Towards better understanding of symptoms associated with disordered esophageal function
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REFLUX-COUGH SYNDROME: ASSESSMENT OF TEMPORAL ASSOCIATION BETWEEN REFLUX EPISODES AND COUGH BURSTS

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ABSTRACT

Background
Gastroesophageal reflux can be the cause of chronic cough. In the assessment of the temporal association between reflux and cough, previous studies have used a two-minute time window, based on studies in patients with heartburn. However, it remains unclear whether the optimal time window duration for the evaluation of reflux-induced cough is two minutes as well. Therefore, we aimed to determine whether a two-minute time window is optimal to diagnose reflux-induced cough.

Methods
In this multicenter study, 137 patients with chronic cough were evaluated using 24-hour pH-impedance-pressure monitoring. Repetitive symptom association analysis was employed using an array of time windows of various duration. For each time window, the symptom association probability (SAP) and symptom index (SI) were calculated.

Results
A total of 4377 cough burst episodes and 5074 reflux episodes were detected. The number of patients with a positive SAP increased with increasing window duration until a plateau was reached around a time window duration of 1.5 minutes. Similarly, the SI increased steeply until a window duration of about 2 minutes, after which a linear increase was seen.

Conclusions
A two-minute time window seems appropriate for evaluation of the relationship between reflux and chronic cough using 24-hour pH-impedance-pressure monitoring. A time window duration of 30 seconds or 1 minute is too short to diagnose patients with reflux-induced cough accurately.
INTRODUCTION

Chronic cough, defined as a cough that lasts for more than 8 weeks, is estimated to affect 9-33% of European and US populations\textsuperscript{1}. Consensus has been reached about the existence of a reflux-cough syndrome as described by the Montreal definition and classification of gastroesophageal reflux disease (GERD)\textsuperscript{2}. Besides asthma and post-nasal drip, GERD is considered to be one of the most important contributing factors to chronic cough\textsuperscript{3}. Two pathophysiological mechanisms have been suggested for reflux-induced cough. The first is that refluxate triggers a cough reflex through stimulation of a vagal esophagobronchial reflex. The second theory suggests that (micro)aspiration of gastric content can stimulate the afferent limb of the cough reflex by irritating the respiratory tract, initiating a sequence leading to cough\textsuperscript{3}.

An upper endoscopy and 24-hour pH-monitoring are often performed to establish a link between GERD and cough\textsuperscript{4}. However, pathological acid exposure or the presence of esophagitis or Barrett's metaplasia do not prove unequivocally that GERD is the cause of the chronic cough. To establish a temporal relationship between the occurrence of reflux events and cough bursts, ambulatory 24-hour pH-impedance monitoring is used in combination with an objective measurement of cough using either an acoustic or a manometric technique\textsuperscript{5,7}. The addition of impedance to pH-monitoring allows for the detection of non-acid reflux episodes, which have been shown to be important in a subset of patients with chronic unexplained cough\textsuperscript{5,6}.

Previous studies have made use of both a two-minute\textsuperscript{5,8} and a five-minute\textsuperscript{9,10} time window to assess the temporal association between reflux and cough. The symptom association probability (SAP)\textsuperscript{11} can be used to assess whether this relationship occurs more frequently than can be explained by chance. It is important to note that the two-minute time window was originally established to assess the temporal association between reflux and chest pain\textsuperscript{12}.

It remains unclear whether the optimal time window for the association between reflux and cough is also two minutes. Therefore, the aim of this study was to determine whether a two-minute time window can be used to diagnose reflux-induced cough. To achieve this, repetitive symptom association analysis was employed using an array of time windows of various duration.

METHODS

Patients

From 02-2010 until 08-2015, 137 patients with chronic unexplained cough were recruited through the outpatient clinic and through referral in two academic medical centers, the Academic Medical Center, Amsterdam, the Netherlands, and the University Hospital Leuven in Leuven, Belgium. All patients underwent simultaneous 24-hour ambulatory esophageal pH-impedance-pressure monitoring. Patients needed to
have at least 4 cough bursts throughout the measurement. The measurement had to have lasted for at least 16 hours to be included. Patients were excluded if an alternative diagnosis such as asthma, postnasal drip or the use of ACE inhibitors could explain the symptoms. Patients were also excluded if they had undergone any upper gastrointestinal surgery. Proton pump inhibitors were stopped at least 7 days prior to the 24-hour study and other drugs affecting gastrointestinal motility or gastric secretion were stopped at least 3 days prior to the measurements. Referral letters and clinician notes were assessed to evaluate whether patients had any typical reflux symptoms (heartburn and/or regurgitation). The study protocol was submitted to the local institutional review board of the Academic Medical Center in Amsterdam, the Netherlands, and formal evaluation was waived according to Dutch law (reference number W15_063 #15.0075).

**Ambulatory 24-hour pressure and pH-impedance monitoring**

The ambulatory 24-hour esophageal pH-impedance-pressure monitoring occurred off acid-suppressive therapy. pH and impedance were measured using a combined pH-impedance catheter assembly (Unisensor in the AMC and Sandhill Scientific, Inc. in Leuven). These catheters consisted of six impedance recording segments 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 located 5 cm above the upper border of the LES. Intraesophageal pressure was recorded using an 8-French solid-sate manometric catheter with 3 or 4 pressure sensors at 5-cm intervals (Unisensor, Attikon, Switzerland), the most distal of which was positioned in the stomach. Both catheters were introduced via the same nostril and were attached to the face. The impedance, pH, and pressure signals were stored in a digital datalogger (Ohmega, MMS in Amsterdam, and Sleuth, Sandhill Scientific, Inc. Highlands Ranch, CO in Leuven) using a sampling frequency of 50 Hz for the pH-impedance and 8 Hz for the esophageal manometry.

Patients were instructed to press the event marker button on the pH datalogger whenever they coughed or when another reflux symptom (heartburn or regurgitation) was experienced. The nature and time of onset of the symptom event had to be noted down in a specially designed diary. Patients were also instructed to restrict their intake to three meals and four beverages at standardized times throughout the 24 hours. These were also marked in the diary. Patients were also encouraged to maintain their normal daily activities throughout the measurement and were instructed to mark the period spent in the supine position.

**Data analysis**

All pH-impedance and manometric tracings were manually analyzed by one and the same investigator (T.H.). Using dedicated software (MMS, Enschede in Amsterdam,
and Bioview, Sandhill Scientific Inc. USA in Leuven), the onsets of all reflux episodes and cough bursts were registered.

Cough detection
All 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\textsuperscript{13}. Furthermore, the pressure configuration had to be identical at all intraesophageal recording sites. Only cough bursts were analyzed during the measurement (single cough events were ignored). A cough burst was defined as two or more rapid simultaneous pressure peaks within 3 seconds\textsuperscript{13}. Consecutive cough bursts had to be separated by at least 30 seconds to be considered as different cough bursts.

Reflux detection
The pH-impedance recordings were analyzed for episodes of gastroesophageal reflux (GER) which were defined as sequential, orally progressing drops in impedance to less than 50% of the baseline values, starting at the most distal impedance segment (2-4 cm above the LES) and propagating in retrograde direction to at least the next impedance segment. Both acid (pH<4) and non-acid (pH≥4) reflux episodes were analyzed as non-acid reflux has an important role in reflux-induced cough\textsuperscript{6}.

The total number of reflux events (acid and non-acid) and the total distal acid exposure time were calculated for each patient. We defined the total distal acid exposure time as the percentage of time that the esophageal pH was below 4 throughout the entire measurement. This was considered to be pathological if this was greater than 6% of the total recording time\textsuperscript{14}. We did not include reflux episodes which consisted of gas reflux without a liquid component (belches) in the analysis.

Association between reflux and cough
The association between reflux episodes and cough bursts was assessed using the symptom association probability (SAP)\textsuperscript{11} and the symptom index (SI)\textsuperscript{15}. Cough bursts were considered related to a reflux episode if they occurred within a certain interval following the onset of a reflux episode (reflux-cough episode). All evaluations were repeated using 10 different intervals which ranged from an interval of 30 seconds up to 5 minutes with increments of 30 seconds. The onset times of all cough bursts and reflux episodes were entered into an Excel spreadsheet (Microsoft Office). Dedicated code within Excel, written by one of the authors (TH), was used to calculate the SAP for each of the time windows automatically for each patient. Cough bursts which occurred outside of the evaluated time window were considered unrelated to that reflux episode. A SAP greater than 95% was considered to be statistically significant. The SAP was calculated per individual for all time windows. Cough bursts
could not be related to more than one reflux episode. Figure 1 shows an example of a reflux-associated cough episode.

**Statistical analysis**
Data are presented as median (interquartile range (IQR)) unless otherwise stated. To calculate the SAP, the Fisher exact test was used. A p-value <0.05 was considered to be statistically significant.

*Figure 1.* Example of a reflux-cough sequence recorded during concurrent measurement of intraluminal esophageal pressure, pH and impedance. The impedance signal shows a retrograde drop consistent with liquid reflux, in the pH signal an acid reflux event can be seen and the manometric tracing shows a cough burst.
RESULTS

Patient population
A total of 137 patients (median age 59 years, 68.6% female) with chronic unexplained cough were studied with 24-hour pH-impedance-pressure monitoring. Seventy patients (51.1%) did not have any typical reflux symptoms (heartburn and/or regurgitation). Fifty-three patients (38.7%) had heartburn symptoms while 36 patients (26.3%) reported regurgitation. Twenty-two patients (16.1%) had both heartburn and regurgitation symptoms. The 137 patients experienced a total of 4377 cough burst episodes, of which 63.1% were registered by the patients by pressing the event marker. Patients had a median of 22 cough bursts (13-42) measured manometrically.

Using the 24-hour pH-impedance measurement, a total of 5074 reflux episodes were detected of which 71.2% were acid and 28.8% were non-acid. A median of 38 (23-49) reflux episodes were found per patient. Most reflux episodes took place in the upright position (93.5%), and a median total acid exposure time of 1.8% (0.7-5.3) was found with 2.4% (1-7.1) in the upright position and 0.1% (0-0.6) in the recumbent position. Twenty-seven patients (19.7%) had a pathological acid exposure time (>6% total acid exposure time).

Association between reflux and cough
The relationship between the duration of the time window and the number of patients with a positive SAP (>95%) for an association between reflux episodes and cough bursts (reflux-cough sequence) is shown in Figure 2. The number of patients with a positive SAP increased steeply with increasing window duration until a plateau was reached around a time window duration of 1.5 minutes. Even though the number of patients with a positive SAP did not change much as the time window changed from 2 minutes to 5 minutes, a total of 55 patients had a positive SAP for at least one of the time windows. Out of the 38 patients with a positive SAP for the two-minute time window, 28 patients continued to have a positive SAP as the time window increased from 2 to 5 minutes. Most of these patients (89.3%) had a SAP >99% for the two-minute time window, and 92.6% of all patients with a SAP > 99% for the two-minute time window continued to have a positive SAP for the time windows from 2 minutes up to 5 minutes. Figure 3 shows the distribution of the SAP for the two-minute time window. It is noteworthy that the majority of patients either showed no association at all or a relatively strong association.

The relationship between the window duration and the SI for the reflux-cough sequence is shown in Figure 4. This curve becomes more linear when the window duration is longer than approximately two minutes.
DISCUSSION

The relation between gastroesophageal reflux and cough is complex. Although there is consensus about the existence of a reflux-cough syndrome\cite{2}, it is difficult to establish the diagnosis in individual patients. However, in the reflux-cough syndrome the crisp onset of the symptom episodes (cough bursts) makes it possible to quantify the relationship between reflux and cough episodes, using prolonged reflux
monitoring with concurrent detection of cough episodes. In previous studies\textsuperscript{5-8} reflux episodes were considered to be associated with cough bursts if they occurred within a two-minute time window before the onset of the cough burst. However, it remains unclear whether this two-minute time window, which was originally established to assess the association between reflux and chest pain and never tested for this indication, can be carried over to reflux-induced cough. This is the first study which assesses different time windows in a patient population in whom reflux is thought to be the cause of chronic cough.

In our study, we evaluated different time windows starting from 30 seconds up to 5 minutes with increments of 30 seconds. As shown in Figure 2, the number of patients with a positive SAP for an association between reflux episodes and cough bursts increased from the 30-second time window to the 1.5-minute time window. This shows that many patients would not have received a diagnosis of reflux-related cough if the 30-second or 1-minute time window was used to evaluate the pH-impedance measurement. Starting from the 1.5-minute time window, the proportion of patients with a positive SAP remains relatively stable as the window is increased to 5 minutes. Because of this, the results of our analysis do not prove incontrovertibly that a window of precisely two minutes is optimal. However, it is evident that a time window duration of 30 seconds or 1 minute would be too short, generating many false negatives. Despite the limitations of the data (in particular the relatively low number of reflux-associated cough episodes) we believe that we can conclude that a two-minute time window, which is customary for the analysis of typical reflux symptoms, is also

\begin{figure}
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\includegraphics[width=\textwidth]{figure4.png}
\caption{Relationship between the symptom index and the time window duration for the reflux-cough sequence. The black line is a trend line based on the 4 points with the longest time window duration (3.5 – 5 minutes). Note that the graph takes on a more linear form as the time window duration increases.}
\end{figure}
appropriate for the evaluation of the relationship between reflux and chronic cough using 24-hour pH-impedance-pressure monitoring. A similar conclusion can be made when looking at Figure 4, which shows the relationship between the window duration and the SI. Considering the way in which the SI is calculated, it is expected that as the window duration increases, the SI will continue to increase until this has reached 100%. This is an inherent weakness of the SI as highlighted by an editorial by Kahrilas et al.\(^\text{16}\). We found that the number of associated cough bursts increased rapidly with increasing window duration until a window duration of about 2 minutes was reached, resulting in a relatively rapid increase of the symptom index until the two-minute time window. Thereafter, a more gradual increase was observed, which can be expected as purely by chance more cough bursts will be associated with reflux episodes as the time window increases, thereby increasing the SI. Again, this observation lends support to the notion that a window of approximately two minutes is appropriate for assessment of the reflux-cough association in patients with the reflux-cough syndrome.

As shown in Figure 2, the number of patients with a positive SAP per time window remained relatively stable between 2 minutes and 5 minutes. However, even though the total number of patients with a positive SAP barely changed, a total of 55 patients had a positive SAP for at least one of these time windows. Therefore, as the time window changes, some patients will receive the diagnosis of reflux-induced cough while others will no longer have a positive diagnosis. Interestingly, out of the 38 patients with a positive SAP for the two-minute time window, 28 patients continued to have a positive SAP as the time window changed from 2 minutes up to 5 minutes. Most of these patients (88.9%) had a SAP > 99% for the two-minute time window, and 92.6% of all patients with a SAP > 99% for this time window continued to have a positive SAP for the time windows from 2 minutes up to 5 minutes. This suggests that, in clinical practice, a diagnosis of reflux-induced cough based on a SAP > 99% for the two-minute time window is more robust. Furthermore, as shown in Figure 3, many patients clearly lack an association between reflux and cough and can confidently be dismissed. Future studies should evaluate the effect of treatment in patients with a positive SAP, using a two-minute time window. In these studies, the SAP should be used to select patients in whom reflux is associated with cough more strongly than can be expected by chance. The SI should only be used as an indication of the strength of the association\(^\text{16}\). We would also like to highlight the importance of objective detection of cough bursts as only 63.1% of all cough bursts were registered by the patient, and therefore an analysis based on this subjective measurement is less accurate. Moreover, objective detection of the cough bursts allows for precise determination of the onset time of the cough burst. This is important as, inevitably, there is a delay between the start of the cough burst and the moment of pushing the event marker button.

One of the two main hypotheses for the pathophysiology of reflux-induced cough is that (micro)aspiration of refluxed content can trigger a cough reflex\(^3\). If this is correct,
it seems logical to assume that the duration between the aspiration of the refluxed content and the cough is shorter than 2 minutes. This is supported by the European Respiratory Society guideline on the assessment of cough which suggests that when the single-breath method of capsaicin and citric acid is used as a cough challenge, that only coughs within 15 seconds after delivery should be counted as coughs that occur beyond that time period may not be induced by the capsaicin nor citric acid\textsuperscript{17}. Another study which evaluated the cough reflex sensitivity in patients in whom reflux was thought to be a cause used a time window of one minute after inhalation\textsuperscript{7}. It is therefore important to know if coughs occurring outside a one-minute time window are still caused by reflux and whether the two-minute time window is too long to evaluate the association between cough and reflux.

Our finding, that a time window duration of 30 seconds or 1 minute would be too short, does not prove that (micro)aspiration is not a pathophysiological mechanism in reflux-induced cough as many patients still had a positive association when short time windows were used. It does suggest however that the second theory, namely that refluxate triggers a cough reflex through stimulation of esophageal vagal afferents and initiates the esophagobronchial reflex\textsuperscript{3}, most likely plays a more important role in patients with reflux-induced cough. The importance of a central mechanism is supported by studies which have shown that gabapentin, a centrally active drug, improved the cough frequency and severity\textsuperscript{18,19}.

In conclusion, the results of this study suggest that, when evaluating patients for reflux-induced cough using 24-hour pH-impedance-pressure monitoring, a two-minute time window seems appropriate. Moreover, this study provides further evidence that central sensitization or an esophagobronchial reflex is the most likely mechanism in reflux-induced cough.
REFERENCES


