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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S

Nonacid Reflux in Patients With Chronic Cough on Acid-Suppressive Therapy*

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Background: It is generally accepted that extraesophageal gastroesophageal reflux disease (GERD) symptoms and their persistence despite acid-suppressive therapy are poor prognostic factors for antireflux surgery. Recent studies indicating that cough can be temporally associated with reflux episodes of pH 4 to 7 (ie, nonacid reflux) reinvigorates the need for a more careful workup in patients with cough suspected to be due to GERD.

Aim: To evaluate the frequency of chronic cough associated with nonacid reflux and the response of these patients to laparoscopic Nissen fundoplication.

Methods: We retrospectively reviewed data from patients with persistent cough despite twice-daily proton pump inhibitor (PPI) with or without the use of nighttime regimens of histamine-2 receptor antagonist (H2RA), who had undergone combined multichannel intraluminal impedance and pH monitoring. The association of cough and reflux was evaluated by calculating the symptom index (SI) [positive if $\geq 50\%$]. A subset of patients with positive SI values for impedance-detected reflux with therapy was referred for laparoscopic Nissen fundoplication.

Results: Of 50 patients (38 female patients; mean age, 43 years; age range, 6 months to 84 years) who were monitored while receiving therapy, 13 patients (26%) had a positive SI for cough. The SI-positive group had a lower percentage of female patients and patients of younger age compared to the SI-negative group. Laparoscopic Nissen fundoplication was performed in six SI-positive patients who became asymptomatic and stopped receiving acid-suppressive therapy during follow-up evaluations (median time, 17 months; range, 12 to 27 months).

Conclusion: Impedance pH monitoring should be performed while receiving therapy in patients with persistent symptoms who are receiving PPI therapy. A positive SI for nonacid reflux may be helpful in selecting patients who will benefit from antireflux surgery.

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Key words: extraesophageal manifestation of gastroesophageal reflux disease; multichannel intraluminal impedance; pH monitoring; proton pump inhibitors

Abbreviations: GERD = gastroesophageal reflux disease; H2RA = histamine-2 receptor antagonist; LES = lower esophageal sphincter; MII = multichannel intraluminal impedance; MUSC = Medical University of South Carolina; PPI = proton pump inhibitor; SI = symptom index

Extraesophageal manifestations of gastroesophageal reflux disease (GERD) include pulmonary symptoms (ie, chronic cough and wheezing) and ear-nose-throat symptoms (ie, hoarseness, throat clearing, sore throat, and globus).¹ Prior studies² have indicated that patients with extraesophageal manifestations of GERD may require longer and high-dose acid-suppressive therapy to control their symptoms. Managing patients with persistent symptoms who are receiving proton pump inhibitor (PPI) therapy represents a further challenge, and the same

authors² have suggested that GERD can be excluded as a cause of persistent atypical symptoms in patients who do not respond to PPI therapy. This concept is further strengthened by reports from the surgical literature suggesting that predictors of a good response to surgery include patients with typical symptoms that respond to acid-suppressive therapy. Thus, caution is advised in considering antireflux surgery for patients with atypical symptoms who are not responding to acid-suppressive therapy.^{3–5}

Conversely, there are reports^{6–9} indicating that

carefully selected patients with persistent atypical GERD symptoms despite twice-daily PPI therapy benefit from anti-GERD surgery. These observations postulate that symptoms in these patients are due to gastroesophageal reflux not detected by conventional pH monitoring (*ie*, nonacid reflux) and underscore the concept that GERD cannot be ruled out as the cause of chronic cough because a patient's condition failed to improve with maximal acid-suppressive therapy (*ie*, PPI bid with or without histamine-2 receptor antagonist [H2RA] with or without prokinetic regimens titrated until the 24-h distal esophageal acid exposure was zero).¹⁰

Combined multichannel intraluminal impedance (MII)-pH monitoring is a relatively new, clinically available technology that allows the detection of gastroesophageal reflux independent of pH.¹¹ Reflux episodes are identified by changes in electrical impedance produced by the presence of the refluxate in the esophagus, and the associated pH is used to classify the reflux as acid (pH < 4) or nonacid (pH ≥ 4).¹² Since acid-suppressive therapy is thought to change primarily the pH of the refluxate without decreasing the total number of reflux episodes, combined MII-pH monitoring is the ideal technique with which to monitor patients with gastroesophageal reflux who are receiving acid-suppressive therapy.¹³

The aims of our study were as follows: (1) to evaluate how frequently nonacid reflux is associated with persistent cough in patients receiving PPI therapy in whom gastroesophageal reflux is suspected as the cause; and (2) to evaluate the clinical significance of the association of cough and nonacid reflux by following the response to antireflux surgery in patients with a positive symptom index (SI) for cough and nonacid reflux.

MATERIALS AND METHODS

The current study consists of a retrospective review of the results of combined MII-pH monitoring performed while continuing acid-suppressive therapy at the Medical University of South Carolina

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(MUSC) and a prospective follow-up of a subset of patients who underwent antireflux surgery at MUSC. The institutional review board of MUSC approved the retrospective review of data and the prospective data collection from phone interviews.

Patients

We retrospectively reviewed the collected data from all patients who had been referred to the Esophageal Function Laboratory of the MUSC with persistent symptoms while receiving acid-suppressive therapy and had undergone combined MII-pH testing between July 2002 and May 2005. Patients with persistent cough were selected based on the symptoms recorded on the day of monitoring. These patients were referred for an esophageal evaluation as part of the workup of their chronic cough. Their pulmonary evaluations were not part of a structured protocol, and the final conclusion regarding a nonpulmonary etiology was based on the opinion of the pulmonary consultant. Patients who underwent laparoscopic Nissen fundoplication were identified based on data from the Department of Surgery at MUSC. At the time of MII-pH monitoring, all patients were taking one of the currently available PPIs twice daily prior to breakfast and dinner with or without H2RAs at bedtime.

Combined MII-pH Monitoring

On the day of testing, all patients who had been referred for reflux monitoring while receiving acid-suppressive therapy arrived at the Esophageal Function Laboratory after having fasted for at least 4 h. As part of the preprocedure interview, patients were queried about both typical and atypical GERD symptoms, and those patients reporting multiple symptoms were asked to identify their primary symptom prior to beginning reflux monitoring.

A 2.1-mm diameter combined MII-pH catheter with six impedance channels and two (esophageal and gastric) antimony pH sensors with external reference was used. Prior to the procedure, the pH sensors were calibrated using buffered solutions of pH 4.0 and 7.0 as specified by the manufacturer (Sandhill Scientific Inc; Highlands Ranch, CO). The probe was then inserted transnasally through the esophagus into the stomach, and the esophageal pH sensor was positioned 5 cm above the manometrically located proximal border of the lower esophageal sphincter (LES). The design of the probe allows the measurement of impedance at 3, 5, 7, 9, 15, and 17 cm above the LES, esophageal pH data at 5 cm above the proximal border of the LES, and gastric pH data at 10 cm below the proximal border of the LES (Fig 1). The catheter was connected to a data logger (Sleuth System; Sandhill Scientific Inc) that stores data from all eight channels (six impedance and two pH) with a frequency of 50 Hz. The patients were provided with and instructed to keep a diary to record the timing of the start and end of meals, changes in position from upright to recumbent and *vice versa*, symptoms, and the timing of medication. Patients were also instructed to enter symptoms by pushing preprogrammed buttons on the data logger. Patients were discharged from the laboratory and asked to reproduce as closely as possible situations known to induce symptoms. The patients returned on the following day for probe removal and a review of the diaries.

Data were downloaded and analyzed using dedicated software (BioView Analysis; Sandhill Scientific Inc). A computerized algorithm (Autoscan; Sandhill Scientific Inc) was used to identify reflux episodes as a decrease in impedance progressing distally to proximally. Tracings were subsequently reviewed manually by experienced investigators to ensure that the automated algorithm correctly separated reflux episodes from swallows.

The temporal association between cough and MII-detected

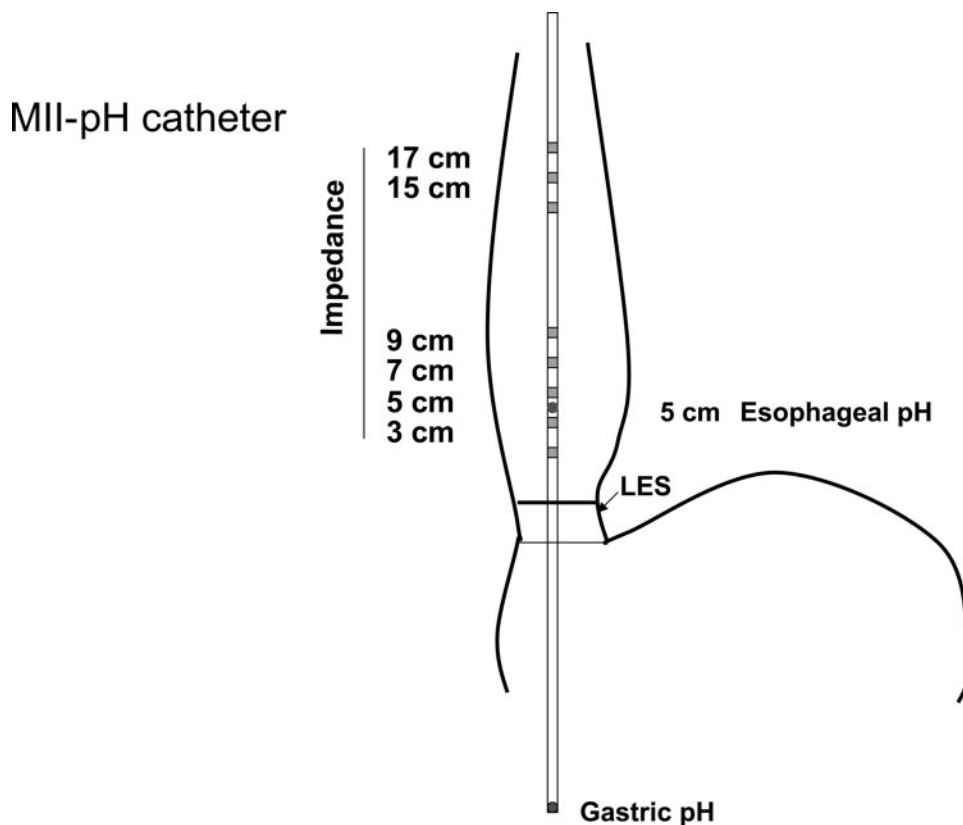


FIGURE 1. Combined MII-pH probe with six impedance measuring segments and two pH sensors (esophageal and gastric) placed in the esophagus for reflux monitoring while the patient was receiving acid-suppressive therapy.

liquid-containing reflux was evaluated using the SI.¹⁴ The SI was calculated by dividing the number of cough events preceded by an MII-detected reflux episode in a 5-min window by the total number of cough events recorded during the monitoring period. An SI $\geq 50\%$ (ie, at least half of the cough events being preceded by reflux) was considered to be positive.

Laparoscopic Nissen Fundoplication

Based on finding a positive SI for cough and nonacid reflux, six of these patients underwent laparoscopic Nissen fundoplication at MUSC. The surgeon involved in the patients' care established the indication for surgery, and the patient in consultation with the surgeon decided for or against the surgical procedure. Experienced surgeons accredited by the American College of Surgery performed the laparoscopic Nissen fundoplication.

Postsurgical Evaluation

Every 3 to 4 months, one investigator (I.M.) contacted patients who had undergone surgery adhering to a protocol approved the Institutional Review Board of MUSC. During the phone interview, the patients were asked whether they were symptomatic or cough-free and whether they had been taking any PPIs. Patients were considered to have benefited from surgery if, in their own assessment, they reported themselves to be asymptomatic and were not taking a PPI on a daily basis.

Statistical Analysis

Descriptive statistics were used to analyze the characteristics of patients with positive and negative symptom associations for

cough and MII-detected reflux. Comparisons between proportions were made using the χ^2 test or Fisher exact test, depending on the number of observations. Parametric or nonparametric tests were used to compare continuous variables according to the normality of the data distribution. A p value of < 0.05 was considered to be statistically significant.

RESULTS

In the 34-month period from June 2002 to May 2005, 50 patients (38 female patients; mean age, 43 years; age range, 6 months to 84 years) presenting with chronic cough underwent combined MII-pH monitoring while receiving at least twice-daily PPI therapy. Patients recorded a median of eight cough events (25th to 75th percentile, 3 to 21 events) during the monitoring period. Thirty-two patients (64%) were studied while they were receiving twice-daily PPI therapy before meals, and 18 patients (36%) were studied while they were receiving twice-daily PPI therapy before meals, plus H2RA at bedtime. The specific PPIs used were rabeprazole (4 patients; 8%), esomeprazole (26 patients; 52%), lansoprazole (12 patients; 24%), omeprazole (3 patients; 6%), and pantoprazole (5 patients; 10%). The specific H2RAs used were ranitidine (15 patients; 83%) and famotidine (3 patients; 17%).

Table 1—Comparison of Patients With Positive and Negative SI

Variables	Positive SI (n = 13)	Negative SI (n = 37)	p Value
Female gender, %	46	83	< 0.01*
Age, † yr	41 (1–57)	51 (39–63)	0.04
Symptoms ‡	3 (1–11)	13 (5–25)	0.06
Acid-suppressive regimen, %			0.4*
PPI bid	69	62	
PPI bid + H2RA	31	38	

* χ^2 test.

†Values are given as the median (25th to 75th percentile).

‡Values are given as No. (range).

In our group of patients, we identified 13 patients (26%) with a positive SI and impedance-detected reflux. In all 13 patients, the SI was positive for nonacid reflux. None of the patients with a positive SI had a positive SI for acid, underscoring the importance of monitoring for reflux episodes in these patients with a pH of > 4 (*ie*, nonacid reflux). All but 1 patient (*ie*, 49 of 50 in these patients; 98%) had a normal distal esophageal acid exposure while receiving acid-suppressive therapy. However, this patient had a negative SI for cough and reflux. Comparing the group of patients with a positive SI (n = 13) to the group of patients with a negative SI (n = 37), we identified that the SI-positive group had a lower proportion of female patients (46% vs 83%, respectively; $p < 0.01$ [χ^2 test]) and patients of younger age (median age, 41 years [25th to 75th percentile, 1 to 54 years] vs 51 years [25th to 75th percentile, 39 to 63 years], respectively; $p = 0.04$ [Mann-Whitney *U* test]). Patients in the SI-positive group recorded fewer cough events ($p = 0.06$ [Mann-Whitney *U*

test]) during the 24-h monitoring period (median, 3 cough events; 25th to 75th percentile, 1 to 11 events) compared to patients in the SI-negative group (median, 13 events; 25th to 75th percentile, 5 to 25 events). The proportion of patients with a positive SI in the group receiving PPI twice a day alone (9 of 32 patients; 28%) did not differ from the proportion of patients with a positive SI in the group of patients receiving PPI twice daily plus an H2RA every hour (4 of 18 patients; 22%); ($p = 0.4$ [χ^2 test]). These comparisons are summarized in Table 1 and Figure 2.

After meeting with the GI surgeon, 6 of the 13 patients with positive SIs for cough and nonacid reflux decided to undergo laparoscopic Nissen fundoplication. The characteristics of these patients are presented in Table 2. The surgical intervention was uneventful in all patients. One patient was lost to follow-up 20 months after surgery. During the phone interviews at a median of 17 months (range, 12 to 27 months), the remaining five patients stated that they were asymptomatic and not receiving PPI therapy.

DISCUSSION

This preliminary study suggests that monitoring both acid and nonacid reflux in patients with suspected reflux-related cough persisting while they received acid-suppressive therapy may be helpful in clinical decision making. The positive clinical outcome in the subset of patients who underwent laparoscopic Nissen fundoplication based on a positive SI suggests a reflux-cough causality of the temporal association between cough and nonacid reflux, which has been suggested by Irwin et al.¹⁵ In the absence of a clinical tool to monitor nonacid reflux, this relationship has been previously postulated in

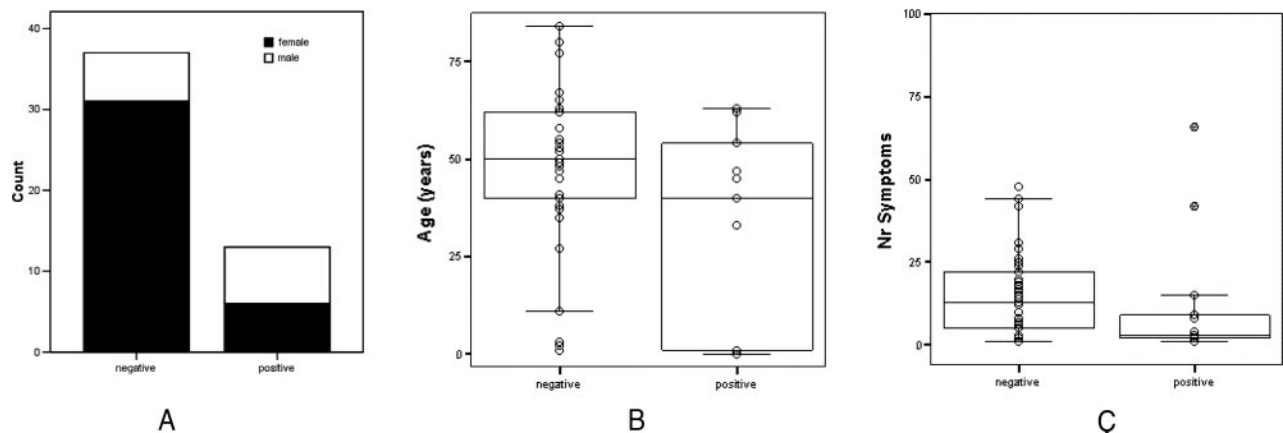


FIGURE 2. Characteristics of 50 patients with a positive SI vs patients with a negative SI. The SI-positive group (n = 13) had a higher percentage ($p < 0.01$) of female patients (*left, A*) and younger age (*middle, B*) [$p = 0.04$; data are presented as the median 25th to 75th percentile] compared to the SI-negative group (n = 37). Patients in the SI-positive group tended ($p = 0.06$) to record fewer symptoms (*right, C*) [data are presented as the median and 25th to 75th percentile; Nr = number].

Table 2—Characteristics of Patients Who Underwent Fundoplication for Cough Associated With Persistent Reflux*

Patient No./Age, yr/Gender	Type of Reflux	SI, %	Follow-up, mo	Referred From
1/46/F	Nonacid	100	27	Pulmonary
2/1/F	Nonacid	67	20†	Pediatrics
3/54/F	Nonacid	73	17	Gastroenterology
4/0.8/M	Nonacid	50	17	Pediatric surgeon
5/46/F	Nonacid	50	16	ENT
6/23/M	Nonacid	67	12	ENT

*F = female; M = male; ENT = ear-nose-throat specialist.

†This patient was lost to follow-up after 20 mo.

patients fitting a “clinical profile” who experienced complete elimination of their cough and near total improvement following antireflux surgery. Using combined MII-pH monitoring, this relationship can be documented, allowing for a better selection of patients who may benefit from antireflux surgery. A positive SI can be used as an argument in the complex referring process, which should include a careful weighing of the risks and benefits of antireflux surgery.¹⁶

Our study follows up and includes the previously published case report.⁹ It describes in more detail the characteristics of patients who were referred for the evaluation of persistent cough despite receiving

acid-suppressive therapy. GERD has been implicated in the past, as one of the most common etiologies for chronic cough, but it has often been difficult to diagnose and treat. We found a positive temporal association between reflux and cough in about a quarter of the patients who were referred to our tertiary care center (Fig 3). In our study population, patients with a positive SI were younger, included a higher proportion of women, and recorded fewer cough events compared to those with a negative SI. Even though at a first glance this may suggest that testing should be focused on young men, we consider that documenting a negative symptom association in patients with persistent cough who are receiving acid-suppressive therapy carries important clinical information. The negative result should be used to move the focus away from GERD as the cause of persistent symptoms, inviting further evaluation for other causes of the cough.

In a recent study, Sifrim et al¹⁷ reported on the relationship between nonacid reflux and cough in 22 patients. They found that the majority of cough episodes (70%) occurred “independent” of reflux, but 30% of cough episodes were temporally associated with reflux. In half of these cases (51%), cough preceded reflux, while in the other half cough was preceded by acid reflux (32%) or nonacid reflux

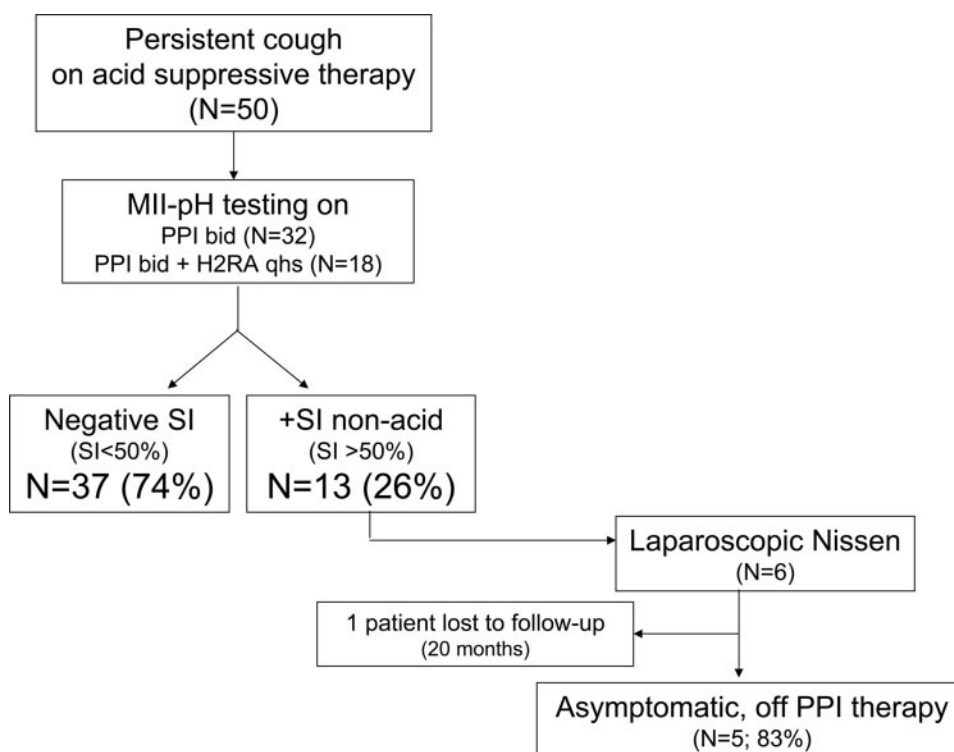


FIGURE 3. Flow chart with the results of MII-pH monitoring and postsurgical follow-up of patients with persistent cough who were receiving acid-suppressive therapy.

(17%). It is, however, important to recognize that these studies were performed “off therapy,” explaining why their proportion of acid and nonacid reflux episodes differ from our data. We consider that patients with persistent symptoms (*ie*, cough) while receiving acid-suppressive therapy should be tested “on therapy” for a more accurate evaluation of the relationship between their symptoms and acid or nonacid therapy. The alternative (*ie*, testing these patients while not receiving therapy) is helpful only when the results of reflux monitoring are negative (*ie*, the patient has no reflux). If the results of the testing conducted while the patient is not receiving therapy indicate an abnormal esophageal acid exposure, the question of why symptoms persist despite maximal acid-suppressive therapy remains unanswered.

The present study has several limitations. First, we did not include a control group for the surgical outcome. We opted for this approach for this initial study as we wanted to collect data on the efficacy of surgery in this population before embarking on a large controlled study. A second critique to our study is that the impedance-pH data were recorded only prior to surgery and there were no objective follow-up data. This limitation resulted in part from the difficulty in convincing patients to undergo a second impedance-pH monitoring session when they have no symptoms after surgery. Third, the retrospective nature of data analysis and the open-access policy to reflux testing did not allow controlling for the duration of PPI therapy. Still, patients who were referred to our tertiary center usually had been treated for several weeks with PPIs before undergoing testing. Nevertheless, this point (*ie*, a “run-in” period during which patients are treated with maximal acid-suppressive therapy [PPI twice daily with or without H₂RA every hour]) needs to be considered when planning prospective studies. A further critique to our study is in using the SI to appreciate the symptom association. This parameter has been used primarily to evaluate the relationship between heartburn and/or chest pain and acid reflux, and not necessarily cough and nonacid reflux. Further, none of these parameters is known to predict the outcome for cough. We decided to use the SI as it is simple to calculate and is more specific among the currently used parameters (*ie*, SI, symptom sensitivity index, and symptom association probability).¹⁸

In conclusion, our study documents that up to a quarter of patients with chronic cough persisting despite acid-suppressive therapy have a temporal association between cough and nonacid reflux. This observation suggests that reflux monitoring to include gastroesophageal reflux episodes with a pH of > 4 is important in evaluating these patients as

documenting nonacid reflux associated cough may be helpful in directing further therapy. Even though these preliminary data are promising, larger multicenter studies are warranted to clarify the appropriateness of the proposed approach.

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