ORIGINAL ARTICLE

# The utility of ambulatory pH monitoring in patients presenting with chronic cough and asthma

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**KF AlHabib, S Vedal, P Champion, JM FitzGerald. The utility of ambulatory pH monitoring in patients presenting with chronic cough and asthma. Can J Gastroenterol 2007;21(3):159-163.**

**OBJECTIVE:** To evaluate the prevalence of gastroesophageal reflux disease (GERD) in patients presenting with asthma and chronic cough.
**PATIENTS AND METHODS:** The charts of 358 consecutive patients who were referred for ambulatory gastroesophageal pH monitoring to the Lung Centre in Vancouver, British Columbia, were reviewed, and the data of 108 (30%) patients with asthma and 134 (37%) patients with chronic cough were analyzed. The maintenance treatment for GERD was discontinued before patients underwent the pH monitoring study. One hundred eighteen (33%) patients were excluded.
**RESULTS:** Reflux episodes identified reflux events as the percentage of time where the pH was less than four. For asthma patients, 70 (64.8%) had distal total reflux, 50 (46.3%) had distal upright reflux, 41 (38.3%) had distal supine reflux and 73 (67.6%) had other distal refluxes. Proximal total reflux in asthmatic patients was present in 56 (52%), proximal upright reflux in 55 (51%) and proximal supine reflux in 56 (52%) patients. For chronic cough patients, 70 (52.6%) had distal total reflux, 59 (44.4%) had distal upright reflux, 45 (34.4%) had distal supine reflux and 75 (56%) patients had other distal refluxes. In chronic cough patients, proximal total reflux was present in 70 (52%), proximal upright reflux in 80 (60%) and proximal supine reflux in 59 (44%). Presenting respiratory and/or reflux symptoms were absent in approximately 25% of patients with asthma and reflux, and in approximately 50% of patients with chronic cough and reflux. During pH monitoring, symptoms did not differ significantly between those with and without distal reflux in both study groups, except for more significant heartburn in patients with chronic cough and reflux (RR 2.0).
**CONCLUSIONS:** The data of the present study support the observation that there is a high prevalence of GERD in patients with asthma or chronic cough. The use of different pH parameters for detecting acid reflux during 24 h ambulatory pH monitoring, such as proximal esophageal acid measurement, should be considered as part of the routine interpretation of such testing. A low threshold for diagnosing GERD in patients with asthma or chronic cough is essential, because respiratory and/or reflux symptoms can be absent or atypical in some of these patients.

**Key Words:** *Asthma; Chronic cough; Gastroesophageal reflux*

## Utilité de la surveillance ambulatoire du pH gastro-œsophagien chez des patients présentant une toux chronique et de l'asthme

**OBJECTIF :** Évaluer la prévalence du reflux gastro-œsophagien (RGO) chez les patients qui souffrent d'asthme et de toux chronique.
**PATIENTS ET MÉTHODES :** Les dossiers de 358 patients consécutifs qui ont été adressés au *Lung Centre* de Vancouver, en Colombie-Britannique, pour une surveillance ambulatoire de leur pH gastro-œsophagien ont été passés en revue et les données relatives à 108 patients asthmatiques (30 %) et à 134 patients présentant une toux chronique (33 %) ont été analysées. Les cas ont été étudiés alors qu'ils n'étaient pas sous traitement pour leur RGO. Cent dix-huit patients (33 %) ont été exclus.
**RÉSULTATS :** Les épisodes de reflux interprétés comme des incidents liés au RGO ont été présentés sous forme de pourcentage du temps où le pH était inférieur à quatre. Chez les patients asthmatiques, 70 (64,8 %) présentaient un reflux distal total, 50 (46,3 %), un reflux distal en position redressée, 41 (38,3 %), en position couchée et 73 (67,6 %) présentaient d'autres types de reflux distal. Le reflux proximal total était présent chez 56 (52 %) asthmatiques, le reflux proximal en position redressée, chez 55 (51 %) et le reflux proximal en position couchée chez 56 (52 %). En ce qui concerne la toux chronique, 70 patients (52,6 %) présentaient un reflux distal total, 59 (44,4 %), un reflux distal en position redressée, 45 (34,4 %) un reflux distal en position couchée et 75 (56 %), d'autres types de reflux distal. En présence de toux chronique, le reflux proximal total s'observait chez 70 patients (52 %), un reflux proximal en position redressée, chez 80 (60 %), un reflux proximal en position couchée, chez 59 (44 %). Les symptômes respiratoires et/ou digestifs (RGO) étaient absents au moment de la consultation chez environ 25% des patients qui souffraient d'asthme et de reflux et chez environ 50 % des patients qui souffraient de toux chronique et de reflux. Durant la surveillance ambulatoire du pH, les symptômes n'ont pas significativement différé selon que les patients souffraient ou non de reflux distal dans les groupes étudiés, à l'exception de brûlures d'estomac plus intenses chez les patients présentant à la fois toux chronique et reflux (RR 2.0).
**CONCLUSIONS :** Les données de la présente étude appuient l'observation selon laquelle le RGO est très répandu chez les patients qui souffrent d'asthme et de toux chronique. L'utilisation de paramètres de pH différents pour le dépistage du reflux acide durant une surveillance ambulatoire du pH sur 24 heures, comme la mesure de l'acidité œsophagienne proximale, devrait faire partie de l'interprétation normale de ce type de test. Il est essentiel de fixer un seuil bas pour le diagnostic du RGO chez les patients qui souffrent d'asthme ou de toux chronique puisque chez certains d'entre eux, les symptômes respiratoires et digestifs sont à peine perceptibles ou sont atypiques.

Both gastroesophageal reflux disease (GERD) and asthma are common medical problems. A population-based study (1) found that 20% of residents aged 25 to 74 years reported weekly reflux symptoms, and approximately 60% had experienced heartburn or regurgitation within the previous year. Likewise, asthma is also a common disease and its prevalence in the United States is approximately 20 million (2). The prevalence of GERD in patients with asthma is estimated to be 34% to 89% (3). Prevalence data vary across groups and may be dependent on whether acid reflux is defined by the presence of symptoms or by abnormal 24 h pH testing (4).

Cough is one of the most common symptoms for which patients seek medical attention from primary care physicians and respiratory physicians (5). It is estimated that approximately

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24,263,000 visits to medical services in the United States in 1991 involved chronic cough (6). Multiple studies (1,7,8) have shown that in approximately 95% of cases in immunocompetent patients, chronic cough results from postnasal drip syndrome (PNDS), asthma, GERD, chronic bronchitis due to cigarette smoking or other irritants, bronchiectasis, eosinophilic bronchitis or the use of an angiotensin-converting enzyme inhibitor. The vast majority of patients present with cough due to the first three conditions. The main objectives of the present study were to evaluate the prevalence of GERD, defined by abnormal pH studies, in patients referred to a tertiary centre with chronic cough or asthma in whom reflux was thought to be a potential complicating factor, and to assess the pattern of pH abnormalities (proximal versus distal and supine versus upright).

## PATIENTS AND METHODS

The charts of 358 consecutive patients referred for ambulatory gastroesophageal pH monitoring at the Lung Centre in Vancouver, British Columbia, between January 1995 and December 1998 were reviewed. Only patients who had been referred with a diagnosis of asthma or chronic cough (ie, cough lasting eight weeks or longer [5]) were reviewed. In addition to recording esophageal pH monitoring results, patient demographics (age, sex and body mass index [BMI]), symptoms (cough, heartburn, chest tightness and shortness of breath) before and during pH monitoring, smoking history, bronchodilators and/or antireflux medications were documented. The maintenance treatment for GERD was discontinued before patients underwent the pH monitoring study; patients were either taking proton pump inhibitors or hydrogen antagonists, but the proportion of patients taking each class of drug could not be determined. Data were collected systematically in all patients using a standardized questionnaire. In addition, postbronchodilation pulmonary function tests (forced expiratory volume in 1 s [$FEV_1$], forced vital capacity [FVC] and $FEV_1$/FVC ratio) were also documented.

### Ambulatory esophageal pH monitoring

Ambulatory esophageal pH monitoring was performed in all patients using a dual pH catheter, containing two antimony pH sensors (Synectics Medical, UK), which recorded the proximal and distal esophageal pH. The catheter was introduced via the nostril to the stomach while the patient sipped small amounts of water; the pH was monitored on a portable digital data recorder. A two-channel catheter was used, and the distal sensor was determined to have entered the stomach when the pH dropped below four. To establish the position of the lower esophageal sphincter, the patient was reclined to approximately 30 degrees, and the catheter was advanced and retracted three times to establish whether the pH had changed. The catheter was then retracted to place the distal sensor 5 cm and the proximal sensor 20 cm above the lower esophageal sphincter. The pH electrodes were connected to a portable digital data recorder (Digitrapper MKIII, Synectics Medical, United Kingdom).

Patients were sent home and instructed to keep a diary of their symptoms, meal times, supine and upright postures, and to activate an event marker button when they experienced the symptoms. They were allowed unrestricted daily activities and had to return the next day to have the catheter removed and the pH data downloaded to a computer for analysis using a software program (EsopHagram, GastroSOFT Ltd, USA). For both upright and supine periods, the analysis included the number of reflux events, the number of reflux events lasting longer than 5 min, the longest reflux in minutes, the total time in which the pH was less than four and the percentage of time in which the pH was less than four. Using the method of Ward et al (9), the beginning of an acid reflux event was defined by a fall in pH to less than four, and the end was defined by a rise in pH greater than five. Abnormal distal reflux was defined as having a pH less than four for 8.5% of the time or more when upright (10,11), and 3.5% of the time or more while supine (10,11), or 4.4% of the total time (9,12) or more.

Abnormal proximal reflux was defined as a pH less than four for 1% of the time or more while upright, more than 0% of the time while supine or more than 1% of the total time (13). Other abnormal distal reflux parameters were defined as those above the 95th percentile of normal physiological values (ie, more than 51 total reflux episodes, more than four total reflux episodes lasting longer than 5 min or longer than 5.6 min and 16.8 min for longest supine and upright reflux events, respectively [9,12]). Results are presented mainly according to the percentage of time that the esophageal pH was less than four, because it is more predictive of reflux than other esophageal pH parameters (10). Using an event marker, cough episodes were also recorded, which are thought to be acid-induced if they occurred simultaneously with an acid reflux episode or no longer than 5 min after an acid reflux episode (pH less than four) (9).

### Statistical analysis

Simple descriptive statistics were used to compare both groups. SPSS version 9.0 (SPSS Inc, USA) was used for the comparisons.

## RESULTS

### Patient population

Of the 358 patients, 108 (30%) had asthma, 134 (37%) had chronic cough and 118 (33%) were excluded because they had reflux symptoms only, atypical chest symptoms, recurrent chest infections, bronchiectasis, chronic obstructive pulmonary disease, interstitial lung disease or a lung transplant assessment. Of the 242 patients included in the analysis, 158 (65.3%) were women with a mean age of 53±15.3 years (range 15 to 91 years) and a mean BMI of 28.03 kg/m$^2$ (range 10.9 kg/m$^2$ to 56.4 kg/m$^2$). The mean duration of symptoms was 62.4±72 months (range one to 360 months). Thirty six per cent of the patients were current smokers, 34% had smoked in the past and the remainder had never smoked. Bronchodilators were used in 90% of patients and antireflux medications in 82.2% of patients.

### Patterns of reflux

There were no significant differences in patient characteristics between asthma patients with versus without abnormal total distal reflux: the mean age was 52.16±14.06 years versus 50.71±17.7 years (P=0.64), sex distribution comprising 22 of 34 men versus 47 of 73 women (P=0.97), mean BMI was 29.5±8.1 kg/m$^2$ versus 25.7±5.7 kg/m$^2$ (P=0.08), mean postbronchodilator $FEV_1$ was 87.3±24.3% versus 83.23±26.13% (P=0.61) and mean postbronchodilator $FEV_1$/FVC ratio was 73±12.2 versus 73.23±14.6 (P=0.96). In contrast, patients with chronic cough and distal total reflux versus those without reflux had statistically significant differences: mean age was 57.93±14.4 years versus 49.6±14.7 years (P=0.0009), there was no statistically significant difference in sex distribution comprising 29 of 46 men versus 44 of 93 women (P=0.08), mean BMI was 28.5±6.1 kg/m$^2$ versus 27.13±6.2 kg/m$^2$ (P=0.38), mean postbronchodilator $FEV_1$ was 101.1±24.1% versus 93.5±20.8% (P=0.26) and mean postbronchodilator $FEV_1$/FVC ratio was 76.9±8.5 versus 80.1±8.1 (P=0.2). Analysis of the above factors

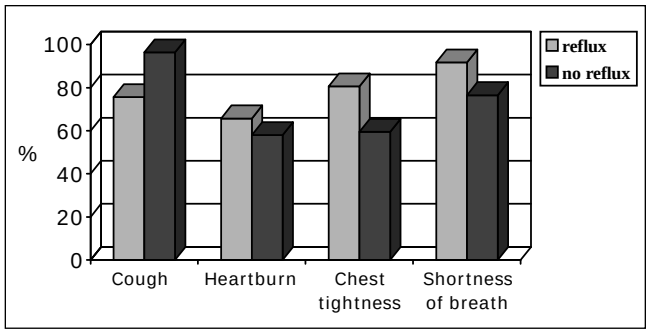


**Figure 1)** *Percentage of asthma patients with and without distal total reflux presenting with symptoms of cough, heartburn, chest tightness and shortness of breath. Chest tightness is significant at P=0.02*

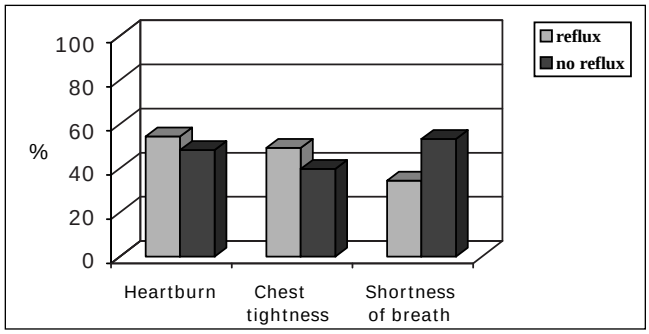


**Figure 2)** *Percentage of chronic cough patients with and without total distal reflux presenting with symptoms of heart burn, chest tightness and shortness of breath. P value is not statistically significant*

using other distal pH parameters showed consistent results in both groups of patients (data not shown). A history of sinusitis was reported in 36 of 108 (33.3%) and in 22 of 134 (16.4%) patients with asthma and chronic cough, respectively. PNDS was reported in 46 of 108 (42.6%) and in 49 of 134 (36.6%) patients with asthma and chronic cough, respectively.

Reflux episodes identified reflux events as the percentage of time where the pH was less than four. For asthma patients, 70 (64.8%) had distal total reflux, 50 (46.3%) had distal upright reflux, 41 (38.3%) had distal supine reflux and 73 (67.6%) had other distal refluxes. In asthmatic patients, proximal total reflux was present in 56 (52%), proximal upright reflux in 55 (51%) and proximal supine reflux in 56 (52%) patients. For chronic cough patients, 70 (52.6%) had distal total reflux, 59 (44.4%) had distal upright reflux, 45 (34.4%) had distal supine reflux and 75 (56%) had other distal refluxes. In chronic cough patients, proximal total reflux was present in 70 (52%), proximal upright reflux in 80 (60%) and proximal supine reflux in 59 (44%).

**Presenting symptoms**

There was more chest tightness (P=0.02) in patients with asthma and abnormal total distal reflux than in those without reflux, but there was no statistically significant difference in the presence of heartburn (P=0.43) or shortness of breath (P=0.13) in these patients than in those without reflux (Figure 1). Patients with chronic cough and total distal reflux had similar episodes of heartburn (P=0.49), chest tightness (P=0.28), and shortness of breath (P=0.12) than in those without abnormal reflux (Figure 2).

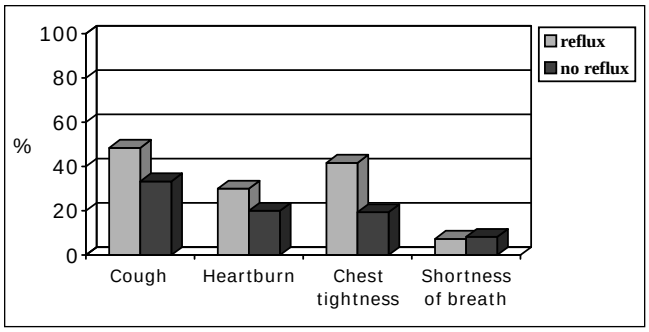


**Figure 3)** *Percentage of asthma patients with and without distal total reflux having symptoms of cough, heartburn, chest tightness and shortness of breath during esophageal pH monitoring. P value is not statistically significant*

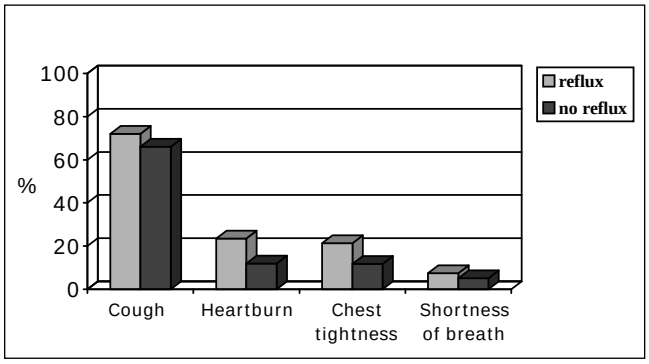


**Figure 4)** *Percentage of chronic cough patients with and without distal total reflux having symptoms of cough, heartburn, chest tightness and shortness of breath during esophageal pH monitoring. P value is not statistically significant*

**Symptoms during esophageal pH monitoring**

Patients with asthma and distal total reflux had no significant differences in cough (P=0.14), heartburn (P=0.28), chest tightness (P=0.27) or shortness of breath (P=0.86) compared with those without reflux (Figure 3). Patients with chronic cough and distal total reflux similarly had no significant differences in chest tightness (P=0.34) or shortness of breath (P=0.6) compared with those without reflux; however, they had more significant heartburn in the supine (P=0.018) and upright (P=0.03) parameters, but not in the total (P=0.089) esophageal pH parameters (Figure 4).

**Reflux-induced cough episodes**

The cough episodes that occurred simultaneously with an acid reflux episode or no longer than 5 min after an acid reflux episode (ie, reflux-induced cough episodes) were present in 20 of 44 (45.5%) patients with asthma and 48 of 88 (54.5%) patients with chronic cough. Cough episodes that occurred more than 5 min after acid reflux were present in 12 of 44 (27.3%) patients with asthma and 18 of 88 (20.5%) patients with chronic cough. Incomplete recording of data was found in 12 of 44 (27.3%) patients with asthma and 22 of 88 (25%) patients with chronic cough.

## DISCUSSION

It is currently accepted that ambulatory esophageal pH monitoring is the 'gold standard' for the diagnosis of GERD. There is compelling evidence that GERD plays an important role in many patients with asthma (4,5). Several mechanisms have

**TABLE 1**
**Percentages of distal reflux in patients with asthma and chronic cough**

| Distal reflux events | Asthma (%) | Chronic cough (%) |
|---|---|---|
| More than 51 reflux episodes | 76.0 | 66.0 |
| More than four total reflux episodes lasting longer than 5 min | 24.0 | 20.3 |
| Longest reflux episode | | |
| Supine: longer than 5.6 min | 41.0 | 36.0 |
| Upright: longer than 16.8 min | 14.8 | 16.5 |

been implicated in identifying the relationship between GERD and asthma, although these are not completely understood. These include vagally mediated reflex triggered by acid in the esophagus (14), heightened bronchial reactivity (15) and microaspiration of gastric acid, resulting in bronchoconstriction (16). However, studies (17,18) establish that reflux into the tracheobronchial tree occurs more commonly in asthmatics than nonasthmatics, but this does not necessarily establish a cause-and-effect relationship. Thus, to identify patients as having GERD-induced worsening of asthma symptoms, antireflux therapy, either medical or surgical, should improve asthma symptoms in many of these patients (18). Several studies (4,19) have shown that aggressive antireflux therapy in such patients results in improvements in asthma outcome in as many as 70% to 80% of patients treated, but design flaws have been identified in many of these studies. In addition, improvement in asthma symptoms has not always been accompanied by an improvement in pulmonary function, despite successful treatment of GERD (19,20). In contrast, a more recent study (21) has shown benefits in reducing exacerbations in asthma patients who were randomly assigned to lansoprazole versus placebo. In patients who fail medical therapy, surgery has been shown to be a successful option (22).

Similarly, GERD and chronic cough have been linked in a cause-and-effect relationship (8,18). Multiple studies (8,18,23,24) have showed that chronic cough may be caused by GERD in 6% to 41.1% of patients. Of interest is the recent publication (25) of a systematic review of proton pump inhibitor therapy in reflux-related cough, which always shows a consistent therapeutic response. This argues for the need to objectively determine reflux, using pH monitoring, as a cause of the cough, as opposed to a trial of therapy.

In the present study, at least some significant distal reflux was present in 67.7% of patients with asthma and 56% of patients with chronic cough. Although these prevalence rates are within the percentage ranges of the studies mentioned above, the trend is toward the higher end of the spectrum, particularly for patients with chronic cough. There are several factors that could account for these findings. First, most of our population were patients with long-standing and difficult-to-control symptoms, who were referred to our tertiary care centre after the standard workup by their usual physicians. This may cause a selection bias for a relatively higher risk group than the general population of patients with asthma and chronic cough. Second, our patients had no dietary restrictions during their 24 h pH monitoring. Rigid restrictions are thought, by some experts in the field, to lead to serious underestimations of the amount of reflux than when patients are under no dietary restrictions (17,26). Third, the prevalence rates of GERD were even higher (ie, 76% in asthmatic patients and 66% in patients with chronic cough) when abnormal reflux was defined on the basis of reflux events exceeding 51 episodes (Table 1). This highlights the importance of reviewing the pH tracing for short reflux episodes that could precipitate symptoms in patients with normal amounts of total acid exposure (27). Fourth, the relatively high mean BMI (which was greater than 25 kg/m$^2$, showing the presence of obesity, particularly in those with GERD), indicates the higher propensity for persons with large body habitus to develop more acid reflux. The use of bronchodilators may have been a confounding factor, but not all studies (28-30) have shown a consistent effect in facilitating GERD by bronchodilators, depending on the agent and population studied.

Regarding the patterns of GERD, both asthma and chronic cough patients had a high prevalence of reflux in the proximal esophagus (up to 60%), which sometimes exceeded that of the distal esophagus in the upright and/or supine positions. Schnatz et al (31) also illustrated this important observation by showing that 67% of patients with chronic cough or asthma who presented with pulmonary symptoms had abnormal proximal acid exposure. This meant that some patients with GERD would have been missed if proximal pH electrode analysis had not been recorded (28). These results would tend to support the concept that microaspiration caused by proximal acid exposure is an important mechanism, if not as important as the 'reflex bronchospasm' mechanism by which asthma and cough are produced by GERD (31,32). It should also be noted that a much smaller amount of acid exposure is needed proximally than distally to reach an abnormal level (31). The observation that reflux occurred predominantly in the upright position has been shown in previous studies (32,33) and implies that most of our patients have normal reflex preservation that suppresses transient lower esophageal sphincter relaxation in the supine posture (34).

Although the majority (greater than 75%) of asthmatic patients with GERD had more pulmonary symptoms than those without reflux, approximately only 60% of those with reflux had heartburn. Overall, the prevalence of symptoms was even lower (less than 50%) in patients with chronic cough. Review of the literature across the spectrum of presentations support the observation that many of the patients presenting with respiratory symptoms of GERD do not have classic symptoms of heartburn or acid regurgitation (35). Classic reflux symptoms are absent in 40% to 60% of asthmatic patients, 57% to 94% of patients with ear, nose and/or throat complaints; and 43% to 75% of patients with chronic cough in whom GERD is suspected or is confirmed to be the cause of the symptoms (36,37). Thus, the treating physician should have a lower threshold for diagnosing GERD in patients with asthma or chronic cough, even when the patients present with no or atypical symptoms. The presence of PNDS and current smoking in 30% and 40% of the patients, respectively, may have played an additional role in causing GERD symptoms. Symptoms did not differ significantly in those with and without distal reflux in both study groups during pH monitoring, except that there was more significant heartburn in those with chronic cough and reflux (RR 2.0). It is more important to determine the temporal relationship between reflux and cough episodes (5). Studies (3,38) have suggested that cough episodes that occur simultaneously with an acid reflux episode or no longer than 5 min after an acid reflux episode (ie, reflux-induced coughs) are more frequently helpful than total esophageal acid contact times, which can be normal in some patients. The majority (greater than 50%) of our

patients with asthma or chronic cough had reflux-induced cough episodes. Although this suggests a strong association between reflux and cough, GERD can only be considered the cause of chronic cough when the cough is treated with specific therapy for reflux (18,38).

## CONCLUSION

The data of the present study support the observation that GERD has a high prevalence in patients with asthma or chronic cough. The absence of dietary restrictions during the 24 h pH monitoring makes the study more reflective of the 'real life' of these patients than other studies. Symptoms of reflux could be absent or atypical in some of these patients, particularly those with chronic cough. In addition, measuring pH parameters such as proximal esophageal acid exposure, number of reflux events and reflux-induced cough episodes can be of added benefit to other standard pH measurements. Overall, these results are consistent with a recent report (39) that showed a significant percentage of patients to have both reflux and chronic cough, with many having no overt reflux symptoms.

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