Towards better understanding of symptoms associated with disordered esophageal function
Herregods, T.V.K.

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ACID AND WEAKLY ACIDIC REFLUX AS A CAUSE OF CHRONIC UNEXPLAINED COUGH

Thomas V.K. Herregods, Ans Pauwels, Jafar Jafari, Daniel Sifrim, André J.P.M. Smout, Albert J. Bredenoord, Jan Tack

Submitted
ABSTRACT

Background
Gastroesophageal reflux is considered to be a significant contributing factor to chronic unexplained cough. Patients are often presumed to have reflux-induced cough and are exposed to high-dose and long-term empirical therapy with proton pump inhibitors (PPIs) despite the limited treatment efficacy in this population. We aimed to assess the importance of 24-hour ambulatory pH-impedance-pressure monitoring in finding a relationship between chronic cough and reflux.

Methods
In this multicenter study, we evaluated 192 patients with chronic cough using 24-hour pH-impedance-pressure monitoring off PPIs. Manometry was used to detect all cough bursts while pH-impedance allowed for the evaluation of all reflux episodes, including weakly acidic reflux. The symptom association probability was used to determine a temporal relationship between reflux and cough.

Results
A diagnosis of reflux-induced cough was made in 25.5% of the patients. If only acid reflux episodes were used, 22.4% of those patients would not have been diagnosed. Significantly more patients with reflux-induced cough had typical reflux symptoms (p=0.031) and a pathological distal acid exposure time (p=0.025) in comparison to patients without the diagnosis. A diagnosis of cough-induced reflux was made in 24.0% of the patients. Only 59% of all cough bursts were registered by the patients.

Conclusions
Approximately one quarter of patients with chronic unexplained cough have reflux-induced cough, explaining the observation that the vast majority of patients with chronic cough do not benefit from anti-reflux therapy. pH-impedance-pressure monitoring helps to identify patients who are likely to have reflux as a cause of their chronic cough.
INTRODUCTION

Chronic cough, defined as a cough that lasts for more than 8 weeks, is a common problem estimated to affect 9-33% of US and European populations. It significantly impairs health-related quality of life and is associated with a substantial socio-economic burden. Besides causes such as post-nasal drip and asthma, gastroesophageal reflux disease (GERD) is considered to be a significant contributing factor to chronic cough. The causal link between GERD and chronic cough is often presumed, resulting in an overdiagnosis of reflux disease as the cause of the patients’ symptoms and many patients being exposed to high-dose and long-term empirical therapy with proton pump inhibitors (PPIs).

The relationship between GERD and chronic cough is particularly complex due to the multifactorial aspect of the latter condition. Pulmonary and ear, nose and throat examination are advised to rule out other causes of chronic cough. Following this, an upper endoscopy and 24-hour pH-monitoring can take place to look for a link between GERD and cough. However, excessive esophageal acid exposure or the presence of esophagitis or Barrett’s metaplasia do not necessarily prove that GERD is the cause of chronic cough. Similarly, the absence of these aforementioned factors does not rule out GERD as a causal factor. This highlights the importance of establishing a causal relationship between the occurrence of reflux events and cough bursts, which can be achieved by combining ambulatory 24-hour pH-impedance monitoring with an objective measurement of cough. Impedance has the added benefit of detecting weakly acidic reflux episodes, which in the past have been shown to be of importance in a subgroup of patients with chronic unexplained cough. In addition, an objective measurement of cough through ambulatory manometry or ambulatory acoustic monitoring, rather than relying on symptom diary alone, is important as many patients do not accurately report their cough events.

Two pathophysiological mechanisms for reflux-induced cough have been proposed. The first is an esophagobronchial reflex where refluxate reaching the distal esophagus triggers a cough reflex through the vagal nerve. The second theory suggests that (micro)aspiration of gastric content that refluxed beyond the upper esophageal sphincter can stimulate the cough reflex by irritating the respiratory tract.

As a causal link between GERD and chronic cough is often presumed but not proven, we aimed to assess the importance of 24-hour ambulatory pH-impedance-pressure monitoring in finding a causal relationship between chronic cough and reflux in a large cohort.
METHODS

Patients
Simultaneous 24-hour ambulatory esophageal pH-impedance-pressure monitoring was performed in 192 patients with chronic unexplained cough from 02-2010 until 08-2015. Patients were recruited through the outpatient clinic and through referral in three different centers, including the Academic Medical Center (AMC) in the Netherlands, the University Hospital Leuven in Belgium and the Barts and the London NHS Trust in the United Kingdom. Patients with an alternative diagnosis which could explain the symptoms, such as asthma, postnasal drip or the use of ACE-inhibitors were excluded. Proton pump inhibitors were stopped at least 7 days prior to the measurements and other drugs affecting gastro-intestinal motility or secretion were stopped at least 3 days prior to the measurements. The presence of typical reflux symptoms (heartburn and/or regurgitation) was assessed by retrospectively reviewing the referral letter and clinician notes. Similarly to previous studies, patients needed to have at least 4 cough bursts throughout the 24-hour measurement to make statistical tests more reliable. The minimum recording time for patients to be included was 16 hours. Patients were excluded if they had undergone any upper gastro-intestinal surgery. The study proposal was submitted to the local institutional review board of the AMC in Amsterdam, the Netherlands, and formal evaluation was waived according to Dutch law as this was a retrospective study with no burden to patients (26-02-2015 reference number W15_063 # 15.0075).

Ambulatory 24-hour pressure and pH-impedance monitoring
All subjects underwent 24-hour esophageal pH-impedance-pressure monitoring off acid suppressive therapy. The intra-esophageal pressure was recorded using an 8 French solid-state manometric catheter with 3-4 pressure sensors which were separated by 5-cm intervals (Unisensor, Attikon, Switzerland in the AMC and Leuven, and Sandhill Scientific, Inc. in the center in London). The most distal sensor was positioned in the stomach. For the 24-hour pH-impedance measurements a combined pH-impedance catheter assembly was used (Unisensor in the AMC and Sandhill Scientific Inc. in the centers in London and Leuven). The catheter contained six impedance recording segments which were located at 2-4, 4-6, 6-8, 8-10, 14-16, and 16-18 cm above the upper border of the lower esophageal sphincter (LES) and one ion-sensitive field-effect transistor (ISFET) pH electrode which was placed 5 cm above the upper border of the manometrically localized LES. Both catheters were introduced via the same nostril and were attached to the face. Impedance, pH, and pressure signals were stored on a digital datalogger (Ohmega, MMS in the AMC, and Sleuth, Sandhill Scientific Inc. Highlands Ranch, CO in London and Leuven), using a sampling frequency of 50 Hz for the pH-impedance and 8 Hz for the ambulatory manometry.
Patients were instructed to push an event marker on the pH datalogger whenever they experienced a coughing episode or another symptom (heartburn or regurgitation) and were instructed to note the nature of the symptom event and its time of onset in a specially designed diary. In addition, patients were instructed to restrict their intake to three meals and four beverages at standardized times throughout the 24 hours and were told to mark these times down in the diary. They were encouraged to maintain their normal daily activities throughout the measurement and were instructed to mark the period spent in the supine position. In general, this measurement is well tolerated by the patients.

Data analysis
The manometric and pH-impedance recordings were uploaded to a computer and were manually analyzed (MMS, Enschede in the AMC, and Bioview, Sandhill Scientific Inc. in the center in London and Leuven).

Cough detection
The manometric tracings were independently analyzed for cough bursts. A cough was defined as a rapid, short duration, simultaneous pressure peak with a time to peak <1 second and with the same pressure configuration at all the intra-esophageal recording sites. A “cough burst” was defined as two or more rapid simultaneous pressure peaks within 3 seconds. Only cough bursts were considered during the analysis. Separate cough bursts needed to be separated by 30 seconds to be considered as a different set of cough bursts. The objectively detected cough bursts were compared to the cough events marked in the data logger and diary information.

Reflux Detection
The pH-impedance recordings were analyzed for gastroesophageal reflux (GER) independently from the pressure recordings. GER was defined as a sequential, orally progressing drop in impedance to less than 50% of baseline values starting at the most distal impedance segment (2-4 cm above the LES) and propagating retrogradely to at least the next measuring segment. Impedance-detected reflux was classified as acid if the pH fell below 4 for at least 4 seconds. If the pH was already below 4 at the onset of the reflux episode, then a further decrease of at least 1 pH unit lasting at least 4 seconds was required. Weakly acidic reflux was defined as a drop in impedance as described above, but not accompanied by a drop in pH below 4.

Gas reflux episodes without liquid component (belches) were not included in the analysis. For each patient the total number of reflux events (acid and weakly acidic) and the total acid exposure time were calculated. The total acid exposure time was defined as the percentage of time that the esophageal pH was below 4 and was considered to be pathological if this was greater than 6% of the total recording time. Esophagitis was classified using the LA Classification.
Association between reflux and cough
The association between reflux and cough was assessed using the symptom association probability (SAP)\(^6\) with a two-minute time window\(^7\). A SAP greater than 95% was considered to be statistically significant. Cough bursts which occurred outside a two-minute time window (both preceding and following a reflux episode) were considered to be unrelated to that reflux episode. A cough was considered to be possibly caused by a reflux episode if this occurred within two minutes following the onset of a reflux episode (reflux-cough episode). A cough was considered to be a possible cause of a reflux episode if this occurred within two minutes prior to the onset of the reflux episode (cough-reflux episode). The SAP was calculated per individual for acid, weakly acidic, and all reflux episodes. If two or more cough bursts were related to a reflux episode within a 2-minute period, then priority was given to the reflux-cough sequence.

Statistical analysis
Data are presented as median (interquartile range (IQR)) unless otherwise stated. The Fisher exact test was used to calculate the SAP. The Shapiro-Wilk test was used to test for normality. When comparing two groups the Mann-Whitney U-test or the Chi-Square test was used. For the comparison between the manometrically detected coughs and the cough events marked in the data logger the Wilcoxon signed rank test was used. The Spearman’s Rank correlation was used to analyze whether the distal acid exposure time or the number of reflux episodes influenced the amount of coughs detected. A p-value <0.05 was considered to be statistically significant.

RESULTS

Patient population
A total of 260 patients with chronic unexplained cough were studied with 24-hour impedance-pH-manometry. Twenty-nine patients were excluded because they had <4 cough bursts throughout the measurement, two because they had had upper gastrointestinal surgery and 14 because they had not stopped their PPIs at least 7 days prior to the measurement. Twenty-three patients were excluded because of technical problems with the catheter (i.e. pH reference electrode disconnection, dysfunction of an impedance channel), or because the measurement lasted less than 16 hours. As a result, analysis was completed in 192 patients (70.3% female, median age 57.5 years). The main patient characteristics are shown in table 1.

Cough
In the 192 patients, a total of 6442 cough burst episodes were detected manometrically. Of these, only 3800 cough bursts (59.0%) were registered by the patients by pressing
REFLUX AS A CAUSE OF CHRONIC COUGH

the event marker. Per patient, a median of 24 (14-43) cough bursts were measured manometrically, while 13 (5-26) were registered by the patients themselves. Only 6 patients (3.1%) reported all cough bursts accurately.

Gastroesophageal reflux

The majority of the patients (52.1%) did not report typical reflux symptoms. Seventy-five patients (39.1%) complained of heartburn while 47 patients (24.5%) reported regurgitation. pH-impedance measurement found a median total acid exposure time of 2.35% and showed that 41 patients (21.4%) had pathological acid exposure (>6% total acid exposure time). Reflux esophagitis was found in 41 patients (21.4%) during upper endoscopy with 33 patients having a Los Angeles grade A esophagitis and 8 people with a Los Angeles grade B.

Table 2 shows details on the reflux characteristics. A total of 7472 reflux episodes were detected, of which 5341 (71.5%) were acidic and 2231 (29.5%) were weakly acidic. A total of 6983 (92.2%) were detected in the upright position while 589 (7.8%) in the recumbent position.

There was no difference in the number of cough bursts between patients with typical reflux symptoms and those without typical reflux symptoms (24.5 vs 22.5, p=0.934). However, patients with typical reflux symptoms did have a significantly higher distal acid exposure time (3.6% vs 1.7%, p=0.008) and significantly more reflux episodes (44 vs 30, p=0.0003). The higher number of total reflux episodes in this subset of patients was mainly due to a higher number of acid reflux episodes (30.5 vs 21.5, p=0.001). There was no difference in the number of weakly acidic reflux episodes between both groups (9 vs 9, p=0.584). The subset of patients with a pathological distal acid exposure time (>6%) did not have significantly more cough bursts compared to those with physiological distal acid exposure time (29 vs 22, p=0.556) and no correlation was found between the number of cough bursts and the number of reflux episodes (p=0.854) or the percentage distal acid exposure time (p=0.813). There was no significant gender difference in the presence of typical GERD symptoms (p=0.594) or

Table 1. Characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>192</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>57.5</td>
</tr>
<tr>
<td>Female gender (n%)</td>
<td>135 (70.3)</td>
</tr>
<tr>
<td>Number of patients presenting symptoms</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>192 (100%)</td>
</tr>
<tr>
<td>Heartburn</td>
<td>75 (39.1%)</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>47 (24.5%)</td>
</tr>
</tbody>
</table>
the number of cough bursts detected (\(p=0.162\)) but females had a significantly lower distal acid exposure time compared to males (1.7% vs 3.8%, \(p=0.007\)).

**Association between reflux and cough**

Out of all 6442 cough burst episodes, 1413 (21.9%) occurred within the two-minute time window around a reflux episode. A total of 687 (48.6%) of these were reflux-cough episodes (67.7% were associated with acid reflux and 32.3% with weakly acidic reflux). Importantly, as shown in Figure 1, in 49 patients (25.5%) a positive SAP was found for reflux-cough and therefore these patients were diagnosed with reflux-induced cough. If we were to only use acid reflux episodes (instead of also including weakly acidic reflux), only 38 patients (19.8%) would have a positive reflux-cough association and therefore 11 patients would not have been diagnosed with reflux-induced cough. Thirty-two patients had a positive SAP based on weakly acidic reflux alone. Nineteen of the patients with a positive SAP lacked typical reflux symptoms. Patients with a positive SAP for the reflux-cough sequence had significantly more cough bursts (31 vs 21, \(p=0.033\)) and reflux episodes (47 vs 36, \(p=0.0003\)). In addition, patients with a positive SAP for reflux-cough also presented more often with typical GERD symptoms (\(p=0.031\)) and more had a pathological distal acid exposure time (\(p=0.025\)). No gender difference was found for the diagnosis of reflux-induced cough (\(p=0.374\)).

In total 726 cough-reflux episodes were detected, of which 63.5% were associated with acid reflux and 36.5% with weakly acidic reflux. Forty-six patients (24.0%) had a positive SAP for cough-induced reflux episodes. Only 30 patients would have had a positive SAP if only acid reflux episodes were considered. Similar to the subset of patients with a positive SAP for reflux-cough, patients with a positive SAP for cough-reflux had significantly more cough bursts (31.5 vs 20, \(p=0.011\)) and reflux episodes (43 vs 36, \(p=0.016\)) compared to patients without this diagnosis. However they did not have more typical GERD symptoms (\(p=0.746\)), a pathological distal acid exposure

**Table 2. Reflux characteristics of the patients**

<table>
<thead>
<tr>
<th>Reflux characteristics</th>
<th>Number of reflux episodes (median, IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total 39 (24-50.25)</td>
</tr>
<tr>
<td></td>
<td>Acid 26 (13-36.25)</td>
</tr>
<tr>
<td></td>
<td>Weakly acidic 9 (5-16)</td>
</tr>
<tr>
<td></td>
<td>Upright position 34 (21-47)</td>
</tr>
<tr>
<td></td>
<td>Recumbent position 2 (0-4)</td>
</tr>
<tr>
<td>Acid exposure time (percentage, IQR)</td>
<td>Total acid exposure time 2.35 (0.87-5.32)</td>
</tr>
<tr>
<td></td>
<td>Upright acid exposure time 3.05 (1.07-8.12)</td>
</tr>
<tr>
<td></td>
<td>Supine acid exposure time 0.1 (0-0.92)</td>
</tr>
</tbody>
</table>
time (p=0.627) or a higher distal acid exposure time (p=0.304). Eighteen patients (9.4%) had a positive SAP for both the cough-reflux and reflux-cough sequence.

**DISCUSSION**

Gastroesophageal reflux is considered to be a frequent cause of chronic unexplained cough and an empirical trial with acid suppressive therapy, such as PPIs, has often been recommended as an initial step. However, as shown in many placebo-controlled trials, acid suppressive therapy often does not result in a significant reduction in cough frequency and/or severity. As a result, we aimed to assess the importance of rigorous patient selection through the use of 24-hour ambulatory pressure-pH-impedance monitoring. In this study, which is the largest study thus far, we evaluated 192 patients with chronic unexplained cough and found an association between reflux and cough in 40.1% of the patients. Importantly, when looking only at reflux-induced cough, an association was found in only 25.5% of the patients. This suggests that in approximately 75% of the patients tested, reflux is not the cause of cough, which could explain the low treatment efficacy and helps to show the value of 24-hour ambulatory pH-impedance-pressure monitoring in determining which patients could benefit from acid suppressive treatment.

The usefulness of adding impedance to the pH-monitoring is emphasized by the importance of detecting weakly acidic reflux episodes. In this study approximately one third of all reflux-cough episodes were associated with weakly acidic reflux, which
is similar to a previous study\(^8\). In addition, if weakly acidic reflux episodes were not included in the analysis, 11 out of 49 patients would not have been diagnosed with reflux-induced cough. Furthermore, this provides an additional reason for the limited efficacy of acid suppressive medication and could explain in part why anti-reflux surgery seems to be more effective than medical treatment\(^20\).

Objective detection of cough bursts, in our case through the use of 24-hour manometry recordings, is very important as only 6 out of the 192 patients reported all cough bursts accurately through the use of the diary or event marker on the datalogger. On average, only 59\% of all cough bursts were registered by the patient and therefore an analysis based on this subjective measurement would be less accurate. In addition, there is a delay between the start of the cough burst and the moment of pushing the event marker button, which may vary between subjects. Knowing the correct onset of the coughing episodes is important as coughs towards the end of the 2-minute interval could be detected outside this interval due to this delay. Moreover, cough bursts followed closely by a reflux episode could be wrongly seen as a reflux-cough episode while the onset of the cough is actually prior to the reflux episode and should therefore be a cough-reflux episode. Furthermore, patients diagnosed with reflux-induced cough had significantly more cough bursts than patients without this diagnosis suggesting that the proper detection of all cough bursts is important.

Approximately half of our patients did not have any typical reflux complaints, such as heartburn or regurgitation. This is similar to previous studies where it was estimated that up to 75\% of patients with reflux-induced cough do not exhibit the classic symptoms of GERD\(^21,22\). As a result, previous studies concluded that the lack of concomitant typical reflux symptoms cannot exclude GERD as a potential cause of chronic cough. Indeed, 19 patients in our study had a diagnosis of reflux-induced cough without having typical reflux symptoms. Conversely, however, patients with a diagnosis of reflux-induced cough had significantly more often GERD symptoms. Similar considerations have led to a previous American College of Chest Physicians (ACCP) guideline that patients with typical reflux symptoms should be considered to have a high likelihood of having reflux be a cause of their chronic cough\(^4\). This is in line with another study reporting that in patients with extra-esophageal reflux symptoms, the presence of heartburn with or without regurgitation was a predictor of symptomatic improvement after fundoplication\(^23\). Similarly, a previous study showed that patients with chronic cough who have a high distal acid exposure time are more likely to benefit from acid suppressive therapy\(^18\). In the present study we found that patients with a diagnosis of reflex-induced cough had significantly more often typical reflux symptoms and significantly more pathological distal acid exposure time. Therefore, the better treatment effect in the subpopulation of patients with typical reflux symptoms and a pathological acid exposure time could be explained by the higher prevalence of patients with reflux-induced cough in those subpopulations.
The current ACCP guideline\textsuperscript{19} highlights the lack of current evidence for acid-suppressive therapy in patients with chronic cough. We believe that this lack of treatment effect in most of the studies is due to the lack of proper selection of patients who are likely to respond to anti-reflux therapy, as these studies did not use 24-hour pH-impedance-pressure monitoring. A positive SAP for reflux-cough indicates that the association between reflux and cough is found more often than by chance alone and is an important factor in identifying patients in whom reflux seems to be the cause of the chronic cough and therefore might benefit from anti-reflux therapy. A study by Hersh et al. using ambulatory pH monitoring showed that a positive SAP for reflux-induced cough was an independent predictor of high degree of response to treatment\textsuperscript{24}. The suggestion by the ACCP guideline\textsuperscript{19} that patients with typical GERD symptoms and pathological distal acid exposure time are more likely to respond to anti-reflux therapy might be due to the higher likelihood of a positive reflux-cough association in that patient population as shown by our study. Nevertheless, our study shows that many patients who have a positive association between reflux and cough would be missed through this selection criterion. We therefore propose to evaluate effects of GERD-directed therapy mainly in chronic cough patients with a positive reflux-cough association based on pH-impedance-pressure monitoring, as these patients are more likely to respond better to anti-reflux treatment.

In conclusion, the results of our study indicate that only approximately one quarter of the patients with chronic unexplained cough has reflux-induced cough, explaining the observation that the vast majority of patients with chronic cough does not benefit from anti-reflux therapy. In order to identify patients who are likely to have reflux as a cause of their chronic cough, it is important to use 24-hour pH-impedance monitoring combined with objective detection of cough episodes, e.g. by simultaneous 24-hour ambulatory manometry. This allows for the evaluation of the temporal association between reflux episodes of all types (acid and weakly acidic) and all cough episodes. Even though the presence of typical GERD symptoms and pathological distal acid exposure time are associated with an increased chance of having reflux-induced cough, many patients will be missed if these criteria alone are used to identify patients who are likely to respond to treatment.
REFERENCES


