Upper esophageal sphincter and esophageal motility in patients with chronic cough and reflux: assessment by high-resolution manometry

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SUMMARY. The pathophysiology of chronic cough and its association with dysmotility and laryngopharyngeal reflux remains unclear. This study applied high-resolution manometry (HRM) to obtain a detailed evaluation of pharyngeal and esophageal motility in chronic cough patients with and without a positive reflux–cough symptom association probability (SAP). Retrospective analysis of 66 consecutive patients referred for investigation of chronic cough was performed. Thirty-four (52%) were eligible for inclusion (age 55 [19–77], 62% female). HRM (ManoScan 360, Given/Sierra Scientific Instruments, Mountain View, CA) with 10 water swallows was performed followed by a 24-hour ambulatory pH monitoring. Of this group, 21 (62%) patients had negative reflux–cough SAP (group A) and 13 (38%) had positive SAP (group B). Results from 23 healthy controls were available for comparison (group C). Detailed analysis revealed considerable heterogeneity. A small number of patients had pathological upper esophageal sphincter (UES) function (n = 9) or esophageal dysmotility (n = 1). The overall baseline UES pressure was similar, but average UES residual pressure was higher in groups A and B than in control group C (−0.2 and −0.8 mmHg vs. −5.4 mmHg; P < 0.018 and P < 0.005). The percentage of primary peristaltic contractions was lower in group B than in groups A and C (56% vs. 79% and 87%; P = 0.03 and P < 0.002). Additionally, intrabolus pressure at the lower esophageal sphincter was higher in group B than in group C (15.5 vs. 8.9; P = 0.024). HRM revealed changes to UES and esophageal motility in patients with chronic cough that are associated with impaired bolus clearance. These changes were most marked in group B patients with a positive reflux–cough symptom association.

KEY WORDS: chronic cough, esophageal motility, high-resolution manometry (HRM), laryngopharyngeal reflux (LPR), pharyngeal motility.

INTRODUCTION

Reflex of gastric contents above the upper esophageal sphincter (UES) into the larynx and pharynx is a cause of chronic cough and other laryngopharyngeal symptoms.¹ Pathologic laryngopharyngeal reflux (LPR) may be present together with gastroesophageal reflux disease (GERD); however, in many patients, acid exposure to the distal esophagus is normal.² Moreover, even occasional LPR events can cause symptoms and inflammation because the laryngeal epithelium is more sensitive to gastric reflux than the esophageal epithelium.³ In clinical practice, the etiology of cough is complex, and it can be difficult to demonstrate a causal relationship between reflux, symptoms, and disease. Other causes of cough include pharyngeal dysfunction, most commonly in the presence of neurological injury but also in the presence of local pathology.⁴ Additionally, case reports have demonstrated that regurgitation of food and fluid retained in the esophagus back to the laryngopharynx can trigger cough,⁶ and several authors have reported a high prevalence of esophageal dysmotility as an accompanying condition and potential pathogenic cofactor in patients with LPR, asthma and related conditions.⁷–⁹ Severe dysmotility disorders are rare, but ‘nonspecific abnormalities’ and ‘ineffective esophageal motility’ are commonly observed on conventional manometry with five to eight pressure sensors in patients with
GERD with and without respiratory symptoms. However, this description of esophageal motility provides little insight into the cause of symptoms or mechanism of disease in patients with these conditions. As a result, recent reviews do not recommend esophageal manometry in the investigation of LPR or chronic cough.

High spatial resolution is required to describe the effects of abnormal motility on the function (i.e., clearance) of the pharynx, UES, and esophagus. High-resolution manometry (HRM) with esophageal pressure topography is an evolution in esophageal manometry that measures pressure activity from sensors spaced at 1-cm intervals from the pharynx to the stomach. This technique detects not only focal dysmotility but also dysfunction and outflow obstruction caused by structural pathology.

We propose that HRM can increase sensitivity of physiological measurement to identify the cause of chronic cough. This study aimed to provide the first, detailed evaluation of pharyngeal and esophageal motility in patients with chronic cough with and without association to reflux events on pH studies.

**METHODS**

From March 2006 to July 2010, the clinical notes of consecutive patients referred for investigation of chronic cough to the esophageal laboratory at St Thomas' hospital were reviewed. Patients with history of esophageal surgery or endoscopic therapy, overt dysmotility (achalasia, diffuse esophageal spasm, nutcracker esophagus, scleroderma), and structural pathology (pharyngeal pouch, diverticulum, Shatzki ring) were excluded. Patients with hiatus hernia were excluded to avoid confounding with esophageal dysmotility common in this group. Additionally, patients with known asthma or other respiratory conditions were excluded. Details of current medication use were not systematically recorded; however, all patients were instructed to stop acid suppression at least 7 days before the investigations were performed.

HRM (ManoScan 360, Given Imaging/Sierra Scientific Instruments, Mountain View, CA, USA) with detailed analysis of esophageal pressure topography (ManoView, Given/Sierra Scientific Instruments) of 10 water swallows was performed followed by catheter-based 24-hour ambulatory pH monitoring (Slimline, Medtronic, Minneapolis, MN, USA). Patients were divided into three groups: (i) cough with negative symptom association probability (SAP) to reflux; (ii) cough with positive SAP to reflux; and (iii) healthy controls for comparison. Pathologic acid exposure was defined as total percent of time pH < 4/24 hours >4.2% over monitoring period. A 2-minute period was applied to assess the reflux SAP.

We evaluated 10 water swallows for each participant. Measured parameters (Fig. 1) included basal and residual (intrabolus) relaxation pressure of UES and lower esophageal sphincter (LES), contractile pressure, temporal duration and spatial length of any break in the contractile front at the ‘proximal transition zone’ (PTZ) between the proximal and distal esophageal contraction, contractile pressure and length of the proximal esophageal (lower UES border to proximal PTZ border), and distal esophageal (distal PTZ to upper LES border) contractions. HRM measurements of contraction length and duration were acquired using a 30-mmHg isobaric contour thresholds. LES pressure and integrated relaxation pressure was referenced to gastric pressure. Other pressures were referenced to atmospheric pressure. The spatial length of contractions is reported as raw data and is also corrected to the length of the esophagus.

The overall percentage of effective and ineffective peristalsis (failed swallow, spasm, wide >3 cm break in the @30 mmHg contractile front) was compared between groups. A secondary analysis to assess the association of GERD (defined by pathologic acid exposure) and motility was performed.

**Statistical analysis**

All statistical computations were performed using SPSS Version 13.0 (SPSS Inc., Chicago, IL, USA). Statistical comparisons were performed using chi-squared and Kruskal-Wallis tests. For comparisons of means derived from repeated measurements, paired t-tests were used. A P-value < 0.05 was considered significant. Data were presented as means and standard deviation.

**RESULTS**

Of 66 patients referred for investigation of cough, patients with hiatus hernia (n = 23), previous esophageal surgery (n = 8 post-fundoplication), and major motility disorder (n = 1 achalasia) were excluded. Thus, 34 (52%) were eligible for inclusion. Of this group, 21 (62%) patients had negative reflux–cough SAP (group A) and 13 (38%) had positive SAP (group B). Results from 23 healthy controls were available for comparison (group C). Mean patient age was 55 ± 15 (19–77); 21 (62%) were female. Mean acid exposure time was not different between groups A and B (4.9% ± 6.5 vs. 3.7% ± 4.0 exposure <pH 4; P = 0.34), and a similar proportion had pathologic reflux > 4.2% acid exposure/24 hour (7/21, 4/13; P = 0.198).

There was no significant difference in baseline UES pressure; however, the median residual (intrabolus) relaxation pressure of UES on water swallows
was higher in groups A and B than in group C controls (−0.2 and −0.8 vs. −5.4; \( P < 0.018 \) and \( P < 0.005 \), respectively) (Table 1). Pathological values (i.e. above the published normal range and never seen in healthy controls) were documented in 4/21 (19%) and 5/13 (38%) patients in groups A and B, respectively.

The percentage of effective primary peristaltic contractions was lower in group B with reflux-associated cough (52%) than in groups A and C (79% and 86%; \( P = 0.0001 \)) (Table 2, Fig. 2). Basal LES pressures were similar in all three groups; however, the median intrabolus pressure at the LES was higher in group A and significantly higher in group B than in controls (11.8 and 15.5 vs. 8.9; \( P = 0.190 \) and \( P = 0.024 \)). Pathological values were documented in only one patient in group B. Additionally, distal contraction time (wave duration) was longer in both patient groups than in controls (4.8 and 4.6 vs. 5.0; \( P = 0.007 \) and \( P = 0.05 \)); however, the distal contractile integral was similar in all groups. Other motility parameters including the characteristics of the PTZ and the

Table 1  Characteristics of HRM measurements at 30 mmHg isobaric counter

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 21)</th>
<th>Group B (n = 13)</th>
<th>Group C (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
<td>Median</td>
</tr>
<tr>
<td>Basal UES pressure (mmHg)</td>
<td>43</td>
<td>22.1–146.2</td>
<td>40</td>
</tr>
<tr>
<td>Residual UES pressure (mmHg)</td>
<td>−0.2†</td>
<td>−16.9–13.4</td>
<td>−0.8‡</td>
</tr>
<tr>
<td>PTZ length (cm)</td>
<td>4.7</td>
<td>0–12.9</td>
<td>3.6</td>
</tr>
<tr>
<td>PTZ duration (sec)</td>
<td>2.5</td>
<td>0.3–5.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Mean PTZ pressure (mmHg)</td>
<td>8.8</td>
<td>4.2–16.1</td>
<td>9.4</td>
</tr>
<tr>
<td>Distal contractile integral (mmHg-cm-s)</td>
<td>926.5</td>
<td>58.9–3932.8</td>
<td>667.2</td>
</tr>
<tr>
<td>Basal LES pressure (mmHg)</td>
<td>9.2</td>
<td>−2.8–27.2</td>
<td>5</td>
</tr>
<tr>
<td>Residual LES pressure (mmHg)</td>
<td>6.7</td>
<td>−4.2–104.7</td>
<td>3.9</td>
</tr>
<tr>
<td>Intrabolus pressure (avg max, mmHg)</td>
<td>11.8</td>
<td>0–23.06</td>
<td>15.5‡</td>
</tr>
</tbody>
</table>

†Group A versus group C \( P = 0.018 \); ‡Group B versus group C \( P = 0.005 \). §Group B versus group C \( P = 0.024 \). LES, lower esophageal sphincter; PTZ, proximal transition zone; UES, upper esophageal sphincter.

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presence of any other break in the contractile front were similar in all groups (Table 1).

Motility parameters were compared also between patients with and without pathologic acid exposure on 24-hour ambulatory pH studies (Table 3). In this study population in which patients with hiatus hernia were excluded, there was no significant interaction between the severity of gastroesophageal reflux as assessed by acid exposure on pH monitoring and any measurement of pharyngeal or esophageal motility.

### Table 2
The percentage of effective/ineffective contractions at 30 mmHg isobaric counter

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (swallow)</td>
<td>%</td>
<td>n (swallow)</td>
</tr>
<tr>
<td>Effective contractions</td>
<td>166</td>
<td>79†</td>
<td>68†</td>
</tr>
<tr>
<td>Ineffective contractions</td>
<td>44</td>
<td>21</td>
<td>62</td>
</tr>
<tr>
<td>Total</td>
<td>210</td>
<td>100</td>
<td>130</td>
</tr>
</tbody>
</table>

†Group B versus group A and group C $P = 0.0001$.

### Table 3
Patients’ characteristic according to presence reflux at 30 mmHg isobaric counter

<table>
<thead>
<tr>
<th></th>
<th>Normal acid exposure ($n = 11$)</th>
<th>Pathologic acid exposure ($n = 23$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Mean basal UES pressure (mmHg)</td>
<td>41</td>
<td>1.4–112</td>
</tr>
<tr>
<td>Mean UES residual pressure (mmHg)</td>
<td>–0.7</td>
<td>–11.4–10</td>
</tr>
<tr>
<td>PTZ length (cm)</td>
<td>5.1</td>
<td>0–15.8</td>
</tr>
<tr>
<td>PTZ time (sec)</td>
<td>2.6</td>
<td>0.1–6</td>
</tr>
<tr>
<td>Mean PTZ pressure (mmHg)</td>
<td>9.3</td>
<td>4.2–23.4</td>
</tr>
<tr>
<td>Distal contractile integral (mmHg-cm-s)</td>
<td>718.8</td>
<td>58.9–3024.1</td>
</tr>
<tr>
<td>Basal LES pressure (mmHg)</td>
<td>7.4</td>
<td>–2.8–19.3</td>
</tr>
<tr>
<td>Residual LES pressure (mmHg)</td>
<td>5.9</td>
<td>–4.2–18.9</td>
</tr>
<tr>
<td>Intrabolus pressure (avg max, mmHg)</td>
<td>12.6</td>
<td>0–26.7</td>
</tr>
</tbody>
</table>
DISCUSSION

Chronic cough is the presenting feature of GERD in some patients and complicates the disorder in others. Among unselected patients with chronic cough, detailed investigation reveals an association with reflux events in approximately 20% of cases. There are a number of potential mechanisms whereby GERD may cause or aggravate coughing. LPR and microaspiration of swallowed material or gastric content trigger cough by direct stimulation of the airways. Distal reflux events trigger cough by indirect stimulation of nerves involved in the tussive reflex. Pharyngeal and esophageal dysmotility may contribute to the pathogenesis of cough either by facilitating reflux (e.g. weak or unstable LES or UES function) or by impairing clearance and prolonging exposure to noxious chemicals in refluxate.

This detailed analysis of HRM data revealed heterogeneous findings. Pathologic UES function and esophageal motility was detected in a small number of patients referred for investigation of suspected LPR. Additionally, there were subtle but statistically significant differences between the study groups that indicate the presence of impaired UES and esophageal clearance function in cough patients. In the majority, dysfunction was not severe, and this is consistent with the possibility that hypersensitivity to impaired clearance as well as to reflux events could trigger chronic cough. Although this study did not address this directly, hypersensitivity to pharyngeal stimulation has been documented in similar patients with chronic cough, and this pathophysiological mechanism may explain also the presence of other pharyngeal and esophageal symptoms of uncertain etiology (e.g. globus, functional dysphagia).

The study population was typical of those referred for investigation of suspected reflux-related cough. The majority had no dysphagia and either no reflux symptoms or only mild, intermittent heartburn. The presence of a hiatus hernia was an exclusion criterion to avoid confounding due to peristaltic dysfunction or outflow obstruction. Patients with overt structural pathology, major esophageal dysfunction, or respiratory disease on other investigations were also excluded. Thus, the study population represented a group with cough of unknown etiology after clinical and endoscopic investigation. The groups were then divided into patients with and without a positive SAP between reflux events and cough on ambulatory pH studies. These groups were analyzed separately to assess whether pharyngeal or esophageal dysfunction predisposed to cough associated with reflux and/or was associated with cough in and of itself. The application of SAP to divide patients into groups was favored in this study since this assessment is more sensitive than symptom index (SI) when the number of symptoms reported by patients is relatively high if typical diagnostic thresholds are applied (i.e. SI > 50%). Note that no patient with a negative SAP had a positive SI in this study.

We found no difference in UES basal pressure in patients with chronic cough and normal controls. This is consistent with previous studies with conventional manometry; however, HRM analysis revealed a small but significant increase in intrabolus pressure at the UES on swallowing in both patient groups compared to controls. Residual intrabolus pressure is an indication of resistance to flow through the pharyngoesophageal segment. In healthy controls, UES residual pressure was very low as the sphincter opens into the negative pressure environment of the thoracic cavity. In patients with cough, UES residual pressure was very variable, but pathologically high values were recorded in a small number (9/34 [26%]) of cases (Fig. 3). This indicates poor UES compliance or other causes of outflow obstruction (e.g. cricopharyngeal hypertrophy) at this level. The increase in residual pressure seen with 5 mL water swallows is small because the resistance to flow of a small volume of liquid is small; however, resistance increases exponentially with volume and is greatly increased with solids (high viscosity increases resistance). Retention in the pharynx occurs when the resistance to flow is greater than the ability of
pharyngeal contraction to force the bolus across the UES. This is a potent stimulus for cough. Normally, multiple reflexes protect against even small amounts of fluid or food collecting in the pharynx; however, reduced laryngopharyngeal mechanosensitivity has been documented in GERD patients with cough and, if present, this would contribute to impaired clearance function and the risk of aspiration.

Peristaltic dysfunction was common in patients with reflux-associated cough. This group had a much lower percentage of effective peristaltic contractions compared with other patients with cough and healthy controls, primarily due to increased failed contractions. This is similar to findings with conventional manometry in patients with cough in general and reflux-associated cough in particular. In this patient group, HRM did not reveal more subtle causes of peristaltic dysfunction such as increased breaks in the contractile front at the PTZ that have been reported in patients with more severe GERD and esophagitis. The only other difference in normal motility on detailed analysis was increased duration of contractions, found in both patient groups, which may be a response to increased resistance to flow across the esophagogastric junction (EGJ) (see below). Clearly, failed contractions impact on esophageal clearance and increase the risk of cough as food, fluid, or refluxate retained in the esophagus pass back into the pharynx.

Impaired structure and function of the EGJ is of key importance in the pathophysiology of GERD; however, having excluded patients with hiatus hernia, we found that this group of patients with cough had no anatomic impairment of the reflux barrier and no difference in basal LES pressure to healthy controls. Although normal function was present on conventional parameters, HRM analysis revealed increased intrabolus pressure across the EGJ, although this attained pathologic levels in only one patient. The cause of this mild outflow obstruction is uncertain; however, especially in combination with peristaltic dysfunction, any degree of obstruction to flow across the EGJ will impair esophageal clearance and, as described above, will likely increase the risk of cough.

This study has limitations common to most retrospective, observational studies, and the investigators that performed the detailed analysis of HRM studies (RV, RS) were not blinded to patient allocation. However, bias was probably mitigated by the use of automatic analysis for many measured parameters (note: manual measurements such as PTZ length showed no differences). The number of patients with and without reflux disease defined by distal acid exposure was relatively small but tightly defined to reduce heterogeneity and to facilitate statistical comparisons. It should be noted that, in this study, only distal pH monitoring was applied in most patients. Combined pH impedance or, possibly, pharyngeal pH monitoring may have increased diagnostic yield for reflux-related cough. This would have affected patient group allocation; however, the principal findings were similar in all cough patients, and so this would not have greatly impacted on the findings.

Overall, patients with cough associated with reflux showed more marked abnormalities of UES and peristaltic function than other patients or controls. This finding was not explained by differences in the severity of GERD as there was no interaction between the findings and the presence of pathologic acid exposure (Table 3). These results suggest that pharyngeal and esophageal dysfunction increase the risk of cough by impairing clearance of noxious refluxate; however, within both patient groups, there were important variations in manometric findings. Thus, any association between dysmotility and cough is not shared among all patients with chronic cough but may be important in individual cases. The addition of videofluoroscopy or impedance to HRM measurements may increase test sensitivity to clinically relevant pressure–flow abnormalities of pharyngeal and esophageal function. Ambulatory monitoring would be necessary to demonstrate a temporal association between physiological events (e.g. dysmotility, reflux) and symptoms. This is not available for HRM; however, observations during and after a test meal may be sufficient to establish a definitive diagnosis in some cases, especially for postprandial cough.

In conclusion, detailed HRM observations reveal a high prevalence of abnormal pharyngeal and esophageal dysfunction in patients with chronic cough. In a few cases, there was clear evidence of pathologic outflow obstruction at the UES. The clinical relevance of mild-moderate peristaltic dysfunction and esophageal outflow obstruction in these patients requires further study. These findings suggest that a range of problems affecting every stage of swallowing can cause or exacerbate chronic cough. Patients with this problem are often very troubled by their symptoms and are very difficult to diagnose and treat. If HRM can identify the cause of symptoms and guide more effective management in even a small proportion of these individuals, then it should be included in the investigation of unexplained chronic cough.

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