasiveness, and reasonable cost.21 The 1-week duration of the standard acid-suppression test is too short a time to evaluate whether otolaryngological and pulmonary symptoms are related to GERD because the extraesophageal manifestations of GERD require months of aggressive acid suppression before substantial improvement is noted.22 Although the acid-suppression test has only been recently described as a formal test, it clearly has an important role in the evaluation of noncardiac chest pain and in assigning these patients either to continued empiric treatment or to definitive 24-hour ambulatory esophageal pH monitoring.

Are There Any Complications of GERD?

In patients with dysphagia, gastrointestinal bleeding, long duration of symptoms, or weight loss, clinicians are concerned about esophagitis, ulceration, stricture, Barrett esophagus, or esophageal cancer. There are 2 types of tests to evaluate the esophagus for such mucosal damage: endoscopy and barium radiography with air contrast. Endoscopy is undoubtedly the best diagnostic test in this setting. The magnified view of the esophageal mucosa is the best way to diagnose and stage gross esophagitis and Barrett esophagus.23 The presence of erosions or ulceration in the distal esophagus is indicative of gastroesophageal reflux, once infectious and medication-induced injuries are excluded. Endoscopy is also sensitive for detecting tumors or severe peptic strictures.24 An additional benefit of endoscopy is that it provides the opportunity for therapeutic stricture dilation, as well as biopsy confirmation of any tumors or Barrett esophagus.
The primary disadvantage of endoscopy is its lack of sensitivity for determining abnormal acid reflux. In patients with abnormal reflux, standard EGD does not reveal obvious mucosal abnormalities in 50% of cases.16 The search for histological markers of GERD in otherwise grossly normal esophageal mucosa is an attempt to overcome the low sensitivity of routine endoscopy for GERD. It was initially reported in the 1970s that histologic features of basal cell hyperplasia and location of the papillae close to the epithelial surface correlate well with the

presence of GERD. However, subsequent experience has found that there is little value in assessing biopsy specimens from normal-appearing squamous mucosa either to confirm or to exclude pathological acid reflux.25

Barium upper GI tract radiography is useful for diagnosing subtle strictures and other structural abnormalities of the esophagus, stomach, or duodenum. Additionally, carefully performed air-contrast barium esophagography may reveal mucosal abnormalities such as erosions or ulcers (but not Barrett esophagus). Comparison between endoscopy and air-contrast esophagography shows the radiographic findings of mucosal injury to be specific but insensitive, with an overall sensitivity of only 50%.26

Esophageal manometry has little role in the diagnosis of GERD. It is primarily used to assess the peristaltic contractions before antireflux surgery is performed. It might also be helpful in the rare situation in which scleroderma or calcinosis cubs, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia syndrome are suspected. Esophageal symptoms may predate the obvious skin changes. The manometry changes are usually markedly diminished peristaltic amplitudes and lower esophageal resting pressure.

SUGGESTED APPROACH IN DIAGNOSING PATIENTS WITH SYMPTOMS ASSOCIATED WITH GERD

Patients who present with typical symptoms but without alarm symptoms should be treated with acid suppression. Complete resolution of symptoms is an indication for either chronic or intermittent treatment with acid-suppressing medications administered 'on an as-needed basis. Partial resolution of symptoms is an indication for titration of therapy to achieve appropriate response. The absence of any substantial improvement in symptoms is an indication for EGD and 24-hour ambulatory esophageal monitoring study with a symptom index to search for an alternative pathology (usually performed while the patient is not taking acid-suppression therapy) or to document acid reflux in spite of current therapy (performed while the patient is undergoing acid-suppression therapy).

If the patient presents with any alarm symptom, then EGD is indicated to diagnose or exclude complications of GERD. Specific complications are then treated as needed, and acid-suppression therapy is begun.

Atypical and extraesophageal symptoms of GERD must be evaluated initially by excluding other causes (eg, angina pectoris). A therapeutic trial of potent acid suppression may be the most reasonable initial test for the atypical symptom of noncardiac chest pain. If symptoms resolve, then the patient should be treated chronically. If symptoms are incompletely resolved, then further evaluation with EGD and 24-hour ambulatory esophageal pH monitoring with a symptom index is indicated. Extraesophageal symptoms require 24-hour ambulatory esophageal pH monitoring. If GERD is confirmed, then long-term acid-suppression therapy is indicated, with subsequent ambulatory esophageal pH monitoring performed as needed to document resolution of esophageal acid exposure if symptoms persist.

For any patient who needs objective documentation of GERD before antireflux surgery is performed or to demonstrate successful suppression of acid reflux, the 24-hour ambulatory esophageal pH monitoring test is the best choice when endoscopy does not reveal erosions.

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Article 2

Measurement of acid exposure of proximal esophagus: a better tool for diagnosing non-erosive reflux disease

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Among gastroesophageal reflux disease (GERD) patients, those not exhibiting esophageal mucosal injury at endoscopy, but a proven relationship between acid reflux and symptoms, namely non-erosive reflux disease (NERD) patients, account for nearly 70% and represent a heterogeneous group, according to the 24-h pH profile and to symptom-reflux association indices: indeed, it has been reported that in 30–50% of symptomatic patients, the results of currently available diagnostic techniques, i.e., endoscopy and pH-metry, remain within the normal range.[1,2] In NERD patients, quality of life impairment is similar to that of erosive reflux disease (ERD) patients,[3–5] moreover the response to standard acid suppressive treatments has been shown to be 20–30% lower than in patients with ERD. Therefore, in clinical practice, the management of NERD patients is still challenging. Indeed, the time-related variability of ambulatory pH monitoring findings is particularly high in NERD patients, in whom poor reproducibility of the findings has also been reported.[6] Attempts have been made to improve the sensitivity of the ambulatory pH test. Increasing the duration of pH monitoring, more in keeping with physiological conditions, by means of wireless systems (Bravo), increases the likelihood of a significant reflux-symptom relationship and, as recently shown, significantly improves the reproducibility of the test.[7,8] This technique, however, is hampered by the sampling rate of 6 s which might not change the overall esophageal acid exposure time (AET), but could potentially alter the correlation between symptoms and reflux episodes, and the capsule

itself may even affect esophageal motility during the test.

Recently, a study aimed at comparing the diagnostic accuracy of pH monitoring at the very distal esophagus, 1 cm above the gastroesophageal junction (GEJ), with that at the traditional location (5 cm above GEJ), reported that measurement of very distal acid exposure improves the diagnostic accuracy as well as symptom-reflux correlation in erosive esophagitis, but not in NERD patients, in whom an improved diagnostic yield would be particularly helpful.[9] Anggiansah *et al.* had shown a significantly reduced acid detection at 10 cm above the lower esophageal sphincter (LES) compared to 5 cm, however a Demeester score was used to define a pathological pH-test and, of interest, 3 out of the 14 patients with physiological acid exposure presented a higher score at the proximal, compared with the distal, esophagus.[10]

Growing evidence demonstrates that the proximal extent of acid reflux is relevant in triggering both typical and atypical symptoms. Weusten *et al.* were the first to suggest that, in GERD patients, the proximal extent of the refluxate is an important determinant for reflux perception.[11] In an earlier study, we not only confirmed the higher frequency of proximal reflux in GERD patients but also reported an increased perception of proximal reflux episodes in NERD patients, particularly in those presenting normal AET at the distal esophagus.[12] The relevance of proximal reflux has also been confirmed in an outcome study[13] and in studies in which the pH-impedance technique was used.[14–16] More recently, it has been demonstrated that the proximal extent of the refluxate is the factor most significantly associated with reflux perception in non-responder patients, during PPI treatment, thus confirming what had previously been shown in patients off therapy.[17,18] The primary hypothesis of the present study was that the assessment of the acid exposure of the proximal esophagus better discriminates NERD patients from healthy control with respect to that of the distal esophagus. Therefore, in the present study, we compared, in NERD patients consecutively enrolled, the diagnostic accuracy of the AET values assessed at 5 cm (distal esophagus) above the LES, with those at 10 cm (proximal esophagus), and 3 cm (very proximal esophagus) below the upper esophageal sphincter (UES) as well as the reproducibility of these parameters.

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Materials and methods

A total of 132 consecutive patients attending our outpatient unit for recurrent typical GERD symptoms – heartburn and/or acid regurgitation – lasting more than 6 months and responsive to PPI treatment (>60% improvement following the full PPI dose for at least 4 weeks), were invited to take part in the study. All patients underwent upper endoscopy, stationary esophageal manometry and multichannel ambulatory 24-h gastroesophageal pH monitoring, the latter performed between 3 and 14 days (median 5 days) after endoscopy.

Following endoscopy, 18 patients were excluded from the study due to duodeno-gastric peptic ulcer disease. Of the remaining 114 patients enrolled, 18 showing erosive esophagitis (ERD) (2 F, 16 M; mean age 45, SD 9 years), and 3 patients not presenting esophageal erosions, but evidence of erosive

esophagitis at previous (3–5 years) endoscopy were also excluded. Our series of patients, therefore, comprised 93 NERD patients (51 F, 42 M; mean age 51, SD 8 years). The pH-metric data were compared with those of 40 asymptomatic, hospital staff volunteers (21 F, 19 M; mean age 46, SD 5 years) (healthy control group), all non-smokers. Patients and controls filled out a diary card on which position, time, and type of symptoms as well as times of meals, were reported. Clinical data were obtained using a standard structured questionnaire (Reflux Disease Questionnaire), which was filled out by all patients immediately prior to endoscopy, and included information concerning type, duration and frequency of symptoms. Patients on antisecretory, H_2 antagonists and/or prokinetic drugs, stopped all treatment at least 3 weeks prior to endoscopy. None of the patients or controls in the study population had a history of gastrointestinal surgery, with the exception of appendectomy.

All NERD patients were invited to undergo a further pH study, 13 of whom agreed (5 F, mean age 42, SD 7 years), and the second study was performed after 2–4 weeks.

Written informed consent was obtained from all individuals and the study protocol was approved by the Ethics Committee of Campus Bio Medico University of Rome.

Stationary esophageal manometry

Esophageal manometry was performed with a perfused Dent-sleeve device assembly that incorporated a 6 cm sleeve sensor (Dentsleeve, Medtronic, Adelaide, Australia) and side-hole recording sites at 5, 10, and 15 cm above the sleeve. The sleeve catheter was passed transnasally and placed within the LES high-pressure zone. Low esophageal sphincter resting pressure was measured at the end-expiratory phase.

Multi-channel esophageal pH-metry

Ambulatory 24-h esophageal pH monitoring was performed using two probes, tied to each other, each with two antimony sensors, with a separate skin reference (Zinetics Medical Inc., Salt Lake City, UT, USA). Data were stored on a single portable digital recorder (Digitrapper pH200; Medtronic, Minneapolis, MN, USA). Before each study, the pH probes were calibrated in buffer solutions of pH 7 and pH 1. The four pH sensors were placed, according to the manometric findings, at gastric level, 5 cm above the LES, 10 and 3 cm below the UES.

Data analysis

A reflux episode was defined as a pH drop below 4 units at the distal esophageal sensor, lasting ≥4 s. AET was calculated at each esophageal site. Heartburn and acid regurgitation were considered in the analysis of symptoms. Reflux episodes were classified as symptom-related if they occurred ≤2 min before the onset of the symptom. The symptoms association probability (SAP) index was calculated according to the formula described elsewhere.[19] AET was defined as pathological if the time, at pH <4, exceeded

4% of the total recording time.

Statistical analysis

The frequency distribution of AET was clearly asymmetric and the log-transformation reduced its asymmetry, providing a better fit to the gaussianity (according to Shapiro–Wilk statistics) as well as a reduction of the potentially detrimental effect of the outliers. The comparison between cases and controls was made by means of Student's *t*-test with degrees of freedom (df), appropriately adjusted in case of variance heterogeneity (adj_df). In a secondary analysis where three groups were considered (healthy controls, NERD pH negative and NERD pH positive), anova was applied, followed by Tukey's *post hoc* comparison to compare AET values of the two groups of patients *vs* the control group.

To compare diagnostic accuracy of AET measured at proximal and very proximal *vs* at distal esophagus level, ROC curves were obtained and compared by means of the procedure ROCCOMP available with the statistical software (STATA10, StataCorp; College Station, TX, USA). In addition, the pairwise comparisons between esophagus sites, in terms of sensitivity and specificity, were evaluated by means of McNemar test.

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Results

There was good compliance (no dropouts) to the procedure in the study population. The duration of pH-recording averaged 21.7 ± 0.1 h. AET values at each esophageal level in NERD patients compared to healthy controls are shown in Table 1. Mean values of AET were significantly higher in the whole group of patients at each esophageal site. When considering the subgroups of pH-positive and negative patients, according to the traditional cutoff related to the distal esophageal site, patients with a 'physiological' distal AET showed a significantly higher AET of the proximal esophagus compared with healthy controls.

Table 1. Acid exposure time, mean (95% CI), at different esophageal levels in healthy controls and NERD patients

	Distal	Proximal
Healthy controls (*n* = 40)	1.80 (1.36–2.31)	0.53 (0.38–0.70)
NERD (*n* = 93)	6.32* (4.97–7.97)	2.78* (2.23–3.42)
NERD pH positive (*n* = 53)	13.71* (11.28–16.61)	4.36* (3.39–5.54)
NERD pH negative (*n* = 40)	1.90† (1.56–2.28)	1.38* (1.03–1.80)

**P* < 0.01 *vs* heal

Despite the significant difference of the overall acid exposure time, the individual values showed an overlap between patients and controls, at each esophageal site, as shown in Fig. 1. The ROC analysis indicated that the area under the curve (AUC) of the distal AET was 0.79 (SE = 0.039), 0.87 (SE = 0.032) of the proximal AET (*P* = 0.029 *vs* distal), 0.85 (SE = 0.033) of the very proximal esophagus (p: n.s. *vs* distal) (Fig. 2).

Figure 1. Individual values of acid exposure time at each esophageal level in healthy control group (c) and in NERD patients.

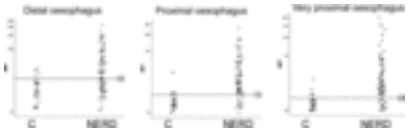
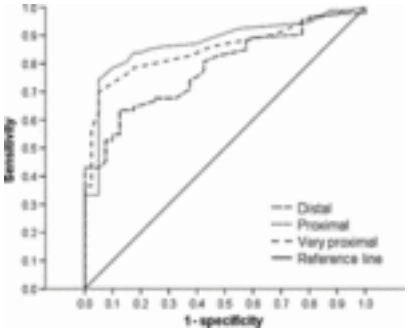


Figure 2. Area under the curve of acid exposure time at distal, proximal, and very proximal esophagus.



The ROC procedure allowed us to define cutoffs which corresponded to specific levels of sensitivity or specificity. Assuming distal site as reference, we found that the traditional cutoff of 4% of 24-h acid exposure time resulted in a good specificity (88%) but in a unsatisfying sensitivity (57%). Looking at more proximal sites and requiring a specificity higher than 80% (thus setting at 20% the upper limit of false positives), we observed that the cutoffs of 1.0% at the proximal and 0.5% at the very proximal esophagus were more 'discriminant' than the 4% reference at distal site. Therefore, this approach identified the following cutoffs for AET: 4% at the distal, 1.0% at the proximal, and 0.5% at the very proximal esophagus.

The corresponding sensitivity and specificity are shown in Table 2, where the pairwise differences, are also reported. As shown in Table 2, sensitivity significantly increased (84% and 78%, *vs* 57%*P* < 0.001) while specificity slightly decreased (82% and 82%, *vs* 88%*P* = ns) when AET was investigated at the proximal and very proximal sites *vs* the distal site. The analysis of discordant cases is shown in the Table 2 (footnotes): a significantly higher proportion of patients showed values higher than cutoffs (true positive patients) when AET was assessed at the proximal and very proximal, *vs* the distal esophageal, site (for details see footnotes Table 2).

Table 2. Sensitivity and specificity of the abnormal pH values at the different esophageal levels

	Sensitivity (%)
Distal esophagus (cutoff 4%)	57
Proximal esophagus (cutoff 1.0%)	84*
Very proximal esophagus (cutoff 0.5%)	78†‡

. *50 true positive at both sites, 12 false negative at both sites, 31 discordant cases, 28 true p
at distal (McNemar, *P* = <0.001). †46 true positive at both sites, 3 false negative a
positive only at proximal, 7 true positive only at distal (McNemar, *P* = 0.001). ‡70 true
both sites, 11 discordant cases, 3 true positive only at proximal, 8 true positive only
negative at both sites, 1 false positive at both sites, 10 discordant cases, 6 false posi

distal (McNemar, $P = 0.754$). ¶29 true negative at both sites, 1 false positive at both s
only at proximal, 4 false positive only at distal (McNemar, $P = 0.754$). **30 true neg
sites, 6 discordant cases, 3 false positive only at proximal, 3 false positiv

Analysis of symptoms

Of the 93 NERD patients, 80 (47 with pathological AET at the distal esophagus, NERD pH+, and 33 with a physiological AET, NERD pH−) reported symptoms during the study day (mean 4.5, range 2–12). Heartburn accounted for 70%, regurgitation for 30% of symptoms. SAP values in patients are listed in Table 3. The percentage of patients with a positive SAP was higher, but not significantly different, at the distal, compared with the proximal esophagus. In particular, six patients with a positive SAP, at the distal esophagus, became negative when the SAP was measured at the proximal esophagus. Of these patients, three showed also a physiological AET at the proximal esophagus. On the other hand, four patients with a negative SAP index, at the distal site, became positive at the proximal esophagus. Of these patients, all but one, showed a physiological AET at the distal esophagus. The proportion of patients classified as SAP negative, at the proximal esophagus, was higher in NERD pH+ than in NERD pH− patients.

Table 3. SAP values assessed in patient groups at different esophageal levels

	Distal	Proximal
NERD SAP positive, *n* (%)	40/80 (50)	36/80 (45)
NERD pH+ SAP positive, *n* (%)	19/41 (46)	16/41 (39)
NERD pH− SAP positive, *n* (%)	21/39 (53)	20/39 (51)

. SAP, symptom association probab

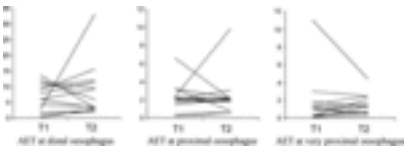
When considering NERD subgroups, according to AET and SAP at the distal esophagus, the statistical analysis performed excluding the 13 patients with normal AET and negative SAP confirmed the findings obtained in the entire sample, being sensitivity 66.2% at distal, 86.2% at proximal, and 77.5% at very proximal (respectively, $P = 0.001$ and $P = 0.093$ *vs* distal).

Moreover, also the AUC values assessed at the proximal and very proximal esophagus were higher than that assessed at the distal esophagus (0.88 and 0.85 *vs* 0.82).

Reproducibility

In the 13 patients who underwent the same study on two separate occasions, the AET did not differ significantly between the two, at the three esophageal sites (Fig. 3).

Figure 3. Individual values of acid exposure time at each esophageal level at time 1 and time 2.



AET showed a reproducibility of 61% (Kappa 0.22) at the distal esophagus

(i.e., 61% of the tested subjects retained a normal or abnormal test result on both study days), 77% (Kappa 0.45) at the proximal and 53% (Kappa 0.05) at the very proximal esophagus. Even if the pH parameters at the proximal esophagus seem to be the most reproducible, the total percentage of time with a pH ≤4 showed a variation between the two study days by a factor of 3.0-fold (Fig. 3).

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Discussion

Results of the present study show that, in NERD patients, the diagnostic yield of the pH test is significantly improved by assessing AET at the proximal, compared with the distal, esophagus.

We focused on patients with recurrent and typical GERD symptoms, responsive to acid suppression, in the absence of mucosal injury at endoscopy. Efforts have been made to select 'true' NERD patients, i.e., those in whom previous endoscopic findings and/or an accurate washout from acid-suppressive treatment should have excluded a history of erosive disease. Over the last few decades, for as long as GERD continued to be identified mainly with the presence of esophagitis, and the diagnosis based upon endoscopy findings, attention was focused on the distal esophagus, 5 cm above the LES. Nevertheless, in NERD patients, the sensitivity of traditional ambulatory 24-h pH monitoring, in diagnosing and in offering an explanation for the disease, is poor (50–60%).[6] As far as concerns pH monitoring, it is a conventional practice to first manometrically localize the proximal border of the LES and then to position the pH electrode, 5 cm proximal to this landmark.[20] Historically, that position was chosen as a reasonable compromise: close enough to the squamo-columnar junction to detect gastroesophageal reflux and sufficiently distant to avoid migration into the stomach.[21] However, no data exist yet confirming that the position 5 cm proximal to the LES is optimal for GERD diagnosis, particularly in the absence of mucosal injury. Results emerging from the present investigation show that the highest percentage of patients with a positive test, in terms of pathological AET, is obtained when considering the pH value at the proximal esophagus. Also findings from subjects classified discordantly, at the three esophageal levels, suggest that the higher sensitivity does not lead to a significant loss of specificity of the pH-metry when shifting the pH sensor from 5 to 10 cm above the LES. Moreover, comparison of the AUC of the pH measurements at the distal, proximal and very proximal esophagus, assessed by means of the ROC curve, indicates that the accuracy of the pH test significantly increases when considering the proximal AET.

According to the more recent definitions, NERD encompasses not only patients with evidence of a pathological acid exposure and/or a significant symptom-reflux association but also patients showing negative findings at the pH-test and symptoms relieved by acid suppression.[4] In our series, in order to overcome possible criticisms, the statistical analysis was also performed after excluding the last subgroup of patients, in whom a placebo effect would have led to a selection bias and did not show different findings.

A recent study, aimed at assessing the accuracy of pH values in a group of GERD patients (erosive and NERD) at 1 cm above the LES, compared with the traditional 5 cm above the LES, failed to show an improvement in the diagnostic yield in the NERD subgroup.[9] Growing evidence now supports the concept that, in the pathogenesis of NERD – and hence, of GERD symptoms – in addition to alterations in central pain processing of visceral stimuli, the spread of refluxate into the proximal esophagus plays a predominant role in eliciting typical symptoms.[22]

In the present study, when assessing the SAP index, at the distal and proximal esophagus, the proportion of patients with positive SAP did not differ, being significantly lower in the very proximal esophagus. We can offer no definite explanations for this finding. In the analysis of the association between symptoms and reflux, rigorous adherence to the threshold of pH 4, in the proximal esophagus, may lead to an underestimation of the reflux-related origin of the symptoms. Indeed, we have recently shown that a not negligible number (nearly 30%) of reflux episodes showed a decrease in acidity when spreading to the proximal esophagus.[23] On the other hand, an improved accuracy of pH-impedance has been shown. It is well known that the SAP index values are related to the time windows chosen (ranging from 2 to 5 min) and the relationship between symptoms and reflux is made in a qualitative fashion. Although SAP values remain the best index to express the relationship between symptoms and reflux episodes,[24] it is not uncommon that symptoms do not occur during the study day – nearly 15% in our series – or that for symptoms like hoarsness, globus, sore throat it is very difficult to discriminate onset and end, thus a quantitative measurement of pathological reflux would be helpful in clinical practice. Therefore, it is tempting to suggest that, shifting the pH sensor from 5 cm above LES to 10 cm below UES and/or having two pH sensors, one proximal and one distal, in the pH-impedance assembly, would achieve a more accurate characterization of the proximal reflux, and to further enhance the sensitivity of the test.

Our results, although emerging from a relatively small group of patients that agreed to undergo the pH monitoring on two separate occasions, also showed that the AET of the proximal esophagus appears to be the most reproducible. In particular, in our asymptomatic control group, the cutoff value was 1.0%; although these findings were derived from a relatively small population of healthy subjects, we are confident regarding the consistency of these data both on account of the very low variability in individual data, and the very similar results published in other series of asymptomatic controls.[25]

It is well known that the day-to-day variability in esophageal acid exposure is high and, as a result, the diagnostic reproducibility of 24-h pH measurement is low.[6]

In conclusion, in NERD patients, the diagnostic yield of the pH test is significantly improved by the assessment of AET at 10 cm below the UES compared to 5 cm above the LES. As this variable seems to be less affected by the day to day variability, it could be considered a reliable and useful diagnostic tool in non-erosive reflux disease.

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Author contribution

SE performed the study and wrote the manuscript; MR and PP analyzed the data; MC designed the research study and wrote the manuscript.

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