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Long-term Therapeutic Outcome of Patients Undergoing Ambulatory pH Monitoring for Chronic Unexplained Cough

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Abstract

Background and Aim—Ambulatory pH monitoring is frequently performed to determine temporal associations between reflux events and chronic unexplained cough. We further explored the clinical value of ambulatory pH monitoring in predicting long-term symptomatic outcome of therapy in chronic cough.

Methods—Symptom scores and reflux indicators from ambulatory pH study [acid exposure time, symptom association probability (SAP), and symptom index] were extracted from records of subjects undergoing esophageal evaluation for chronic cough. Intensity of antireflux therapy administered and symptomatic outcome were determined by telephone interview. Univariate and logistic regression analysis were performed to identify predictors of a high degree response (HDR), defined as sustained, durable symptom improvement lasting >3 months.

Results—Fifty-three subjects (mean age 63 ± 2 y, 42 females) fulfilled the inclusion criteria. Reflux parameters were abnormal on ambulatory pH monitoring in 54.7%. After a mean interval of 3 ± 0.3 years, cough intensity improved significantly, 19 subjects (35.8%) achieving HDR. Only female sex and positive SAP predicted HDR on univariate analysis; SAP and intensity of antireflux therapy were retained as independent predictors ($P = 0.03$) on logistic regression analysis. Sequential use of acid exposure time, SAP, and symptom index had the best value, with the highest likelihood of HDR when all three were positive (85.7%, $P < 0.01$).

Conclusions—Reflux disease is a frequent cause of chronic unexplained cough and aggressive antireflux therapy forms a vital component of management. Positive SAP is an independent predictor of outcome, but hierarchical or sequential use of abnormal gastroesophageal reflux disease parameters on ambulatory pH testing has value in predicting long-term symptomatic response.

Keywords

gastroesophageal reflux disease; ambulatory pH monitoring; cough

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Both chronic unexplained cough and gastroesophageal reflux disease (GERD) are encountered frequently in clinical practice. As many as 14% to 23% of nonsmoking adults report chronic cough, and over 40% of adults report heartburn in population studies.^{1–3} Chronic cough can account for up to 38% of pulmonary referrals with a significant negative impact on quality of life.⁴ Along with asthma and postnasal drip syndrome, GERD is 1 of the 3 most common causes of chronic unexplained cough.^{5,6} Successful management intuitively requires accurate suspicion of the cause-and-effect relationship between reflux events and chronic cough. Practice guidelines suggest initiating prolonged maximal empiric acid suppression therapy when suspicion of chronic cough induced by GERD is high, with variable symptom response.^{5,7–11} Difficulty arises when symptom response is inadequate, or when clinical suspicion for a GERD association is less clear. Further, GERD can be “silent” without typical symptoms in up to 3 quarters of cases where it is conclusively linked to chronic cough.¹²

Esophageal physiologic testing is frequently used to evaluate chronic cough in the setting of GERD. Ambulatory pH monitoring can be useful in documenting elevated esophageal acid exposure times (AET) and eliciting a temporal relationship between cough events and reflux episodes.^{4,12} Using such techniques, demonstration of a clinically meaningful association between chronic cough and GERD has been reported over a rather large range, from as little as 10% to as many as 56% of cases.^{4,12–15} Simple pH parameters such as the symptom index (SI) and AET largely are not predictive of treatment response in chronic cough, and have not been demonstrated to be particularly useful in selecting candidates for aggressive antireflux therapy, including antireflux surgery.¹⁶ This emphasizes the need for more sophisticated interpretation of ambulatory pH data to identify subjects most likely to experience symptom improvement with aggressive anti-reflux therapy. Symptom association probability (SAP) uses a statistical algorithm to account for the possibility that the association between symptoms and reflux events could have occurred by chance alone.¹⁷ We previously have reported that SAP can predict a successful response to laparoscopic antireflux surgery in an unselected reflux patient cohort.¹⁸ Further, SAP has been used in conjunction with pH-impedance monitoring to successfully evaluate the temporal association between reflux events and chronic cough.¹⁹ We have also suggested that tests of symptom association be used hierarchically or sequentially, evidence for GERD as a definitive etiology for symptoms being most conclusive when both SAP and SI are positive in the setting of an abnormal AET.²⁰

The goal of this observational study was to determine if clinical presentation and parameters from esophageal physiologic testing can predict long-term therapeutic outcome in a cohort of patients with chronic unexplained cough. Further, we aimed to determine if evidence of GERD on ambulatory pH testing could be used hierarchically or sequentially to predict response.

METHODS

All adult outpatients (age ≥ 18 y) referred for ambulatory pH monitoring to investigate chronic cough over a 5-year period (2000 to 2005) were eligible for inclusion. Subjects with chronic cough as a dominant symptom were retrospectively identified from interrogation of

the computerized esophageal physiologic testing database at our institution. Ambulatory pH testing had to be performed off antisecretory therapy for inclusion to this study, to determine pathologic esophageal acid exposure and to assess symptom-cough correlation in subjects with failure or incomplete response to a proton pump inhibitor (PPI) trial. Subjects who reported cough as a secondary symptom, had incomplete or inadequate pH tracings or chose not to participate in the study were excluded. None of the subjects tested with ambulatory pH monitoring were concurrently using angiotensin converting enzyme inhibitors. Clinical presentation, symptom characteristics, and results of esophageal physiologic testing were extracted from outpatient and inpatient clinical charts. Eligible subjects were subsequently contacted for a telephone interview to determine the nature and outcome of treatment directed by the ambulatory pH study, corroborated with chart review. The study protocol was approved by the Human Research Protection Office (Institutional Review Board) of Washington University School of Medicine.

Before esophageal physiologic testing, all subjects completed a subjective symptom survey to allow characterization of their dominant symptom and associated symptoms. Cough frequency and severity were individually rated by the subjects on a 5-point Likert scale generated a priori for esophageal physiologic studies at our institution. Using this scale, the spectrum of cough frequency ranged from 0 for no episodes to 4 for multiple daily episodes; cough severity similarly ranged from 0 for mild symptoms to 4 for severe, life-altering symptoms. Cough intensity was calculated as the product of cough frequency and cough severity, with a maximum possible score of 16.

All ambulatory pH studies were performed off anti-secretory therapy and after an overnight fast. Subjects had been asked to discontinue PPIs at least 7 days prior and histamine-2 receptor antagonists, prokinetic agents, and antacids at least 3 days before the ambulatory pH study; they were also asked to refrain from using antitussive medications during the pH study. The location of the lower esophageal sphincter was determined by high resolution manometry (HRM) using a 21-lumen water-perfused catheter system (Medical Measurement Systems USA, Dover, NH). The tip of the pH catheter (Medical Measurement Systems USA, Dover, NH) was placed 5 cm above the proximal extent of the lower esophageal sphincter. Ambulatory manometry was not used to identify cough events. Instead, subjects were asked to keep a symptom, meal and medication diary, and to push the symptom indicator button on the pH recorder each time they experienced cough. Subjects returned in 24 hours for removal of the pH catheter.

Ambulatory pH tracings were scrutinized to evaluate and quantify acid exposure. AET was defined as the percent time the esophageal pH remained below 4. A total AET of 4.0% was used to define elevated acid exposure; upright and recumbent AET were not separately calculated. The SI was extracted and calculated according to the method of Wiener et al,²¹ as a proportion of cough events associated with reflux events to all symptom events, expressed as a percentage. Cut-off values of both 25% and 50% were assessed in evaluating symptom association.²² SAP was then calculated as described by Weusten et al.¹⁷ The SAP indicated a significant association between cough and a preceding reflux event when the likelihood of a chance association was <5%. Only cough symptoms occurring within the period of 2 minutes after a reflux event were included in calculations of SI and SAP; other

reflux symptoms were not used in these calculations. Cough symptoms preceding reflux events or occurring during meals were excluded from the analysis. Multiple cough symptoms recorded within a single 2-minute period after a reflux event was counted as a single symptom. Calculations were automated, however, each pH study was manually reviewed to ensure that only appropriate symptoms and reflux events were included in calculation of symptom association. Finally, the esophageal motor pattern was evaluated from the HRM plots.

Subjects were subsequently contacted over the telephone and a brief questionnaire administered to extract further symptom characteristics and treatment. Potential cough comorbidities (including lung disease, asthma, postnasal drip syndrome, and ongoing tobacco use) were further characterized. Subjects were asked about previous GERD treatments and responses to each treatment trial. Treatment approaches were implemented by each patient's gastroenterologist based upon the ambulatory pH study findings and conventional clinical algorithms; these were not influenced or altered by this study. Subjects were categorized into 4 groups based on the treatment approach prescribed by their treating physicians after the ambulatory pH study, corroborated with chart review: (a) minimal medical therapy, consisting of over-the-counter, intermittent or PRN antisecretory medications, (b) submaximal medical therapy, consisting of once daily PPI use, (c) maximal medical therapy, consisting of twice a day PPI use for >3 months, and (d) antireflux surgery. Each subject was asked to characterize changes in their cough symptoms as a direct result of GERD therapy, and was assigned into one of three outcome groups: (a) no improvement or transient improvement in symptoms, wherein subjects remained symptomatic and considered their management to be inadequate, (b) limited or partial improvement in symptoms, wherein subjects reported improved symptoms, but continued to experience troublesome symptoms requiring additional changes in therapy, and (c) definite, sustained improvement in symptoms for >3 months, wherein subjects were either asymptomatic on stable PPI doses or were off medications after successful antireflux surgery. We termed definite, sustained improvement in symptoms "high degree response" (HDR). Finally, subjects were asked to rate their current cough frequency and severity on the same 5-point Likert scale used in the preprocedure symptom survey; cough intensity was again calculated as the product of cough frequency and severity.

Data are reported as mean $\pm$ standard error of the mean, unless otherwise indicated. Grouped data were compared using 2-tailed Student *t* test; a *P* value of <0.05 was required for statistical significance. Fisher exact test was used to evaluate differences between groups, and analysis of variance to evaluate differences across groups. Logistic regression analyses were used to determine independent predictors of HDR. All statistical calculations were made using SPSS version 14.0 (Chicago, IL).

RESULTS

An initial interrogation of the ambulatory pH database revealed 167 subjects who underwent ambulatory pH testing for a "cough" indication during the study period. Of these, 20 subjects were studied on antisecretory therapy, 8 had prior fundoplication, 16 had an alternate dominant symptom or disease, 9 had artifactual pH recordings and 4 had

incomplete symptom records; these subjects were excluded. Of the remainder, 50 subjects could not be traced, and 7 declined to participate. Therefore, a total of 53 subjects (63 ± 2 y, 42 females) fulfilled study inclusion criteria, were successfully contacted by telephone, and consented to participate in the study (Table 1). In accordance with the study protocol, all subjects endorsed cough as their dominant symptom, and reported an average of 24 ± 3.6 cough episodes during the ambulatory pH study. Further, 21 subjects (39.6%) reported cough as an isolated symptom without other GERD symptoms. In the remainder, heartburn coexisted in 26 (49.1%), regurgitation in 14 (26.4%), chest pain in 10 (18.9%), and dysphagia in 8 subjects (15.1%). Twenty-four subjects (45.3%) had at least 1 other cough comorbidity that had been fully evaluated and excluded as a dominant etiology for chronic cough before ambulatory pH monitoring (asthma = 18.9%, postnasal drip syndrome = 24.5%, chronic obstructive pulmonary disease or other chronic lung disease = 7.5%) and 1.9% reported ongoing tobacco use. The mean cough intensity was rated at 12.2 ± 0.7 at the time of the ambulatory pH study, and was not statistically different in the presence of comorbid conditions (with comorbidities, 13.0 ± 0.8 vs. without comorbidities, 11.5 ± 1.0 , $P = 0.3$).

Twenty-nine subjects, or 54.7%, had at least 1 abnormal finding on their ambulatory pH monitoring study. Elevated AET was noted in 25 subjects (47.2%) (Fig. 1). The SAP was positive, indicating a statistically significant relationship between cough and preceding reflux events, in 15 subjects (28.3%). The SI was 50% in 3 subjects (5.7%), and 25% in 11 subjects (20.8%). Only 3 of the 15 subjects (20.0%) with a positive SAP had SI 50%, whereas 8 (53.3%) of these subjects had SI >25%; further, a significant correlation was demonstrated between SI 25% and SAP ($R = 0.5$, $P < 0.001$). Therefore, SI 25% was also included as an additional cut-off value for further data analysis.²² Evaluation of the HRM plots demonstrated a spastic pattern in 22 subjects (41.5%), a hypomotile pattern in 6 (11.3%), a mixed spastic and hypomotile pattern in 5 (9.4%), and a normal pattern in the remaining 20 subjects (37.7%).

Follow-up telephone interview was performed after a mean of 3.0 ± 0.3 years. There was a good distribution of treatments reported by the subjects to allow for comparison of outcomes. Overall, 47.0% received maximal GERD management for their cough symptoms (20.6%, maximal medical therapy; 26.4% antireflux surgery), whereas the remainder were prescribed minimal (18.9%) or submaximal (34.0%) GERD therapy by their treating physicians (Fig. 2). Segregation into these treatment subsets closely paralleled the degree of GERD evidence on ambulatory pH testing. Mean cough intensity scores improved significantly on follow-up for the entire study cohort (5.0 ± 0.5 , 58.8% change, $P < 0.001$). Subjects with HDR had the lowest follow-up symptom scores (3.2 ± 0.8 , 74.1% change, $P < 0.001$).

HDR was achieved by 19 subjects (35.8%). More intense therapy groups had the highest rates of HDR, with 45.5% of the maximal medical therapy group and 64% of the antireflux surgery group achieving HDR. In univariate analyses, HDR was only associated with female sex ($P = 0.04$) and positive SAP ($P = 0.03$). Other objective GERD indicators obtained from the pH study did not seem to predict response of cough symptoms to GERD therapy. As comorbidities and demographic features may be important covariates in considering the

predictive value of GERD parameters, a logistic regression model was constructed, using HDR as the outcome variable. This model included GERD indicators from the ambulatory pH monitoring study including AET and symptom association tests, as well as demographics, comorbidities, tobacco use, intensity of antireflux therapy, and esophageal motor pattern as independent variables. Female sex remained a significant predictor of response ($P = 0.02$). The regression model also revealed that a positive SAP ($P = 0.03$) and intensity of antireflux therapy ($P = 0.03$) were additional significant predictors of cough response to GERD therapy. Elevated SI trended toward, but did not reach statistical significance ($P = 0.1$) (Fig. 3). On subgroup analysis, frequency of abnormal GERD parameters on ambulatory pH testing did not differ based on the presence or absence of cough comorbidities, neither did the likelihood of HDR.

The sensitivity, specificity, and positive predictive value of a positive SAP in predicting HDR were modest (0.47, 0.82, and 0.28, respectively), but the negative predictive value was more robust (0.72) (Table 2). In contrast, sensitivity and specificity of elevated AET were 0.58 and 0.59 respectively, with a positive predictive value of 0.47 and a negative predictive value of 0.53. We further explored the use of esophageal physiologic parameters from the ambulatory pH test in hierarchical or sequential fashion. Of 25 subjects with elevated AET, 11 (44.0%) achieved HDR. When AET was elevated in conjunction with a positive SAP, 66.7% (8 of 12 subjects) achieved HDR. If, in addition to elevated AET and positive SAP, SI was 25%, 85.7% (6 of 7 subjects) achieved HDR (Fig. 1, $P < 0.01$ compared with subjects with <3 abnormal parameters); use of SI 50% as the cut-off value in this calculation only yielded 2 subjects with HDR and 1 without. Sensitivity decreased while specificity increased for HDR when these physiologic parameters were used hierarchically or sequentially (Table 2), and the addition of SI to the mix substantially lowered sensitivity and positive predictive values. Negative predictive values were significantly more robust than positive predictive values.

DISCUSSION

In this observational study, we demonstrate that over half of subjects with chronic unexplained cough with a clinical suspicion for GERD have objective evidence of reflux on ambulatory pH testing. Despite this, only one-third reported sustained high quality symptom relief over a 3-year follow-up period. Whereas AET and SI from ambulatory pH testing failed to predict response, SAP proved to be useful in this regard, with the highest likelihood for a durable symptom response when symptom association tests were used hierarchically. Further, subjects managed with aggressive anti-secretory therapy or antireflux surgery had statistically better symptomatic outcomes compared with subjects receiving therapies of lesser intensity.

GERD is considered to be one of the most common etiologies for chronic unexplained cough along with asthma and postnasal drip syndrome.⁵ While diagnosis and treatment of cough associated with asthma and post nasal drip syndrome can be straightforward in many instances, the correlation between GERD and chronic cough is often more vague.²³ Furthermore, these etiologies can coexist in the same patient, and can dampen the likelihood of a robust response. This was evident in our cohort, where the lack of potentially

confounding comorbidities resulted in a numerically higher proportion of subjects achieving HDR, 41.4%, as compared with 29.2% subjects with comorbid conditions, though the difference was not statistically significant ($P = 0.4$). Mechanisms proposed for GERD-induced chronic cough include microaspiration or macro-aspiration of refluxate into the airway, and a vagally mediated esophago-tracheo-bronchial reflex triggered by mechanical or chemical stimulation of the distal esophagus by the refluxate leading to increased bronchial reactivity.^{24–26} Although these mechanisms are generally accepted, establishing a cause and effect relationship between cough and esophageal acid reflux events remains difficult.²⁷

Temporal correlation between esophageal acid reflux events and cough requires use of tests to establish the proportion of cough events that follow reflux events, either simple ratios such as the SI, or statistical tests such as the SAP. SAP testing is different from SI in that this incorporates statistical methods in determining if the symptom (ie, cough) cooccurred by chance alone, or if a true association exists.^{28,29} We and others have previously shown that the SAP performs better than the SI in predicting a successful outcome after antireflux therapy including antireflux surgery, and that it is useful in determining the association of other perceptible atypical symptoms such as chest pain to reflux events.^{18,29–31} By convention, for the SI to be abnormal, 50% of symptoms need to be associated with reflux events, that is, the SI has to be 50%. Some investigators have suggested that 25% is a more clinically relevant cut-off value when addressing chronic cough.^{21,22,32} Our findings suggest there may be value in the use of an SI cut-off value of 25% when evaluating the relationship between cough and reflux events, as this seemed to correlate somewhat with a more robust test of symptom association, the SAP (albeit with an r value of 0.5 indicating modest correlation at best). However, despite our attempts to be as inclusive as possible, our cohort failed to demonstrate an association between a positive SI alone (using either 25% or 50% cut-off) and improvement of cough with aggressive GERD therapy.

The SI, therefore, may be subject to more variability compared with SAP, but may have clinical utility in further establishing the strength of symptom-reflux association in patients who already have a positive SAP.²⁰ Using results from ambulatory pH testing in such an hierarchical or sequential fashion, the likelihood of HDR increased from 44.0% when AET alone was elevated, to 66.7% when SAP was positive in addition to elevated AET, and subsequently to 85.7% when SI 25% was added to the mix. This suggests that hierarchical use of symptom association tests may add value to clinical decision making. This is further supported by our finding that none of the parameters of GERD evidence on ambulatory pH testing had robust independent sensitivity or specificity for HDR, although SAP had a modest negative predictive value of 0.72. In contrast, when used hierarchically, specificity and negative predictive values incremented considerably (Table 2), indicating that the stronger the evidence for GERD, the more likely it is that cough will respond to GERD management. Multiple diagnostic tests do improve diagnostic yield, but negative predictive value is more robust than positive prediction of an association in these instances—a finding that is supported by our results (Table 2).³³ However, accurate symptom recording is critical in determining symptom association; our results are limited by the fact that the symptom diary method was used for symptom recording. A more accurate assessment would be to

evaluate for pressure changes on concurrent ambulatory manometry with ambulatory pH testing, which would allow identification of individual cough events.^{19,34}

Independent of GERD parameters on ambulatory pH testing, the likelihood of a high degree symptomatic response was directly predicted by the intensity of antireflux therapy offered to the subjects, as demonstrated both by direct comparison (Fig. 2) and on logistic regression analysis (Fig. 3). Others have also reported the fact that GERD parameters on ambulatory pH testing alone may not accurately predict response to antireflux therapy.¹⁶ This suggests that ambulatory pH testing may be inadequate to fully document the relationship between reflux events and cough episodes, and that there may be reflux episodes remaining unmeasured with pH monitoring alone.³⁵ This unmeasured component could be mechanical, from either esophageal distension or actual retrograde movement of the refluxate to the airway, or chemical, from chemoreceptor stimulation by weakly acid, nonacid, or alkaline components of the refluxate. Esophageal sensitization could also result from acid exposure in susceptible individuals, adding yet another component to the already complex equation in the form of esophageal hypersensitivity.^{26,36} Indeed, characterization of all reflux events independent of pH using multichannel intraluminal impedance (MII) testing in the esophagus has been reported to provide additional clinical utility in the evaluation of chronic cough that may have a GERD etiology.^{37–41} Sifrim et al¹⁹ demonstrated the value of MII testing using SAP. They showed that MII testing together with SAP allows for a more precise determination of the temporal association between reflux events and chronic cough.¹⁹ Zerbib et al⁴² report an improved diagnostic yield of MII over pH testing alone for symptom analysis by including weakly acid reflux episodes in the SAP algorithm. An additional advantage of MII testing is that it allows for the assessment of adequate acid suppression when testing is performed on maximal antisecretory therapy. These studies support our observation that GERD is an important aspect of chronic unexplained cough; that MII testing may be superior to ambulatory pH testing alone in demonstrating significant symptom-reflux associations, and that management involving aggressive antireflux therapy including antireflux therapy may have a positive impact on symptoms when symptom association is demonstrated.

High intensity PPI seems to suppress cough symptoms in patients suspected of having GERD-induced chronic cough when comorbidities are fully established and treated.^{15,43,44} Although the results for chronic cough are not as striking as for typical GERD symptoms, a significant improvement was seen in this patient population when GERD was adequately controlled.^{10,45} Our results also support a consideration for antireflux surgery when intense antisecretory therapy is insufficient in symptom control in the face of significant symptom-reflux associations, but MII testing may be more appropriate to demonstrate these associations.³⁵ In our cohort, 67% of subjects who underwent antireflux surgery had a durable HDR, which is in keeping with 51% to 85% response reported in the literature.^{23,46–49} We also note that 7 subjects (13.2%) without positive GERD parameters on ambulatory pH testing achieved HDR (Fig. 1). These subjects on direct questioning could not attribute symptom improvement to any therapeutic event. Such “spontaneous” recovery defies a rational explanation with a retrospective study design, but is not uncommon in clinical practice.

There are several limitations inherent in our study. First, supporting evidence for GERD induced chronic cough was partly obtained through patients' subjective reports during telephone questionnaire. Further, there was a wide range of treatments offered to patients, ranging from occasional acid suppression to fundoplication, an aspect of the report that was beyond our control as patient management was left up to the treating physicians. Although all subjects in this study were studied off antireflux therapy primarily because they had failed an empiric PPI trial, the length and intensity of the trial could not be determined in this retrospective study. Some failures may therefore be due to imperfect treatments, a false positive pH test result and/or the presence of non-acid reflux. This study does not account for the contribution of non-acid reflux as a cause for symptoms. Lastly, as this study relied on patient's ability to recall previous therapies and symptoms during the completion of a telephone questionnaire, this study is subject to recall bias. Because this was a retrospective review, we could not standardize evaluations for nongastroenterologic causes of chronic cough, though the telephone questionnaire consistently suggested formal ear-nose-throat and pulmonology evaluations as reported by the subjects. Therefore, the possibility of an alternate etiology for chronic cough remains possible in our subjects. Nevertheless, the study represents a "real world" situation, and ambulatory pH tests continue to be requested in patients with unexplained cough; our study attempts to provide an assessment of the clinical utility of this diagnostic test while exposing some of the limitations.

In conclusion, more than half of patients with chronic unexplained cough have objective indicators of GERD on ambulatory pH monitoring despite confounding comorbidities. Upon ambulatory pH testing, hierarchical use of symptom association tests provides a basis for recommending GERD therapy, but aggressive antireflux therapy has independent utility in predicting a durable symptomatic response. The value of ambulatory esophageal physiologic testing may be augmented by the use of symptom association testing in conjunction with MII, but further outcome studies are required to validate this approach.

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REFERENCES

1. Di Pede C, Vieg G, Quackenboss JJ, et al. Respiratory symptoms and risk factors in an Arizona population sample of Anglo and Mexican-American whites. *Chest*. 1991; 99:916–922. [PubMed: 2009795]
2. Wynder EL, Lemon FR, Mantel N. Epidemiology of persistent cough. *Am Rev Respir Dis*. 1965; 91:679–700. [PubMed: 14280941]
3. Locke GR III, Talley NJ, Fett SL, et al. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. *Gastroenterology*. 1997; 112:1448–1456. [PubMed: 9136821]
4. Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Am Rev Respir Dis*. 1990; 141:640–647. [PubMed: 2178528]

5. Irwin RS, Boulet LP, Cloutier MM, et al. Managing cough as a defense mechanism and as a symptom. A consensus panel report of the American College of Chest Physicians. *Chest*. 1998; 114:133S–181S. [PubMed: 9725800]
6. Alhabib KF, Vedal S, Champion P, et al. The utility of ambulatory pH monitoring in patients presenting with chronic cough and asthma. *Can J Gastroenterol*. 2007; 21:159–163. [PubMed: 17377644]
7. Irwin RS. Chronic cough due to gastroesophageal reflux disease: ACCP evidence-based clinical practice guidelines. *Chest*. 2006; 129:80S–94S. [PubMed: 16428697]
8. Poe RH, Kallay MC. Chronic cough and gastroesophageal reflux disease: experience with specific therapy for diagnosis and treatment. *Chest*. 2003; 123:679–684. [PubMed: 12628862]
9. Chang AB, Lasserson TJ, Gaffney J, et al. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. *Cochrane Database Syst Rev*. 2006:CD004823. [PubMed: 17054216]
10. Dore MP, Pedroni A, Pes GM, et al. Effect of antisecretory therapy on atypical symptoms in gastroesophageal reflux disease. *Dig Dis Sci*. 2007; 52:463–468. [PubMed: 17211695]
11. Chandra KM, Harding SM. Therapy Insight: treatment of gastroesophageal reflux in adults with chronic cough. *Nat Clin Pract Gastroenterol Hepatol*. 2007; 4:604–613. [PubMed: 17978817]
12. Irwin RS, French CL, Curley FJ, et al. Chronic cough due to gastroesophageal reflux. Clinical, diagnostic, and pathogenetic aspects. *Chest*. 1993; 104:1511–1517. [PubMed: 8222816]
13. Smyrniotis NA, Irwin RS, Curley FJ, et al. From a prospective study of chronic cough: diagnostic and therapeutic aspects in older adults. *Arch Intern Med*. 1998; 158:1222–1228. [PubMed: 9625401]
14. Pratter MR, Bartter T, Akers S, et al. An algorithmic approach to chronic cough. *Ann Intern Med*. 1993; 119:977–983. [PubMed: 8214994]
15. Waring JP, Lacayo L, Hunter J, et al. Chronic cough and hoarseness in patients with severe gastroesophageal reflux disease. Diagnosis and response to therapy. *Dig Dis Sci*. 1995; 40:1093–1097. [PubMed: 7729270]
16. Patterson RN, Johnston BT, MacMahon J, et al. Oesophageal pH monitoring is of limited value in the diagnosis of “reflux-cough”. *Eur Respir J*. 2004; 24:724–727. [PubMed: 15516662]
17. Weusten BL, Roelofs JM, Akkermans LM, et al. The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. *Gastroenterology*. 1994; 107:1741–1745. [PubMed: 7958686]
18. Diaz S, Aymerich R, Clouse RE. The symptom association probability is superior to the symptom index for attributing symptoms to gastroesophageal reflux: validation using outcome from laparoscopic anti-reflux surgery. *Gastroenterology*. 2002; 122:A75.
19. Sifrim D, Dupont L, Blondeau K, et al. Weakly acidic reflux in patients with chronic unexplained cough during 24 hours pressure, pH, and impedance monitoring. *Gut*. 2005; 54:449–454. [PubMed: 15753524]
20. Prakash C, Clouse RE. Wireless pH monitoring in patients with non-cardiac chest pain. *Am J Gastroenterol*. 2006; 101:446–452. [PubMed: 16542279]
21. Wiener GJ, Richter JE, Copper JB, et al. The symptom index: a clinically important parameter of ambulatory 24-hour esophageal pH monitoring. *Am J Gastroenterol*. 1988; 83:358–361. [PubMed: 3348191]
22. Green BT, O'Connor JB. Most GERD symptoms are not due to acid reflux in patients with very low 24-hour acid contact times. *Dig Dis Sci*. 2004; 49:1084–1087. [PubMed: 15387325]
23. Irwin RS, Zawacki JK, Wilson MM, et al. Chronic cough due to gastroesophageal reflux disease: failure to resolve despite total/near-total elimination of esophageal acid. *Chest*. 2002; 121:1132–1140. [PubMed: 11948043]
24. Ing AJ, Ngu MC, Breslin AB. Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. *Am J Respir Crit Care Med*. 1994; 149:160–167. [PubMed: 8111576]
25. Irwin RS, Madison JM, Fraire AE. The cough reflex and its relation to gastroesophageal reflux. *Am J Med*. 2000; 108(suppl 4a):73S–78S. [PubMed: 10718456]
26. Kollarik M, Ru F, Undem BJ. Acid-sensitive vagal sensory pathways and cough. *Pulm Pharmacol Ther*. 2007; 20:402–411. [PubMed: 17289409]

27. Wunderlich AW, Murray JA. Temporal correlation between chronic cough and gastroesophageal reflux disease. *Dig Dis Sci*. 2003; 48:1050–1056. [PubMed: 12822861]
28. Prakash C, Clouse RE. Value of extended recording time with wireless pH monitoring in evaluating gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2005; 3:329–334. [PubMed: 15822037]
29. Snedegar CT, Clouse RE. Comparison of reflux-associated symptom probability (RASP) tests from ambulatory pH monitoring. *Gastroenterology*. 2004; 126:A323.
30. Taghavi SA, Ghasedi M, Saberi-Firoozi M, et al. Symptom association probability and symptom sensitivity index: preferable but still suboptimal predictors of response to high dose omeprazole. *Gut*. 2005; 54:1067–1071. [PubMed: 15845561]
31. Colas-Atger E, Bonaz B, Papillon E, et al. Relationship between acid reflux episodes and gastroesophageal reflux symptoms is very inconstant. *Dig Dis Sci*. 2002; 47:645–651. [PubMed: 11911354]
32. Singh S, Richter JE, Bradley LA, et al. The symptom index. Differential usefulness in suspected acid-related complaints of heartburn and chest pain. *Dig Dis Sci*. 1993; 38:1402–1408. [PubMed: 8344094]
33. Connor J, Richter J. Increasing yield also increases false positives and best serves to exclude GERD. *Am J Gastroenterol*. 2006; 101:460–463. [PubMed: 16542280]
34. Decalmer S, Woodcock AA, Smith JA. Patient misreporting may lead to underestimation of cough events. *Chest*. 2007; 132:358. author reply 358–359. [PubMed: 17625100]
35. Sifrim D, Mittal R, Fass R, et al. Review article: acidity and volume of the refluxate in the genesis of gastro-oesophageal reflux disease symptoms. *Aliment Pharmacol Ther*. 2007; 25:1003–1017. [PubMed: 17439501]
36. Javorkova N, Varechova S, Pecova R, et al. Acidification of the oesophagus acutely increases the cough sensitivity in patients with gastro-oesophageal reflux and chronic cough. *Neurogastroenterol Motil*. 2008; 20:119–124. [PubMed: 17999650]
37. Silny J. Intraluminal multiple electrical impedance procedure for measurement of gastrointestinal motility. *J Gastrointest Motil*. 1991; 3:151–162.
38. Sifrim D, Holloway R, Silny J, et al. Acid, nonacid, and gas reflux in patients with gastroesophageal reflux disease during ambulatory 24-hour pH-impedance recordings. *Gastroenterology*. 2001; 120:1588–1598. [PubMed: 11375941]
39. Shay S, Tutuian R, Sifrim D, et al. Twenty-four hour ambulatory simultaneous impedance and pH monitoring: a multicenter report of normal values from 60 healthy volunteers. *Am J Gastroenterol*. 2004; 99:1037–1043. [PubMed: 15180722]
40. Sifrim D, Castell D, Dent J, et al. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. *Gut*. 2004; 53:1024–1031. [PubMed: 15194656]
41. Bajbouj M, Becker V, Neuber M, et al. Combined pH-metry/impedance monitoring increases the diagnostic yield in patients with atypical gastroesophageal reflux symptoms. *Digestion*. 2007; 76:223–228. [PubMed: 18174685]
42. Zerbib F, Roman S, Ropert A, et al. Esophageal pH-impedance monitoring and symptom analysis in GERD: a study in patients off and on therapy. *Am J Gastroenterol*. 2006; 101:1956–1963. [PubMed: 16848801]
43. Vaezi MF, Richter JE. Twenty-four-hour ambulatory esophageal pH monitoring in the diagnosis of acid reflux-related chronic cough. *South Med J*. 1997; 90:305–311. [PubMed: 9076302]
44. Ours TM, Kavuru MS, Schilz RJ, et al. A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. *Am J Gastroenterol*. 1999; 94:3131–3138. [PubMed: 10566703]
45. Richter JE. Ear, nose and throat and respiratory manifestations of gastro-esophageal reflux disease: an increasing conundrum. *Eur J Gastroenterol Hepatol*. 2004; 16:837–845. [PubMed: 15316405]
46. Giudicelli R, Dupin B, Surpas P, et al. Gastroesophageal reflux and respiratory manifestations: diagnostic approach, therapeutic indications and results. *Ann Chir*. 1990; 44:552–554. [PubMed: 2241079]

47. Johnson WE, Hagen JA, DeMeester TR, et al. Outcome of respiratory symptoms after antireflux surgery on patients with gastroesophageal reflux disease. *Arch Surg.* 1996; 131:489–492. [PubMed: 8624193]
48. Allen CJ, Anvari M. Gastro-oesophageal reflux related cough and its response to laparoscopic fundoplication. *Thorax.* 1998; 53:963–968. [PubMed: 10193396]
49. So JB, Zeitels SM, Rattner DW. Outcomes of atypical symptoms attributed to gastroesophageal reflux treated by laparoscopic fundoplication. *Surgery.* 1998; 124:28–32. [PubMed: 9663248]

FIGURE 1.

Hierarchical use of parameters from ambulatory pH testing in predicting response to antireflux therapy. The highest likelihood of a sustained, durable response (high degree response, HDR) to antireflux therapy was achieved when acid exposure time (AET), symptom association probability (SAP) and symptom index (SI) were all abnormal ($P < 0.01$).

FIGURE 2.

Relationship between intensity of GERD therapy, GERD evidence on pH study and high degree response (HDR). Evidence of GERD on pH study prompted more aggressive therapy recommendations by treating physicians ($P < 0.05$ across groups), which in turn resulted in a higher frequency of high degree response ($P = 0.02$ across groups). GERD indicates gastroesophageal reflux disease.

FIGURE 3.

Results of logistic regression analysis using high degree response (HDR) as the outcome variable. Female sex, positive SAP (but not elevated AET, abnormal SI, or esophageal motor pattern) and intensity of GERD therapy predicted HDR. AET indicates acid exposure time; GERD, gastroesophageal reflux disease; SAP, symptom association probability; SI, symptom index.

TABLE 1

Demographics and Clinical Characteristics

	All Subjects N=53	HDR N=19	Non-HDR N=34	P (HDR vs. Non-HDR)
Mean age (y)	63.0±1.9	66.5±3.1	61.0±2.5	0.18
Sex (F/M)	42/11	18/1	24/10	0.04
Comorbidities	24 (45.3%)	7 (36.8%)	17 (50.0%)	0.40
Cough intensity				
Pretreatment	12.2±0.7	10.9±1.3	12.9±0.7	0.16
Follow-up	5.0±0.5	3.2±0.8	6.1±0.7	0.01
AET 4.0	25 (47.2%)	11 (57.9%)	14 (41.2%)	0.27
SI 25%	11 (20.8%)	6 (31.6%)	5 (14.7%)	0.17
SI 50%	3 (5.6%)	2 (10.5%)	1 (2.9%)	1.0
Positive SAP	15 (28.3%)	9 (47.4%)	6 (17.7%)	0.03
GERD evidence	29 (54.7%)	12 (63.2%)	17 (50.0%)	0.40

AET indicates acid exposure time; GERD, gastroesophageal reflux disease; HDR, high degree response; SAP, symptom association probability; SI, symptom index.

TABLE 2

Sensitivity, Specificity, Positive and Negative Predictive Values of GERD Parameters on Ambulatory pH Testing for High Degree Response (HDR) to Antireflux Therapy

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
AET 4.0	0.58	0.59	0.47	0.53
Positive SAP	0.47	0.82	0.28	0.72
Either AET 4 or positive SAP	0.63	0.50	0.55	0.45
AET 4.0 and positive SAP	0.42	0.88	0.23	0.77
AET 4.0 and positive SAP and SI 25%	0.32	0.97	0.13	0.87
AET 4.0 and positive SAP and SI 50%	0.03	0.89	0.06	0.94

AET indicates acid exposure time; GERD, gastroesophageal reflux disease; HDR, high degree response; SAP, symptom association probability; SI, symptom index.