

Improved diagnosis of gastro-oesophageal reflux in patients with unexplained chronic cough

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Publication data

Submitted 20 October 2006
First decision 7 November 2006
Resubmitted 15 December 2006
Resubmitted 8 January 2007
Accepted 9 January 2007

SUMMARY

Background

Symptoms, oesophageal pHmetry and proton pump inhibitor treatment are used for diagnosing gastro-oesophageal reflux-related cough. Weakly acidic reflux is now increasingly associated with reflux symptoms such as regurgitation or chest pain.

Aim

To study the association between weakly acidic reflux and cough in a selected, large group of patients with unexplained chronic cough.

Methods

A total of 100 patients with chronic cough (77 'off' and 23 'on' a proton pump inhibitor) were studied using impedance-pHmetry for reflux detection and manometry for objective cough monitoring. Symptom Association Probability (SAP) Analysis characterized the reflux-cough association.

Results

Acid reflux could be a potential mechanism for cough in 45 patients (with either heartburn, high acid exposure or +SAP for acid reflux). Weakly acidic reflux could be a potential mechanism for cough in 24 patients (with either increased oesophageal volume exposure, increased number of weakly acidic reflux or +SAP for weakly acidic reflux). Reflux could not be identified as a potential mechanism for cough in 31 patients.

Conclusion

A positive association between cough and weakly acidic reflux was found in a significant subgroup of patients with unexplained chronic cough. Impedance-pH-manometry identified patients in whom cough can be related to reflux that would have been disregarded using the standard diagnostic criteria for acid reflux.

Aliment Pharmacol Ther 25, 723–732

INTRODUCTION

Chronic cough, defined as cough lasting more than 8 weeks, has a high socio-economic impact and can significantly impair the quality of life. Gastro-oesophageal reflux (GER), in addition to asthma and post-nasal drip syndrome (PNDS), is considered a common cause of chronic cough in all age groups.¹⁻⁵ Because only a minority of patients with GER-related cough have typical reflux symptoms such as heartburn or regurgitation,^{1, 2, 4, 6, 7} other tests are frequently used to establish a possible GER-cough association. Empirical treatment with proton pump inhibitors (PPI), aiming to reduce gastric acid secretion, and oesophageal pH monitoring have been incorporated in the diagnostic routine of patients with unexplained chronic cough.^{8, 9} If heartburn and regurgitation are absent, if pH monitoring does not show an increased oesophageal acid exposure and/or if the response to PPI treatment is inconclusive, the diagnosis of GER-related cough is discarded. It is possible, however, that these criteria are still insufficient to disregard GER as the cause of cough in some of these patients. It is known, for example, that a subgroup of patients with gastro-oesophageal reflux disease (GERD) may have heartburn with normal oesophageal acid exposure and incomplete response to PPI treatment.^{9, 10} One of the mechanisms that have been proposed to explain symptoms and refractoriness to PPI in these patients is the occurrence of oesophageal distension by weakly acidic (WA) reflux.¹¹ A similar mechanism might be present in patients with unexplained chronic cough.¹²

Oesophageal impedance-pH monitoring is a new technique that improves detection and quantification of acid GER and incorporates the possibility to assess WA reflux.¹³⁻¹⁵ An objective detection of cough, using simultaneous gastro-oesophageal manometry, allows both quantification and precise analysis of the temporal association between cough and reflux.^{16, 17}

We hypothesized that a number of patients with unexplained chronic cough might still have their cough associated with GER even if they do not have heartburn or regurgitation, their pH monitoring is normal or they do not respond to standard PPI treatment.

The aim of this study was to further characterize the reflux-cough association in a large number of thoroughly selected patients with unexplained chronic cough using combined 24-h impedance-pH-manometry.

METHODS

Subjects

Simultaneous 24 h ambulatory GER and cough monitoring was performed in 112 consecutive patients with chronic unexplained cough (33 men; median age 54 years, range: 22-81). The patients were recruited at the out-patient 'chronic cough' clinic of the University Hospital Gasthuisberg, K.U. Leuven, and presented daily cough of unclear aetiology for at least 8 weeks. Before reflux testing, other causes of chronic cough were excluded according to new cough diagnostic guidelines^{9, 18} (Figure 1). All patients had a normal chest X-ray and none of them was using angiotensin-converting enzyme inhibitors. Fifteen patients were ex-smokers with normal pulmonary function data (spirometry, body plethysmography and measurement of diffusion capacity). Asthma and eosinophilic bronchitis were excluded by negative histamine provocative tests, normal sputum eosinophilia and absence of improvement with inhaled steroids. Postnasal drip syndrome was excluded both clinically and by lack of improvement with nasal steroids and/or antihistamine treatment. Silent sinusitis was excluded by means of a computerized tomography scan of the sinuses. A standardized questionnaire was used to obtain a history of each patient regarding typical and atypical symptoms of GERD.

All patients had reflux monitoring because of persisting cough. Eighty-five patients were studied 'off' PPI therapy and 27 patients were studied 'on' PPI. These patients had persistent cough in spite of empirical PPI treatment prescribed by the referral pneumologist. Six patients received omeprazole 20 mg/day, 13 patients received omeprazole 20 mg/b.d. and eight patients received omeprazole 40 mg/b.d.

The study was approved by the Ethics Committee of the University Hospital Gasthuisberg, KU Leuven and informed consent was obtained from all subjects.

Recording equipment and technique

Cough and GER were monitored simultaneously using an ambulatory manometric-impedance-pH system. Manometry was used for accurate cough recognition, whereas impedance-pH monitoring allowed detection of acid and WA reflux (Figure 2a).

A manometric catheter with two solid-state pressure sensors (15 cm apart; Unisensor AG, Attikon,

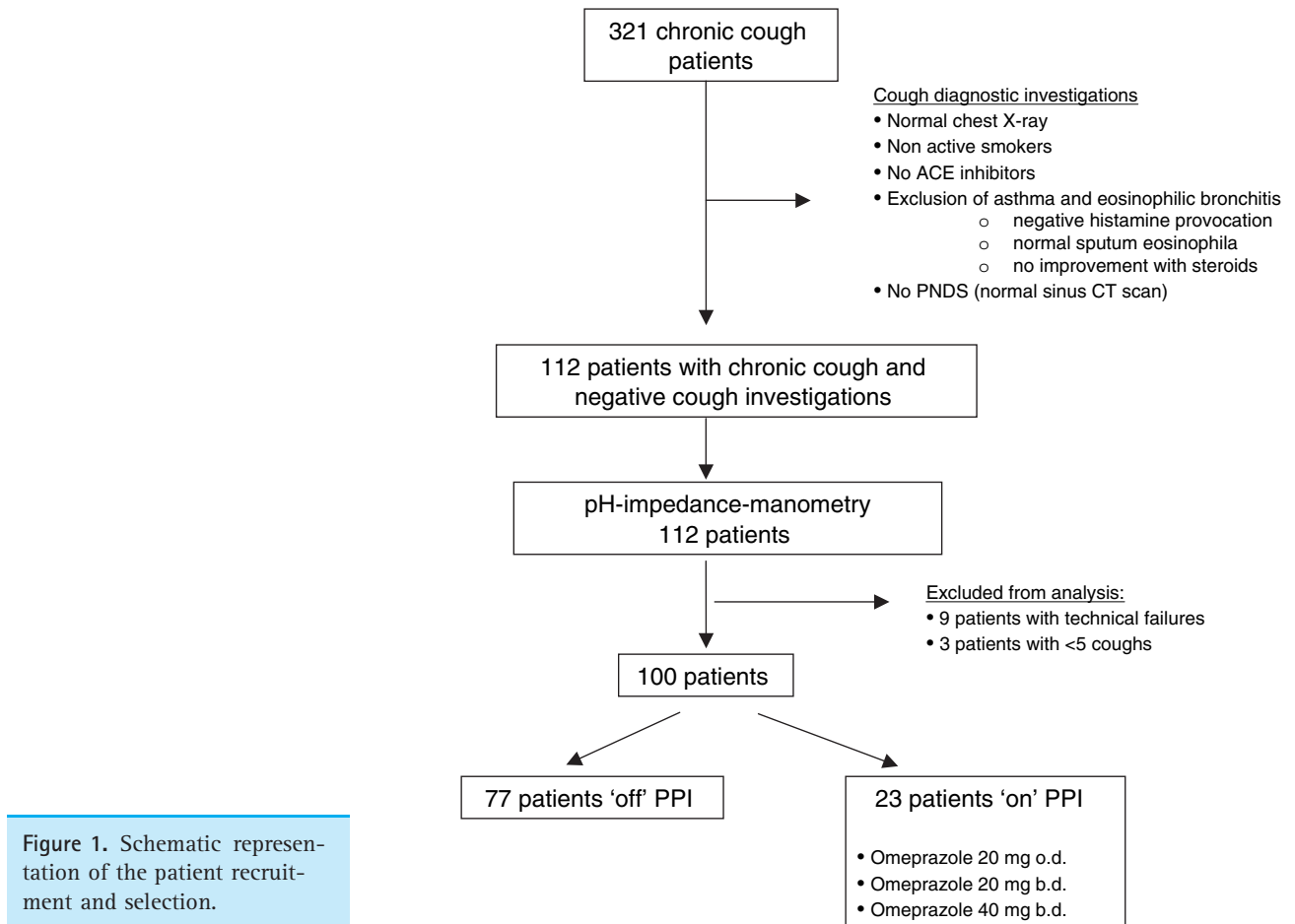


Figure 1. Schematic representation of the patient recruitment and selection.

Switzerland; 2.7 mm external diameter) was passed transnasally. A slow pull through technique was used to locate the proximal margin of the lower oesophageal sphincter (LOS) and the catheter was positioned so that one pressure channel was located in the oesophageal body (5 cm above LOS) and the other in the stomach.

Oesophageal impedance-pH was recorded with a 2.1-mm-diameter catheter that comprised six electrode pairs to measure intraluminal impedance and two antimony pH sensors (Sandhill Scientific, Inc.; Highlands Ranch, CO, USA). The impedance-pH and manometric catheters were connected to a single ambulatory device containing their respective amplifiers (Sleuth, Sandhill Scientific, Inc.). The impedance amplifier delivered ultra-low current in a range of 1–2 KHz with resulting current flow variations in response to intraluminal impedance changes. The impedance, pH and manometric signals were digitized at 50 Hz and stored in the data logger. Before the start of the recording, the pH electrodes were calibrated using pH 4.0 and 7.0 buffer solutions.

Study protocol

The study was performed as an out-patient procedure after an overnight fast. The catheters were passed transnasally and positioned to record pressures and pH in the stomach and pressure pH and impedance in the oesophageal body. Oesophageal pH was measured at 5 cm and impedance at 3, 5, 7, 9, 15 and 17 cm proximal to the LOS (Figure 2a).

The patients were encouraged to maintain normal activities, sleep schedule and eat their usual meals at their normal times. They were asked to remain upright during the day, and lie down only at their usual bedtime. Event markers on the data logger recorded meal times and posture changes. Between meals, patients abstained from snacks, beverages with a pH < 5, and were asked to avoid lozenges and gum chewing. Before the study, patients were instructed to keep a careful diary and trained to use a dedicated event marker in the data logger, to record cough episodes and other events.

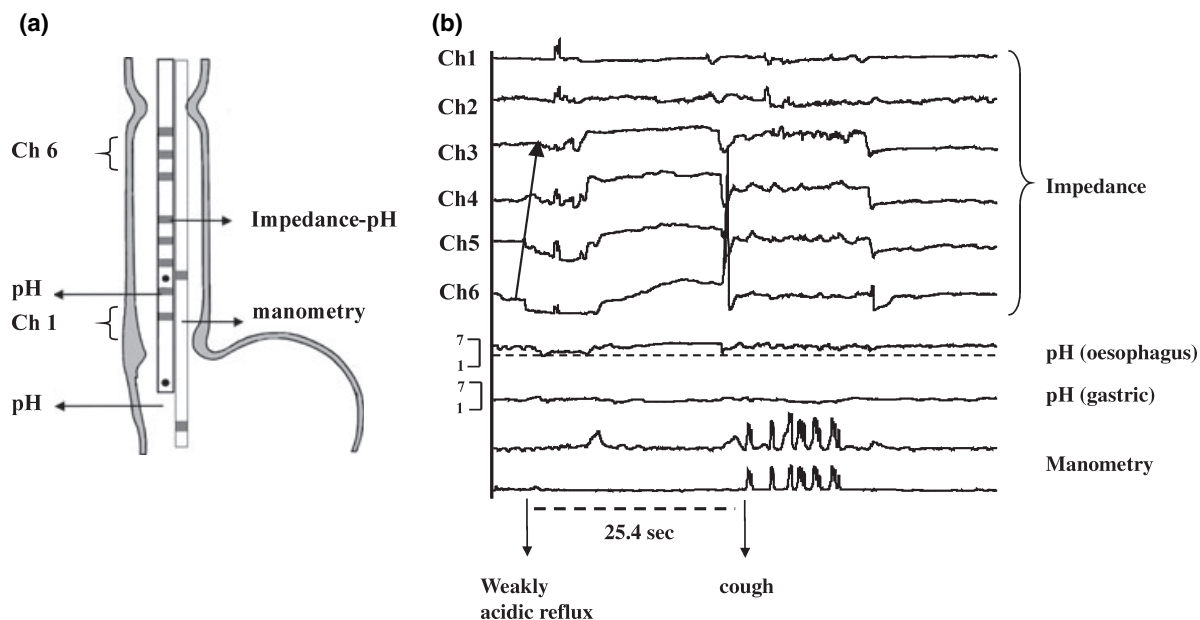


Figure 2. (a) Schematic representation of the pH-impedance and manometry catheters, positioned in the oesophagus. The proximal pH electrode is positioned 5 cm above the LOS and the distal pH electrode in the stomach, allowing impedance measurements at 3, 5, 7, 9, 15 and 17 cm above the LOS. The proximal manometric pressure channel is positioned 5 cm above the LOS and the distal channel is positioned in the stomach. (b) Tracing of combined oesophageal impedance-pH and manometry. Example of a weakly acidic reflux preceding a cough burst. The impedance tracing shows a retrogradely propagated drop consistent with liquid reflux, while the oesophageal pH falls more than 1 pH unit but remains above 4 (weakly acidic reflux). The manometric tracing shows a cough burst consisting of phasic, short duration, rapid pressure rises occurring simultaneously and with the same pressure configuration at all manometric recording sites. Cough occurred 25.4 s after the start of a weakly acidic reflux event.

Data analysis

The manometric-impedance-pH recordings were uploaded into a personal computer and were manually analysed using dedicated software (BIOVIEW, Sandhill Scientific Inc.).

Cough detection

Cough events were both marked by the patients in the data logger and/or diary and objectively detected in the manometric tracing.

The manometric tracing was independently analysed for cough episodes. A single cough was defined according to Paterson and Murat as phasic, short duration, rapid pressure rises (time to peak <1 s) occurring simultaneously and with the same pressure configuration at both manometric recording sites.¹⁶ A 'cough burst' was defined as two or more rapid simultaneous pressure peaks within 3 s (Figure 2b). The

cough events marked by the patient in the data logger and diary information were used for comparison with objective detection of cough bursts by manometry. A pilot analysis from 68 patients showed that 87% of episodes marked by patients corresponded with 'cough bursts' detected by manometry. Therefore, only 'cough bursts' were considered in the reflux-cough association analysis and patients with <5 cough bursts in 24 h were not included.

Reflux detection

The impedance-pH recording was independently analysed for GER. The impedance recording was analysed using criteria described in a recent consensus report on detection and definitions of acid, non-acid and gas reflux.¹³ Gastro-oesophageal reflux was defined as a sequential orally progressing drop in impedance to <50% of the baseline values starting distally (3 cm above LOS) and propagating retrograde to at least the

next two more proximal measuring segments. According to the corresponding pH change, impedance-detected reflux was classified as acid if pH fell below 4 for at least 4 s or, if pH was already below 4, as a decrease of at least 1 pH unit sustained for more than 4 s. Weakly acidic reflux was defined as a pH drop of at least 1 pH unit sustained for more than 4 s with the basal pH remaining between 7 and 4. Reflux was judged to be weakly alkaline when there was impedance evidence of reflux but the pH did not drop below 7 (Figure 3).

The proximal extent of each reflux event was evaluated from the impedance tracings. For each patient, the total number of reflux events (acid, WA and weakly alkaline), the average proximal extent of reflux and the exposure of the oesophageal body to acid and volume were calculated.

Total 24-h acid exposure was calculated as the percentage of time that the oesophageal pH was below 4. Total volume exposure/24 h was obtained from the impedance tracing by addition of the volume exposures during reflux measured at 5 above LOS. The number of reflux events and the volume exposure were regarded as increased if these values were above the 95th percentile of normal data obtained in healthy subjects 'off' and 'on' PPI therapy¹⁹ (Dr R. Tutuian, personal communication).

Association reflux-cough

In each patient, the association between reflux and cough was assessed using the Symptom Association Probability Analysis (SAP).²⁰

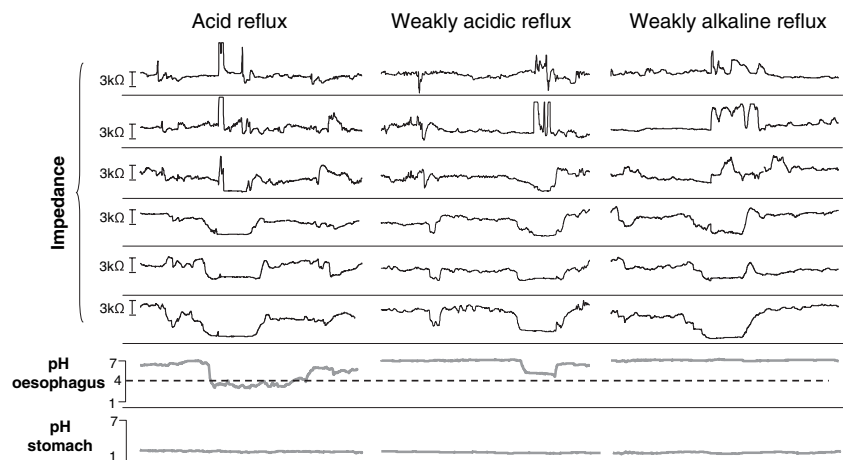
A 2-min time interval following the start of a reflux episode was used to delimitate the time window for reflux-cough association. A 2-min period was chosen based on previous analysis of acid reflux-chest pain association.²¹ Thus, if a cough episode occurred in the 2-min time period after the start of a reflux event, cough was considered 'associated to reflux' (Figure 1b). Cough episodes preceding a reflux event were evaluated separately.

The SAP was calculated as follows: the entire recording was subdivided into consecutive 2-min time intervals. Each time interval was evaluated for the presence of reflux. When reflux was detected at any point during the 2-min period, the period was considered positive for reflux (R+). In a second step, the 2-min periods containing a reflux episode followed by cough (R+S+), those with only cough but no reflux (R-S+) and those with neither cough nor reflux (R-S-) were counted. A contingency table was constructed containing the number of the four different types of 2-min periods. Fisher's exact test was used to calculate the probability (*P*-value) that the observed association between reflux and cough occurred by chance. The SAP was calculated as $(1.0 - P) \times 100\%$. SAP values >95% were considered statistically significant.^{20, 22}

Statistical analysis

Data are presented as median (25–75th centile). Comparisons between 'off' PPI and 'on' PPI groups were undertaken using the unpaired *t*-test. Fisher's exact test was used to calculate SAP. Statistical significance was accepted when *P* < 0.05.

Figure 3. Schematic representation of the three different types of GER as identified by impedance pH-measurements. Oesophageal impedance recording detected reflux as a retrograde movement of a liquid bolus (impedance drop). Simultaneous oesophageal pH recording allowed classification into acid (pH <4), weakly acidic (pH 4–7) and weakly alkaline reflux (pH ≥7).¹⁰



RESULTS

Patient population

A total of 112 patients with chronic unexplained cough were studied with 24 h impedance-pH-manometry (Figure 1). Twelve patients were excluded from the final analysis: nine patients had incomplete or technically defective recordings (i.e. accidental pH reference electrode disconnection, prolonged gastric or oesophageal pH drifts, dysfunction of more than two impedance channels) and three patients had <5 cough bursts/24 h. As a result, 100 patients were included in the final analysis: 77 patients were studied 'off' PPI [26 men, median age 54 (22–81 years)] and 23 patients were studied 'on' PPI [seven men, median age 56 (39–73 years)]. All patients studied 'on' PPI had gastric pH above 4 during more than 60% of the 24-h recording period. A table with individual patients' data can be provided by E-mail from the corresponding author.

Cough

The objective manometric cough measurement detected significantly more cough than that marked by the patients, using either the diary or the event marker. The median number of 'single cough' episodes and 'cough bursts' detected manometrically was 126 (70–226) and 25 (16–39), respectively. Patients marked significantly less cough bursts [six (2–16)] than those detected manometrically.

Gastro-oesophageal reflux

From the 100 patients studied, 20 had typical heartburn. In eight patients, heartburn was associated with increased acid exposure, whereas 12 had hypersensitive oesophagus (normal acid exposure).

Twenty-seven patients studied 'off' PPI showed an increased oesophageal acid exposure [10% (7.4–16.1)]. Only one patient 'on' PPI showed a slow oesophageal pH drift during the night associated with increased nocturnal gastric acidity. Fifteen patients had increased oesophageal volume exposure [3% (2.4–3.4)] as measured by impedance at 5 cm above the LOS.

The median number of total reflux events (acid + non-acid)/24 h was 38 (25.5–57.5) and 35 (21.5–49) in patients 'off' and 'on' PPI, respectively. As expected, in patients 'off' PPI, more than half of reflux episodes were acid, whereas in patients 'on' PPI, the majority of reflux events were WA or alkaline (Table 1). Compared with asymptomatic controls,¹⁹ only a minority of patients with unexplained chronic cough had increased number of reflux episodes, i.e. seven patients had increased number of acid reflux events, 12 had an increased number of WA reflux and three of weakly alkaline reflux. Furthermore, compared with GERD patients, patients with unexplained chronic cough had similar number of reflux episodes both 'off' and 'on' PPI therapy.²³ The proximal extent of reflux in patients with chronic cough was similar to that observed in normals or patients with GERD, i.e. in 92 of 100 patients a median of 6 (3–15) reflux episodes reached a level higher than 15 cm above LOS.

Association reflux–cough

The association between reflux events and cough was studied first considering only the cough events marked by the patients and then repeated considering all objectively detected cough bursts with manometry.

Considering only the cough events marked by the patient, a positive SAP for reflux–cough was observed in 11 of 100 patients (one SAP+ for acid reflux, nine SAP+ for WAc reflux and one SAP+ for both acid and WA reflux). In contrast, when we used 'cough bursts' detected manometrically, 36 of 100 patients had a

	'off' PPI (n = 77)	'on' PPI (n = 23)	P-value
Reflux events/24 h	38 (25.5–57.5)	35 (21.5–49)	0.07
Percentage acid reflux	51.5 (33.9–73.3)	4.4 (0–18)	0.0001
Percentage weakly acidic reflux	33.3 (21–55.7)	73.6 (1–50)	0.003
Percentage weakly alkaline reflux	6.7 (0–17.4)	16.6 (0–39)	0.16

Table 1. Different types of reflux in patients 'off' and 'on' PPI [median (25–75th)]

SAP+ between reflux and cough (nine SAP+ for acid reflux, 23 patients SAP+ for WA reflux and four SAP+ for both acid and WA reflux). The association between WA reflux and cough was observed in 15 patients 'off' PPI and eight patients 'on' PPI. Some of these patients had also concomitant increased in acid exposure and/or number of acid reflux episodes.

Association cough–reflux

We observed cough–reflux sequences in 42 patients. Reflux induced by coughing had a very small impact on the total oesophageal acid or volume exposure. The total acid exposure in these patients was 2.1 (0.6–3.8). Cough–reflux sequences contributed with 0.11% (0.03–0.4) of the acid exposure. The total volume exposure was 1.1% (0.6–1.9). Cough reflux events contributed with 0.05% (0.02–0.1) of the volume exposure.

Identification of 3 subgroups

After GERD symptoms assessment, testing for reflux with ambulatory pH-impedance-manometry, and Symptom Association Analysis, we identified three different subgroups of patients with unexplained chronic cough: (i) acid GER [manifested as either increased acid exposure, clear presence of heartburn with normal acid exposure (hypersensitive oesophagus) or positive

SAP between acid reflux and cough] could be the potential mechanism for cough in 45 patients, (ii) WA GER (manifested as either by increased oesophageal volume exposure, increased number of WA reflux events or positive SAP between WA reflux and cough) could be the potential mechanism for cough in 24 patients and (iii) no symptom or objective measurement of GER could be identified as a potential mechanism for cough in 31 patients (Figure 4).

DISCUSSION

Acid GER has long been implicated in the pathogenesis of chronic cough of extrapulmonary origin. The data implicating acid GER, however, can be equivocal as the correlation between measured acid reflux episodes and cough are inconsistent and as PPI treatment only variable relieves symptomatology. In the present study, we re-assessed the association between GER and cough in a highly selected group of 100 patients who had undergone negative thorough investigation for the aetiology of their chronic cough. We used the most sensitive available method for reflux detection together with objective cough recognition. Using these techniques we could identify a higher number of patients having cough associated with reflux than previously recognized and we identified a subgroup of patients showing a temporal association between their cough and WA GER.

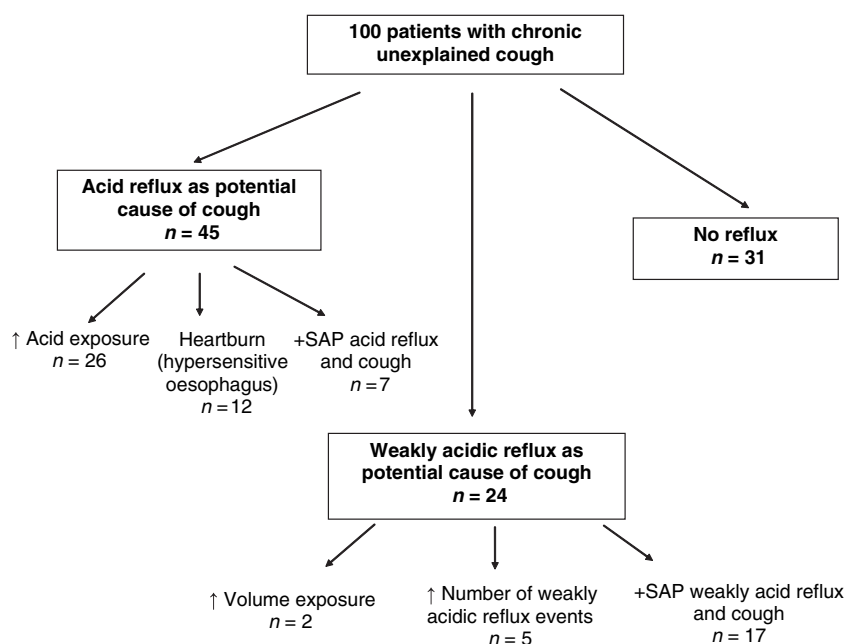


Figure 4. Schematic representation of the three subgroups identified in the study: (i) patients with acid reflux as a potential cause of cough; (ii) patients with weakly acidic reflux as a potential cause of cough and (iii) patients without any type of reflux as a possible cause of cough.

Acid GER was identified as a 'potential cause' of chronic cough in almost half of the patients, i.e. they had either typical heartburn, increased oesophageal acid exposure, increased number of acid reflux events, significant temporal association between individual cough and acid reflux events or a combination of all these.

The presence of heartburn or regurgitation is often used as a first indication of reflux-induced cough. However, in a large number of chronic cough patients, acid GER was clinically silent.^{1, 6, 7, 24, 25} Our study confirmed the limited value of heartburn assessment in patients with chronic cough. Only 19 patients with objective demonstration of increased reflux by impedance-pHmetry had heartburn or regurgitation.

Several studies using 24-h pH monitoring have shown an increased oesophageal acid exposure in patients with chronic cough.^{26–28} In this study, only 28 of 100 patients had increased acid exposure. The increased acid exposure was mainly due to spontaneous reflux followed by cough rather than a consequence of cough. The use of manometry allowed identification of sequences cough–reflux in many patients, but their impact on total acid exposure or volume exposure was minimal. We could also identify the sequence cough–reflux–cough and confirmed previous descriptions by Ing *et al.* suggesting that a self-perpetuating mechanism may exist whereby acid reflux causes cough and the cough in turn amplifies reflux via increased transdiaphragmatic pressure or by inducing transient LOS relaxation.^{28–30}

Patients with normal oesophageal acid exposure could still have a positive temporal association between acid GER events and cough. Wunderlich and Murray have first demonstrated, using the SAP analysis, a temporal association between individual cough events, marked by the patients and acid reflux episodes, detected with pH monitoring.³¹ In this study, we found a higher number of patients with positive SAP for acid reflux. Recent studies using 48 h wireless pHmetry showed a significant gain in the likelihood of establishing a relationship between chest pain and reflux by increasing the number of symptoms and reflux episodes.²² By using impedance-pH-manometry we detected many more reflux and cough episodes per subject that could have been identified by pHmetry and cough markers activated by the patient. Although the SAP analysis seems to be the most appropriate method, so far, to characterize the association between reflux and heartburn or chest pain, it still requires

adaptation to other symptoms, like cough. A positive SAP between acid reflux and chest pain is predictive of good response to PPI therapy.³² The SAP between reflux and cough still needs to be prospectively validated against an independent criterion of diagnostic accuracy such as prediction of symptomatic response to antireflux therapy. A recent uncontrolled study showed that patients with positive Symptom Index (another algorithm for Symptom Association Analysis) between WA reflux and cough in patients 'on' PPI was predictive of good response to antireflux surgery.³³

According to current guidelines for the management of chronic cough, empiric treatment with PPI could be regarded as an alternative diagnostic test of acid GER-induced cough.⁹ Our study did not include a formal therapeutic intervention which makes it difficult to speculate on the diagnostic value of this treatment. On the other hand, our results demonstrated that a significant number of patients, not responding to PPI treatment ('on' PPI subgroup) still showed objective evidence of WA reflux with a positive association with cough.

The diagnostic value of pH-monitoring is limited to acid reflux. During the postprandial period when the gastric acid is buffered by the meal and in patients 'on' PPI treatment, the ability of pH-monitoring to diagnose or exclude reflux is reduced.^{9, 34} Oesophageal impedance monitoring can overcome this limitation and combined with pH-metry, allows detection of all types of reflux events. Weakly acidic reflux has been previously associated with symptoms such as chest pain and regurgitation^{15, 29, 35, 36} and more recently implicated in the pathogenesis of respiratory symptoms. Using pH-impedance recording in infants, Wenzl *et al.* showed a significant temporal correlation between episodes of apnoea and GER of which only a minority (22%) involved acid reflux.³⁷ Rosen and Nurko described the usefulness of impedance testing to diagnose reflux in paediatric population with a cardio-respiratory event.³⁸ In a recent preliminary study, we have shown the presence of WA reflux in five of 22 patients with unexplained chronic cough, who had not been treated with acid suppression therapy.¹⁷ In the present study, we have confirmed such association in a much larger group of patients 'off' PPI and also included individuals with persistent cough in spite of empirical PPI treatment ('on' PPI).

In the present study, WA reflux (manifested as either increased non-acid oesophageal volume exposure, increased number of WA reflux or positive SAP between WA reflux and cough) could be considered a

potential mechanism for cough in 24 of 100 patients. The mechanisms by which WA reflux can trigger cough are still undetermined and might involve: (i) micro-aspiration of WA gastric contents containing pepsin, bile acids and duodenal pancreatic enzymes; (ii) a vagal oesophageal-bronchial reflex, initiated by the presence of reflux in the distal oesophagus and/or (iii) bronchial hypersensitivity following previous contact of the airway mucosa with gastric contents. In this study, a minority of WA reflux episodes reached high oesophageal levels, arguing against microaspiration as an immediate trigger of cough. Most patients with a positive association between WA reflux and cough did not have increased number of reflux events suggesting that hypersensitivity to one or more components of the refluxate might play a role in such association.

After taking an extensive history for reflux symptoms and testing for reflux with ambulatory pH-impedance-manometry, and Symptom Association Analysis, we identified 31 patients with unexplained chronic cough without any subjective and/or objective evidence of reflux. We acknowledge, however, that cough might still result from airway hypersensitivity to other stimuli such as cold air or cigarette smoke, induced by previous reflux injury, without the need of a current reflux-cough temporal association.³⁹

Although we found in the present study that WA reflux can be temporally related to cough, this does not imply a direct causal relationship. A recent case report and uncontrolled studies described resolution of cough after antireflux surgery in patients that had chronic cough associated with WA reflux in spite of PPI treatment.^{33, 40, 41} This finding might be an indication for the relevance of WA reflux as cause of persistent cough symptoms.

In conclusion, a positive association between cough and WA reflux was found in a significant subgroup of patients with unexplained chronic cough. Impedance-pH-manometry identified patients in whom cough can be related to reflux that would have been disregarded using the standard diagnostic criteria for acid reflux. Additional pharmacological or surgical outcome studies are needed to confirm the role of WA reflux in these patients.

ACKNOWLEDGEMENTS

Author's declaration of personal interests: D. Sifrim has received funding from Sandhill Scientific (Highlands Ranch, Colorado 80129).

Declaration of funding interests: this study was funded in part by the F. W. O. and the 'Geconcentreerde Onderzoeksactie' of the University of Leuven.

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