Temporal associations between coughing or wheezing and acid reflux in asthmatics

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Abstract

Background and aims—The pulmonary symptoms of patients with lung disease may be ascribed to gastro-oesophageal reflux although a causal relationship between acid reflux and coughing or wheezing has not been proved. Does cough cause reflux or does reflux cause cough? The aim of this study was to evaluate 24 hour oesophageal pH tracings of asthmatics with gastro-oesophageal reflux to determine the temporal association between acid reflux and coughing or wheezing.

Methods—The oesophageal tracings of 128 asthmatics from the outpatient clinics who underwent oesophagogastroduodenoscopy, oesophageal manometry, and 24 hour oesophageal pH monitoring were analysed. Three possible temporal relationships between the occurrence of acid reflux and the occurrence of coughs or wheezes were evaluated: (1) pulmonary symptoms preceding reflux; (2) reflux preceding pulmonary symptoms; and (3) unrelated occurrence of both events.

Results—Of 128 asthmatics, 53 recorded five or more coughs and 19 recorded three or more wheezes during the 24 hour recording period. Mean acid contact time was similar in asthmatics with and without pulmonary symptoms (12.2 (1.2)% vs 10.4 (0.6)%). Of all coughs and wheezes, 46% and 48%, respectively, were associated with acid reflux. For the individual asthmatic, the likelihood of reflux induced coughing increased as the number of coughs increased.

Conclusions—Half of all coughs and wheezes in asthmatics are associated with acid reflux into the oesophagus. While an occasional coughing episode can lead to reflux, it is rather the reflux episode in the vast majority of instances that leads to cough.

Keywords: asthma; gastro-oesophageal reflux disease; erosive oesophagitis; oesophageal pH monitoring; lung disease; pulmonary symptoms

Gastro-oesophageal reflux is common in asthmatic patients, and an increased prevalence of gastro-oesophageal reflux disease (GORD) has been observed in both children and adults with asthma.1–6 The association between GORD and pulmonary disease is further supported by the reduction or even disappearance of asthma symptoms of patients with lung disease; pulmonary symptoms can be unequivocally ascribed to gastro-oesophageal reflux, the extent of the relationship between acid reflux and coughing or wheezing has remained unclear. Does cough cause reflux or does reflux cause cough? If both scenarios are possible, which one is dominant, causing most of the morbidity? The aim of our study was to evaluate 24 hour oesophageal pH tracings of asthmatics to determine the nature of the relationship between acid reflux and coughing or wheezing.

Methods

Patients
A total of 128 pH tracings from 134 consecutive asthmatics (six patients refused) who were...
selected from the medicine and pulmonary outpatient clinics of the Veterans Affairs Hospital in Hines, Illinois were analysed. Asthma was defined as discrete episodes of diffuse wheezing and either a 20% improvement in forced expiratory volume in 1 s (FEV1) following bronchodilator administration or a 20% decrease in FEV1 after methacholine broncho-provocation performed in accordance with the American Thoracic Society guidelines. The presence of reflux symptoms or severity of pulmonary symptoms were not used as criteria for the recruitment of patients into the study. Endoscopy and pH metry were performed only after medical management of asthma had been optimised. Patients whose pH testing was performed within a few weeks of an asthma attack were not included. During the study, patients maintained their regular pulmonary medications. A standardised questionnaire was used to obtain a history from each patient regarding demographic characteristics, social habits, and intake of medications. None of the patients was treated with antiresecretory medications prior to endoscopy and pH metry. Bronchodilators were used by 72% of patients at the time of the study. Patients who smoked cigarettes or drank alcohol during the 12 months preceding the interview were considered active smokers or drinkers. Lifetime consumption of cigarettes and alcohol was recorded as pack years and ounce years, respectively. All patients underwent oesophagogastroduodenoscopy, oesophageal manometry, and oesophageal 24 hour pH metry as part of a Veterans Affairs study that was funded to determine the effect of gastro-oesophageal reflux treatment on asthma. The study was approved by the human studies committee of the Hines VA Hospital and VA Central Office.

ENDOSCOPY
All endoscopies were performed by two endoscopists (TGS and SJS) using a set of pre-defined criteria to record abnormalities of the upper gastrointestinal tract. A diagnosis of erosive oesophagitis was made if endoscopy revealed an exudative break in the squamous epithelium. Oesophagitis was graded based on the scoring system developed by Hetzel and colleagues. A hiatus hernia was diagnosed if during quiet respirations gastric folds were seen extending at least 2 cm above the diaphragmatic hiatus.

OESOPHAGEAL MANOMETRY AND pH METRY
The manometric studies were performed after an overnight fast using a solid state catheter (Narco, Houston, Texas, USA). A transnasal catheter was passed in the supine position. The recording sites were positioned across the gastro-oesophageal junction in such a way that the most distal site was in the stomach, the most proximal site was in the distal oesophagus, and the recording sites came to lie within the lower oesophageal sphincter. The location of the sphincter was defined as the area of sustained elevation of the resting pressure that relaxed during swallowing. When resting pressure was not elevated, the point of initial peristalsis, as determined on withdrawal of the catheter, was used to define the lower oesophageal sphincter area. End expiratory pressure of the lower oesophageal sphincter was calculated as the average of five individual measurements. Mean resting pressure of the upper oesophageal sphincter, mean oesophageal contraction amplitude in the body and the distal section of the oesophagus, and percentage of peristaltic contractions in response to 5–10 ml of swallowed water were determined following previously described methodology.

Before the actual pH metry, patients were scheduled to meet with the nurse coordinator for a two hour structured teaching session. Patients were taught on an individual basis how to use the digitrapper for symptom recording. During the training session, which included multiple simulated events, patients gained experience in activating the event monitor to discriminate between coughs, wheezes, heartburn, and other symptoms. They were instructed to remain upright (sitting, standing, or walking) during the day and to assume the supine position only when in bed during the night. Supine and upright positions were recorded by using a separate switch on the recorder. Patients were further instructed to eat their regular meals during breakfast, lunch, and dinner, and to refrain from all other food intake, including bedtime snacks. A detailed diary was kept to record all events, symptoms, meals, and body positions.

The standard method of determining ambulatory 24 hour acid reflux was used. The model 700 Gastroreflux Recorder (Del Mar Avionics) was used to determine the presence of acid in the oesophagus. After calibration, a transnasal pH electrode (Beckman No 39043; Fullerton, California, USA) was passed and positioned 3 cm above the superior border of the manometrically determined lower oesophageal sphincter. The degree of reflux was determined by continuous sampling and storage at six second intervals if pH <4.0 and at 30 second intervals if pH >4.0. After the test, the recorder was connected to a Gastroreflux Data Analyzer computer. All episodes of acid reflux were reported in both tabular and graphic printouts. Because of potential technical errors (for example, forgetting to change the upright/supine switch or accidentally disconnecting the lead wire, which could lead to erroneous interpretation of data), all recorder generated data were verified by a detailed review of the graphic form of the printout in the presence of the patient. Problems with inconsistencies were resolved by direct interview of the patient and analysis of the diary.

STATISTICAL ANALYSIS
A reflux episode was defined as a drop in pH to values <4 that lasted for more than 10 seconds. The acid contact time was calculated as the percentage of the total 24 hour period with pH <4. A cough or wheeze was considered to have occurred before a reflux episode if the cough or wheeze indicator was activated at any point
Acid reflux in asthmatics

Results

A total of 134 consecutive patients with asthma were invited to enter a Veterans Affairs study on the treatment of gastro-oesophageal reflux. All patients were offered upper gastrointestinal endoscopy and oesophageal function tests. Six patients (4.5%) declined to participate. The pH tracings of the remaining 128 patients were analysed. During the pH metry, patients did not experience more symptoms than usual, and the 24 hour recording periods proved to be typical of their presenting symptomatology. Episodes of coughing or wheezing occurred in 60 and 25 of 128 patients, respectively. The number of coughing episodes ranged between 1 and 79 (mean (SD) 21 (3)), and the number of wheezing episodes ranged between 1 and 27 (8 (1)). Among patients who coughed, five had only one cough and two had only two coughs during the entire monitoring period. Among patients with wheezing, six had one or two wheezing episodes only. These 13 patients were excluded from the subsequent statistical analyses. No abnormal oesophageal motility was recorded in all but one patient with low amplitude contractions. (This patient had only three coughs and no wheezes during the 24 hour pH metry and was not included in the further analysis.) A flow diagram of all patients is shown in fig 1. Table 1 contains the characteristics of the entire patient population and the two subgroups of 53 patients with frequent coughs and 19 patients with frequent wheezes. Demographic characteristics, consumption of alcohol and cigarettes, acid contact time, prevalence of oesophagitis, and hiatal hernia were similar in all patient groups.

Table 2 shows the temporal relationships between coughing or wheezing and acid reflux. Assuming a latency period of two minutes or less, acid reflux preceded a coughing episode about seven times more often than vice versa—that is, coughing preceded acid reflux. Both types of events occurred about 2–3 times more frequently than expected based on chance alone, the outcome being statistically significant. Overall, nearly half of all coughs were found to be associated with a reflux episode. An increase in the latency period from two to five minutes increased the percentage of associations, with reflux preceding cough remaining the far more frequent relationship. About half of all wheezing episodes were associated with acid reflux (table

Figure 1 Flow diagram of the study population.
Table 2  Relationships among coughing, wheezing, and reflux

<table>
<thead>
<tr>
<th>Type of relationship</th>
<th>No patients</th>
<th>Observed* (SD)</th>
<th>Ratio†</th>
<th>z Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough and reflux</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of interaction: 0–2 min</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough precedes reflux</td>
<td>28</td>
<td>6% (1%)</td>
<td>3.21</td>
<td>1.71</td>
<td>0.043</td>
</tr>
<tr>
<td>Reflux precedes cough</td>
<td>49</td>
<td>40% (3%)</td>
<td>5.08</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Association of reflux and cough</td>
<td>49</td>
<td>46% (3%)</td>
<td>5.35</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Length of interaction: 0–5 min</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough precedes reflux</td>
<td>28</td>
<td>12% (2%)</td>
<td>2.18</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>Reflux precedes cough</td>
<td>50</td>
<td>50% (3%)</td>
<td>4.07</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Association of reflux and cough</td>
<td>50</td>
<td>62% (4%)</td>
<td>4.17</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Wheezes and reflux</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Association of reflux and wheezes (for 2 min)</td>
<td>16</td>
<td>48% (7%)</td>
<td>2.71</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Association of reflux and wheezes (for 5 min)</td>
<td>17</td>
<td>56% (7%)</td>
<td>1.66</td>
<td>0.050</td>
<td></td>
</tr>
</tbody>
</table>

*The total number of coughs or wheezes corresponds to 100%, mean percentage calculated as mean of individual patient means with SD.
†The ratio represents the fraction of observed over expected coincidences of coughs and reflux or wheezes and reflux.

2). In 43% of all wheezing episodes, reflux preceded wheezing. Because of the relatively small number of patients with frequent wheezing, we abstained from a more detailed statistical analysis of the temporal relationship between wheezing and reflux.

Of all reflux, coughing, and wheezing events, 81%, 78% and 80%, respectively, were recorded during the upright position. In general, separate analysis of the pH metry data by upright versus supine body position revealed rather similar patterns of association. Assuming a latency period of two minutes, 49% versus 36% of all upright versus supine coughs were associated with reflux events, reflux preceding cough in 43% and 30%, respectively. Of all wheezes, 51% and 41% were associated with reflux events during the upright and supine periods, respectively. Assuming a latency period of five minutes, 60% versus 71% of all upright versus supine coughs were associated with reflux events, reflux preceding cough in 48% and 58%, respectively. Of all wheezes, 57% and 53% were associated with reflux events during the upright and supine periods, respectively.

Figure 2 contains a sensitivity analysis of varying the length of interaction between cough and reflux from one to 10 minutes. Progressive lengthening of the coughing period raises the chances for a reflux event to fall into that period. As the duration of influence exerted by coughing is artificially extended from one to 10 minutes, an increasing fraction of coughs appears to result in a reflux episode (fig 2A). Assuming the influence of coughing on reflux to last as long as 10 minutes after the coughing event was first recorded, about 15% of all coughs appear to be followed by a reflux episode. In fig 2B, a reflux episode is assumed to exert its influence on coughing 1–10 minutes after the pH value returned to pH >4. The fraction of reflux episodes leading to coughing increases accordingly from 14% to 25%. Most importantly, the sensitivity analysis shows that the measured strength of the relationship between coughing and reflux depends in part on the type of assumptions built into the analysis. The analysis also demonstrates that, regardless of such assumptions, more reflux episodes result in coughing than coughing episodes result in reflux. When each individual patient is considered, a similar pattern is revealed. Table 3 shows the association of coughing and reflux in each individual patient. In 49 of 53 patients, acid reflux preceded a coughing episode while in 28 of 53 patients a cough preceded a reflux episode. All patients with cough preceding reflux also had reflux preceding cough. In only four patients was there no relationship between the two events.

In the baseline analysis, a minimum of five coughing episodes was chosen as the threshold

Table 3 Association of coughing with reflux episodes

<table>
<thead>
<tr>
<th>Cough leads to reflux</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflux leads to cough</td>
<td>28</td>
<td>21</td>
<td>49</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>25</td>
<td>53</td>
</tr>
</tbody>
</table>

χ²=19.05, p<0.001 (McNemar’s test).
Acid reflux in asthmatics

The primary aim of our study was to evaluate the temporal relationship between acid reflux and cough and make inferences about their causal association. Patients underwent extensive training on how to use the event markers for coughing and wheezing episodes. During evaluation of the pH metry data it became obvious nevertheless that even a seemingly simple analysis of the temporal relationships was open to multiple types of bias. With frequent consecutive and overlapping episodes of reflux and cough, it was difficult to establish unequivocally a cause and effect pattern. Two minutes were chosen as a baseline latency period between two events because this time period had been reported previously to provide reliable estimates. If two events occurred within a two minute time frame, the first event was considered to have caused the second one. Because other investigators also used latency periods as long as five and 10 minutes, we decided to subject our data to a computer analysis that automatically assigned to all latency periods lengths that varied between one and 10 minutes. Although the fraction of observed associations increased with increasing latency periods, the overall pattern remained robust. Regardless of the length of the latency period, reflux of acid remained a more common event to precede cough than to follow a cough. For clinical purposes therefore the choice of a single latency period of two minutes would probably be sufficient to establish a relationship between pulmonary symptoms and reflux.

In a second sensitivity analysis, thresholds for the total number of coughs and wheezes were varied. Patients with very few events were characterised by extreme R values and extreme fractions of coughs or wheezes associated with reflux. The thresholds of three and five events for wheezes and coughs, respectively, were chosen as a compromise between two opposing goals. On the one hand, a large number of events assured a more reliable estimate for the true fraction of associated events in the individual patient. On the other hand, the very stringent criteria of high thresholds led to exclusion of many patients. Fortunately, most parameters remained unaffected by the choice of a particular threshold. Thus the dependence of reflux induced coughing on the total number of coughs appeared to reflect an underlying pathophysiological mechanism rather than an artefact of measurement.

Fifty three of our 60 patients with cough had five or more coughing episodes during the 24 hour period, and 92% of the 53 patients had...
cough associated with reflux. These findings are consistent with the results of DeMeester et al and Ing et al who reported that 70% and 90%, respectively, of all patients with chronic cough also presented with abnormal pH monitoring. 18 19 Laukka et al attempted to establish a causal relationship between coughing and reflux in a small population of 10 patients with gastrooesophageal reflux symptoms. 20 Although in the majority of instances the two events were not related, in a few instances cough preceded reflux more often than reflux preceded cough. Compared with our study however the authors investigated only a few patients, most of whom had a low acid contact time with little evidence to support reflux induced pulmonary symptoms that Raiha et al observed in a series of 105 patients undergoing oesophageal pH monitoring that respiratory symptoms did not appear unless the acid contact time of pH < 4.0 exceeded 10%. 21 It is presently unknown whether reflux of acid into the oesophagus is sufficient to initiate a cough or whether actual aspiration of the refluxed acid is necessary. Indeed, changes in airway calibre and resistance in response to acid in the distal oesophagus have been described in asthmatic patients as a possible reflex mechanism for reflux induced cough. 22 Our results support recently published data by Harding et al who showed that among asthmatics with reflux disease, 78% of respiratory symptoms and 90% of coughs were associated with oesophageal exposure to acid. 23 The statistical associations between pulmonary symptoms and acid reflux found by us and by previous investigators do not prove causality and still require confirmation by treatment trials. Studies demonstrating improvement or even cure of asthma after antireflux surgery however do lend support to the contention that gastro-oesophageal reflux contributes to the occurrence of asthma. 24 In conclusion, half of all coughs and wheezes in asthmatics are associated with acid reflux into the oesophagus. While an occasional coughing episode can lead to reflux, it is the reflux episode, in the vast majority of instances, that leads to cough. Our study establishes a possible link between reflux and coughing or wheezing. The potential of antireflux therapy to break the cycle of reflux induced cough and, to a lesser degree, cough induced reflux is in need of study.

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References
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