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Chronic Cough and Gastroesophageal Reflux Disease: New Twists to the Riddle

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In this issue of *GASTROENTEROLOGY*, Smith et al¹ report on a meticulous analysis of the relationship between chronic cough and reflux in a carefully characterized series of patients studied with ambulatory reflux monitoring. This is not a new topic, but it is one that sorely needed fresh data and to those who have followed this saga through the years, this paper will not disappoint. Chronic cough, defined as that which persists for >8 weeks, is an extremely common problem faced in primary care as well as in several subspecialties: pulmonary medicine, otolaryngology, allergy, and gastroenterology to name the dominant ones.^{2,3} Implicit in this heterogeneity is that chronic cough has a diverse set of potential causes that are often elusive. Compounding the difficulty is that cough is often an atypical presentation of a common disease. Thus, for example, a patient with cough variant asthma may not exhibit typical wheezing and a patient with reflux-associated cough may not report heartburn. Thus, not only is the etiology of chronic cough difficult to establish, but it is often unclear in which direction to turn for help.

Recognizing this problem, multispecialty cough clinics have been developed to combine subspecialist expertise. Such clinics have reported success rates in improvement of chronic cough patients ranging from 82% to 99%.³ However, the causal distribution among the 3 most common diagnoses reported by these chronic cough clinics varies widely: asthma syndrome (mean, 25%; range, 6%–59%).³ esophageal disease (mean, 20%; range, 0%–41%); rhinitis (mean, 34%; range, 8%–58%).³ These widely discrepant data suggest that diagnostic criteria for establishing causation vary among centers and/or that the etiology of chronic cough can be multifactorial. Nowhere are these observations more germane than in the relationship between chronic cough and gastroesophageal reflux disease (GERD). That such a relationship exists is no longer disputed, but beyond that lurk a host of vexing questions. Consider some of these questions along with the wealth of data contributed toward unraveling them by the Smith et al paper.¹

What Constitutes Reflux–Cough Association in an Ambulatory Reflux Monitoring Study?

Reflux monitoring studies quantify esophageal acid exposure and detect gastroesophageal reflux events. It is accepted widely that adding impedance to pH monitoring improves the sensitivity for detecting reflux events,⁴ thereby making the impedance–pH combination the

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Conflicts of Interest

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preferable technology for establishing symptom–reflux association. However, on the other side of this equation is the need for accurate symptom reporting (or detection) and that has been the Achilles heel of the technology. Many patients simply do not reliably activate the event monitor button in a timely manner; this is especially true with frequent, sometimes subconscious, symptoms such as cough. In an elegant solution to this problem, these investigators used a microphone to record sound concurrently with the pH-impedance recording and then used an investigator/sound analysis combination that precisely identified the signature acoustic waveform of coughs throughout the study. As a result, they report a cough rate averaging 8.6 per hour, equating to 205 cough sounds per day. Because coughs tended to cluster, this reduced to 59 cough epochs per 24 hours, which is 6–18 times more coughing than reported in prior studies relying on patient reported cough⁵ and 2–3 times more than in studies that utilized manometry to infer when cough might be occurring.^{6,7} The implications of this with respect to the validity of event correlation are enormous and the results compelling. The bar has been raised. At least within the domain of reflux testing done to evaluate chronic cough patients, a physiologic event detector independent on patient input, preferably the acoustic monitoring used in this study, is essential to confidently establish reflux–cough association.

Side questions raised (and de facto answered) by this study were what index of symptom association to use when evaluating potential reflux-related cough in pH impedance monitoring studies and whether to conduct the study “on” or “off” proton pump inhibitor (PPI) therapy? The 2 main choices for evaluating reflux–cough association are the symptom index or the symptom association probability. In this case, the answer (symptom association probability) is easy because with cough occurring an average of 8.6 times an hour in this study, the probability of the symptom index being positive on the basis of chance⁸ is sufficiently high to make it essentially meaningless. With a 2-minute window of association and an average of 1 reflux event per hour, the symptom index would be positive by chance 29% of the time; with 2 reflux events per hour that would 58% of the time. If one widens the window of association to 5 minutes as is sometimes done, then these numbers become 73% and virtually 100%. With respect to whether or not to withhold PPI therapy, coughs were associated with acid (pH < 4) or “nonacid” reflux events equally often in this study. Because it is unknown how much therapeutic benefit can be expected with PPI therapy for reflux-induced cough, and it is quite possible that conducting the test “on” PPIs will reduce its sensitivity, it would seem to make little sense to add this variable to an already difficult clinical situation.

Reflux Causing Cough or Cough Causing Reflux?

Cause and effect is always difficult to establish with respect to atypical manifestations of GERD.^{9,10} Even if an association can be confidently established, it is ultimately an assumption that this is indicative of a cause and effect relationship. The situation gains complexity with a symptom such as cough because cough can cause reflux, and reflux can cause cough. Esophageal perfusion with acid can elicit cough in selected patients¹¹ and the act of coughing can provoke reflux in others.¹² Hence, the tighter the association established with an ambulatory monitoring study, the better. Data in this regard from the Smith et al¹ study are fascinating. It was equally frequent for reflux to follow cough or for cough to follow reflux. Overall, 72% of the 71 chronic cough patients analyzed exhibited 1 relationship or the other and, in fact, one third of these 51 reflux–cough patients exhibited both. The most consistent feature of the patients with reflux–cough association was not related to the severity of reflux during the ambulatory study, proximal extent of reflux, coexistent typical esophageal symptoms, presence of esophagitis, or hiatal hernia. Rather, patients with reflux–cough association were best characterized by a sensitized cough reflex

as quantified by a standardized challenge of inhaled citric acid. Coughers are prone to cough in response to a variety of stimuli.

Focusing on sensitization of the neural substrate of cough as a mechanism of reflux-related cough fundamentally alters the clinical paradigm. Sensitization has been demonstrated experimentally with the observation that esophageal acid perfusion acutely increases cough sensitivity in reflux-cough patients.¹³ Cough reflex sensitization may occur in the central nervous system (as advocated by the authors), at the sensory level, or both. Hints that transient lower esophageal sphincter relaxations are sensitized in concert with the cough pathway are intriguing. The suggestion stems from the observation that when reflux occurred within 2 minutes of a cough, the latency between the events usually exceeded what would be consistent with the straining effect of the cough itself. If reflux is not strain induced, transient lower esophageal sphincter relaxations are the likely culprit. The transient lower esophageal sphincter relaxation pathway closely neighbors that of cough in the medulla and the suggestion that both are sensitized in reflux-cough could conceivably represent a field effect on neurons in that part of the brain. Clearly, these observations pose many new questions.

Another offshoot of the sensitization concept is that the diagnostic challenge is no longer to identify chronic cough patients with reflux as “the” cause, but instead to broaden this construct to identify patients in whom reflux is a contributing factor to chronic cough. It is not an either–or situation. Equal numbers of patients found to have reflux-related cough in the Smith et al series¹ did or did not have additional diagnoses (rhinitis, asthma, eosinophilic bronchitis) emerge during their evaluation. This theme of reflux as a cofactor rather than the sole factor in causation is emerging as a commonality among the bronchopulmonary manifestations of reflux disease,¹⁴ being similarly true of laryngitis and asthma.¹⁵ It also helps to rationalize the divergent conclusions among cough centers as to the relative contributions of rhinitis, asthma and reflux to chronic cough alluded to earlier.³ In essence, they may all be correct.

Implications for Management of Chronic Cough

Although always recognized as a complex relationship, the findings of Smith et al¹ reveal the relationship between cough and reflux to be even more complex than previously envisioned. Not only can reflux cause cough and cough cause reflux, but reflux seems to sensitize the neural pathways of cough even when the cough syndrome has multiple etiologies. Clearly, a multispecialty approach is wise in approaching such patients and the gastroenterologist should consider carefully the counsel of colleagues in pulmonary medicine, allergy and/or otolaryngology before closing the book on a reflux-induced cough diagnosis. This is especially true given the limitations of current GERD therapies in treating chronic cough. Although it is harmless enough to prescribe a therapeutic trial of PPIs in the chronic cough patient, a negative result by no means vindicates GERD as a contributing factor. In fact, evidenced by the conclusion of a recent meta-analysis on the subject, any significant benefit from PPI therapy has been difficult to demonstrate: “From this systematic review and meta-analysis we conclude that PPIs for cough associated with GORD probably have some effect in some adults, though the effect is less universal than reported in cohort studies.”¹⁶ Given what we now know of the pathophysiology, one might anticipate somewhat greater therapeutic efficacy with antireflux surgery and uncontrolled trials do support that contention.¹⁷ However, surgery also entails greater risks to the patient and is fundamentally an irreversible intervention. Hence, the importance of maximal confidence in the diagnosis before embarking on that treatment and it is that frontier that was greatly advanced by the current study. The ultimate test will be in whether or not this sophisticated approach of establishing that chronic cough is reflux related translates into improved

outcomes in treating the patients and that will only be established by appropriate treatment trials.

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References

1. Smith JA, Decalmer S, Kelsall A, et al. Acoustic cough—reflux associations in chronic cough: potential triggers and mechanisms. *Gastroenterology* 2010;139:754–762. [PubMed: 20600028]
2. Chung KF, Pavord ID. Chronic cough 1. Prevalence, pathogenesis, and causes of chronic cough. *Lancet* 2008;371:1364–1374. [PubMed: 18424325]
3. Morice AH, Fontana GA, Sovijarvi AR, et al. The diagnosis and management of chronic cough. *Eur Respir J* 2004;24:481–492. [PubMed: 15358710]
4. Sifrim D, Casteil D, Dent J, Kahrilas PJ. 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]
5. Tutuian R, Mainie I, Agrawal A, et al. Nonacid reflux in patients with chronic cough on acid-suppressive therapy. *Chest* 2006;130:386–391. [PubMed: 16899836]
6. Sifrim D, Dupont L, Blondeau K, et al. Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring. *Gut* 2005;54:449–454. [PubMed: 15753524]
7. Bogte A, Bredenoord AJ, Smout AJ. Diagnostic yield of oesophageal pH monitoring in patients with chronic unexplained cough. *Scand J Gastroenterol* 2008;43:13–19. [PubMed: 18938747]
8. Kahrilas PJ. When proton pump inhibitors fail (editorial). *Clin Gastroenterol Hepatol* 2008;6:482–483. [PubMed: 18378500]
9. Kahrilas PJ, Shaheen NJ, Vaezi M. AGAI technical review: management of gastroesophageal reflux disease. *Gastroenterology* 2008;135:1392–1413. 135. [PubMed: 18801365]
10. Kahrilas PJ, Shaheen NJ, Vaezi M, in collaboration with the AGAI Medical Position Panel on GERD management. AGAI medical position statement: management of gastroesophageal reflux disease. *Gastroenterology* 2008;135:1383–1391. [PubMed: 18789939]
11. 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]
12. Sloan S, Rademaker AW, Kahrilas PJ. Determinants of gastroesophageal junction incompetence: hiatus hernia, lower esophageal sphincter, or both? *Ann Intern Med* 1992;117:977–982. [PubMed: 1443984]
13. 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]
14. Kiljander TO, Harding SM, Field SK, et al. Effects of esomeprazole 40 mg twice daily on asthma: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2006;173:1091–1097. [PubMed: 16357331]
15. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006;101:1900–1920. [PubMed: 16928254]
16. Chang AB, Lasserson TJ, Kiljander TO, et al. Systematic review and meta-analysis of randomised controlled trials of gastro-oesophageal reflux interventions for chronic cough associated with gastro-oesophageal reflux. *BMJ* 2006;332:11–17. [PubMed: 16330475]
17. Allen CJ, Anvari M. Does laparoscopic fundoplication provide long-term control of gastroesophageal reflux related cough? *Surg Endosc* 2004;18:633–637. [PubMed: 15026893]