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The utility of oesophageal pH monitoring in diagnosing gastroesophageal reflux disease-related chronic cough

Użyteczność pH-metrii przełyku w diagnozowaniu przewlekłego kaszlu związanego z chorobą refluksową przełyku

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Abstract

Introduction: Chronic cough is a common medical complaint, which may deteriorate patients' quality of life and cause many complications. Gastroesophageal reflux disease (GERD) is one of the frequent reasons for chronic cough. Oesophageal pH monitoring is one of the diagnostic methods performed to confirm diagnosis of GERD-related cough.

The aim of the study was to analyse the utility of oesophageal pH monitoring in diagnosing GERD-related cough and to identify the most sensitive pH monitoring parameters for diagnosing GERD-related cough.

Material and methods: 24-hour oesophageal pH monitoring was performed in 204 patients suffering from chronic cough. The group consisted of 65% females and the median age was 59 years. An acid reflux episode was defined as a rapid drop in pH to a value below 4 for at least 12 seconds. The diagnosis of GERD was based on total fraction time of $pH < 4$, upright or supine fraction time of $pH < 4$, or DeMeester score. The diagnosis of GERD-related cough was made if cough episodes, marked by the patients, appeared within 2 minutes after the reflux. The association between reflux episode and appearance of cough was analysed using two parameters: symptom index ($SI \geq 50\%$) and/or symptom association probability ($SAP \geq 95\%$).

Results: Based on results of pH monitoring, 135 patients (135/204, 66%) were diagnosed with GERD. Among them, 117 patients (117/135, 87%) were diagnosed based on DeMeester score. Among patients with GERD, 61 patients met the criteria of GERD-related cough (61/135, 45%), i.e. 30% of the group as a whole. Thirty-six patients (36/61, 59%) were diagnosed based on SAP, 12 patients (20%) based on SI, and 13 (21%) based on both parameters. Spearman rank correlation coefficient for $SAP \geq 95\%$ and $SI \geq 50\%$ was 0.46 ($p < 0.05$).

Conclusions: Based on pH monitoring results, GERD was diagnosed twice as often as GERD-related cough. SAP index is more sensitive than SI for the diagnosis of GERD-related cough.

Key words: chronic cough, oesophageal pH monitoring, gastroesophageal reflux disease

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Streszczenie

Wstęp: Przewlekły kaszel jest częstą dolegliwością, która może pogarszać jakość życia chorych oraz wywoływać liczne powikłania. Jedną z częstych jego przyczyn jest choroba refluksowa przełyku (GERD). Do metod diagnostycznych stosowanych w celu potwierdzenia diagnozy kaszlu związanego z GERD należy pH-metria przełyku.

Celem badania była ocena przydatności pH-metrii przełyku oraz określenie, który z parametrów mierzonych w czasie jej wykonywania jest najczulszy w diagnostyce kaszlu związanego z GERD.

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Materiał i metody: U 204 chorych z przewlekłym kaszlem wykonano 24-godzinną pH-metrię przełyku. Kobiety stanowiły 65% pacjentów, a mediana wieku wyniosła 59 lat. Epizod kwaśnego refluksu rozpoznawano, gdy nagły spadek pH poniżej 4 trwał co najmniej 12 sekund. Rozpoznanie GERD opierało się na całkowitym czasie pH poniżej 4, czasie pH poniżej 4 w pozycji stojącej lub leżącej oraz wskaźniku DeMeester. Kaszel związany z GERD diagnozowano, jeżeli epizody kaszlu odnotowane przez pacjentów pojawiały się nie później niż 2 minuty po epizodzie refluksu. Związek pomiędzy epizodem refluksu i wystąpieniem kaszlu oceniono za pomocą następujących parametrów: *symptom index* (SI ≥ 50%) lub *symptom association probability* (SAP ≥ 95%).
Wyniki: Na podstawie wyników pH-metrii przełyku u 135 chorych (135/204, 66%) wysunięto podejrzenie GERD. U większości z nich (117/135, 87%) diagnozę postawiono na podstawie wskaźnika DeMeester. Wśród pacjentów z GERD 61 osób (61/135, 45%) spełniło kryteria kaszlu związanego z GERD, co stanowiło 30% wszystkich pacjentów. U 36 pacjentów (36/61, 59%) kaszel związany z GERD zdiagnozowano na podstawie parametru SAP, u 12 chorych (20%) na podstawie parametru SI, natomiast u 13 (21%) na podstawie obu parametrów. Współczynnik korelacji Spearmana dla SAP ≥ 95% i SI ≥ 50% wyniósł 0,46 ($p < 0,05$).
Wnioski: Na podstawie wyników pH-metrii GERD został zdiagnozowany 2-krotnie częściej niż kaszel związany z GERD. Parametr SAP jest bardziej czuły niż SI w diagnozowaniu kaszlu związanego z GERD.

Słowa kluczowe: przewlekły kaszel, pH-metria przełyku, choroba refluksowa przełyku

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Introduction

Chronic cough (lasting more than eight weeks) may affect up to 10% of the adult population aged between 20–48 years and may influence their quality of life [1–3]. Gastroesophageal reflux disease (GERD) is one of the most common reasons for chronic cough in non-smoking adult patients with a normal chest radiogram, accounting for as many as 40% of patients with chronic cough [4, 5]. Reflux of gastric contents to the oesophagus may be physiological, but if it causes troublesome symptoms (i.e. cough) or oesophageal lesions, it is pathological and is then defined as GERD. GERD -related cough may be diagnosed based on either successful empirical treatment or on results of oesophageal pH monitoring, either alone or combined with impedance monitoring [6–8]. Prolonged oesophageal pH monitoring is the gold standard for diagnosing gastroesophageal reflux disease as it enables measurement of oesophageal acid exposure and correlation of clinical symptoms (i.e. cough) with the observed reflux episodes [6, 9].

The aim of the study was to analyse the utility of pH oesophageal monitoring in diagnosing GERD-related cough and to identify the most sensitive pH monitoring parameters for diagnosing GERD-related cough.

Material and methods

The study included 204 patients who underwent pH monitoring because of chronic cough. They were diagnosed in the Department of Internal Medicine, Pneumonology, and Allergology of the Medical University of Warsaw between January 2006 and December 2012. Oesophageal pH monitoring was one of the few tests performed to diagnose cough aetiology. Active smokers were not included. Most patients were never smokers (72%), and the remaining 28% were ex-smokers. All patients with chronic cough had a chest radiograph. Patients with significant abnormalities in the chest radiograph were treated in accordance with the revealed pathology; in these patients pH monitoring was not performed. Patients with abnormal results of spirometry were also not included. Patients suspected of asthma or upper airway cough syndrome were managed adequately. pH monitoring was performed in patients with chronic cough of unknown aetiology despite thorough diagnostic work-up, with symptoms suggesting GERD, or in patients with chronic cough previously treated unsuccessfully. Treating with proton pump inhibitors or H_2 blockers was terminated at least seven days before pH monitoring. The median age of the patients was 59 years (range 20–84 years), and women accounted for 65% of the group. The study was approved by the Institutional Review Board.

In all patients oesophageal pH monitoring was performed using two antimony pH-electrodes. Electrodes were placed at the distal tip of a catheter and 18 cm above it. Oesophageal catheter was connected with a Digitrapper pH 400 recorder (Simline MU, Medtronic A/S; Denmark). The catheter was introduced transnasally and the distal probe was located about 5 cm above the lower oesophageal sphincter for 24 hours using the pH "step up" technique [9–12]. Patients were advised not to change their normal daily activity.

An acid reflux episode was defined as a rapid drop of pH < 4 for at least 12 seconds. This parameter was reported as a total and separately for upright and supine positions. GERD was diag-

nosed when the patient met at least one of the four criteria presented in Table 1. The DeMeester score includes and weighs six different parameters: the total percentage of time during which the pH < 4, the percentage of time with pH < 4 in the upright position, the percentage of time with pH < 4 in the supine position, the total number of reflux episodes, the total number of reflux episodes lasting longer than 5 minutes, and the duration of the longest reflux episode [10].

The patient was diagnosed with GERD-related cough if cough episodes marked by the patients on the recorder and noted down in the diary appeared less than two minutes after the reflux [13]. The single cough episodes or the first of peals of coughing were noted. The correlation between reflux episode and appearance of cough was shown by either symptom index (SI) or symptom association probability (SAP) [9, 13]. SI was defined as the percentage of reflux-related symptom episodes. SAP was a statistical evaluation of the distribution of cough and reflux episodes measured within two-minute periods. GERD-related cough was confirmed if SI ≥ 50% or SAP ≥ 95% [9, 13].

Table 1. Criteria for the diagnosis of non-physiological gastroesophageal reflux based on the results of oesophageal pH monitoring

Parameter	Value
DeMeester score*	> 14.72
Percentage of total fraction time of pH < 4	≥ 4.2%
Percentage of upright fraction time of pH < 4	≥ 6.3%
Percentage of supine fraction time of pH < 4	≥ 1.2%

*DeMeester score includes six parameters:
— total percentage of time with pH < 4,
— percentage of time with pH < 4 in the upright position,
— percentage of time with pH < 4 in the supine position,
— total number of reflux episodes,
— total number of reflux episodes lasting longer than 5 minutes,
— duration of the longest reflux episode.

Statistical analysis

Data are presented as median and range. Spearman rank correlation coefficient between SAP ≥ 95% and SI ≥ 50% was calculated. Statistical analysis of the pH monitoring results was performed with non-parametric Mann-Whitney test and chi-squared test, $p < 0.05$ being regarded as significant.

Results

Among 204 patients with chronic cough, 135 (66%) were diagnosed with GERD based on the results of pH monitoring. Sixty-two per cent of females and 73% of males were diagnosed with GERD. Most of these patients (117, 87%) met the criteria of GERD based on DeMeester score. The second most frequent parameter to diagnose GERD was total fraction time (of pH < 4) ≥ 4.2% (91, 67% patients). In 18 of 135 patients (13%) GERD was diagnosed despite a negative DeMeester score (Tab. 2). Among the patients with a negative DeMeester score, the most common parameter was the percentage of time with pH < 4 in the supine position (n = 12).

GERD was the cause of chronic cough in 61 patients (61/204, 30%) (Figure 1). The diagnosis was confirmed by either SAP ≥ 95% or SI ≥ 50%. GERD-related chronic cough was diagnosed in 36 (59%) patients based only on SAP ≥ 95% parameter, whereas only SI parameter not lower than 50% was reported in 12 (20%) patients. The remaining patients (13, 21%) met the criteria of the disease based on both parameters (Tab. 3). Spearman rank correlation coefficient for SAP ≥ 95% and SI ≥ 50% was 0.46 for $p < 0.05$.

The group of patients with GERD-related cough was slightly younger ($p = 0.05$) than the patients with GERD without cough, but they expressed gastroesophageal reflux more. Subjects with GERD-related chronic cough had a higher DeMeester score ($p = 0.005$), percentage of total ($p = 0.005$), upright ($p = 0.008$), and

Table 2. Distribution of pH monitoring results in patients diagnosed with GERD

	GERD	DeMeester Score > 14.72	Total fraction time when pH < 4.0 ≥ 4.2%	Upright fraction time when pH < 4.0 ≥ 6.3%	Supine fraction time when pH < 4.0 ≥ 1.2%
Females	83	71	55	54	17
Males	52	46	36	34	16
Total	135	117	91	88	33

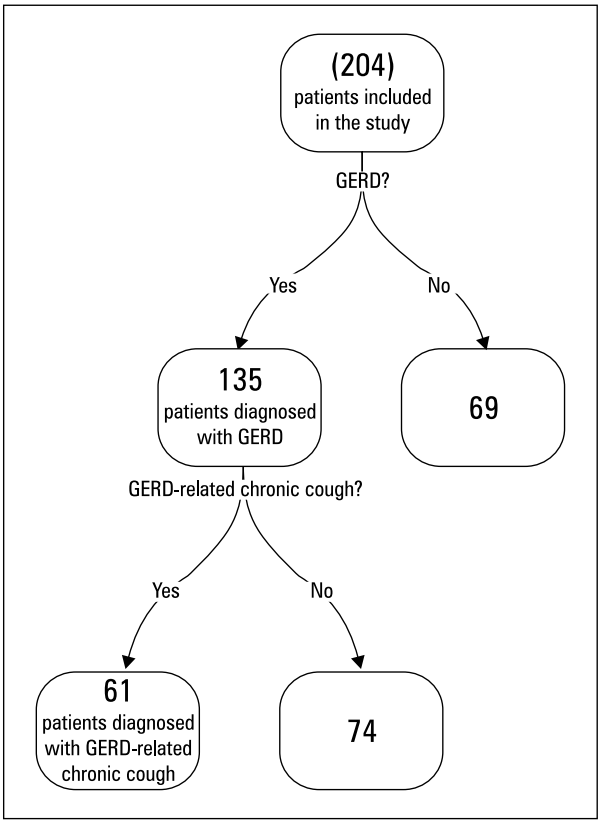

Figure 1. Flow chart presenting the results of pH monitoring

supine (p = 0.04) acid exposure times than subjects with GERD without cough. A comparison of patient characteristics and pH monitoring parameters between patients with GERD-related chronic cough and GERD alone is shown in Table 4.

Cough was the only symptom in 71% of patients included in the study while the remaining 29% of subjects complained not only of cough, but also of other symptoms, such as hoarseness, chest pain, dyspepsia, breathlessness, sore throat, or heartburn. Patients with cough as the only symptom did not differ from patients with cough and other symptoms as far as age, gender, diagnosis of GERD, or GERD-related cough were concerned.

Discussion

The results of our study show that pH monitoring is a useful method in diagnosing both GERD and GERD-related cough. GERD was diagnosed twice as often as GERD-related cough. Furthermore, reflux episodes were more expressed in patients with GERD-related cough than in patients with GERD not associated with cough.

Our results are comparable to other studies, in which GERD was diagnosed in about 50% of patients, while GERD-related cough was found in 20–35% patients who underwent pH monitoring [11, 14, 15].

There are few diagnostic parameters commonly used to assess the association of reflux episodes and symptoms of GERD: SI, SSI (symptom sensitivity index), and SAP. Firstly, they were created to assess typical GERD symptoms such as heartburn or regurgitations, but then they were also adapted for extra-oesophageal reflux manifestations such as cough, chest pain, or laryngitis. In this study, the most sensitive parameter in diagnosing GERD was DeMeester score, while SAP was the most sensitive for GERD-related cough. Similar results were found by Wunderlich et al., who found SAP to be the most sensitive measurement for temporal association of cough and GERD [15]. Higher SAP means better predicted response to anti-reflux therapy (decrease of cough) [14]. Although SAP is the most sensitive parameter in diagnosing GERD-related symptoms, it is not ideal as it does not discriminate enough to accurately predict the response to PPI (proton pump inhibitor) therapy [16].

According to these results, GERD was more expressed in patients with GERD-related cough than in patients with GERD but without cough. It is not a common observation, as pH-monitoring parameters do not correlate with the severity of patients' cough [6]. On the contrary, Lee et al. also noted a higher DeMeester score in patients with GERD-related cough than subjects with GERD only [17]. Recent studies emphasise the signifi-

Table 3. Distribution of pH monitoring parameters necessary to diagnose GERD-related cough

	GERD-related chronic cough	SAP ≥ 95% and SI ≥ 50%	Only SAP ≥ 95%	Only SI ≥ 50%
Females	35	6	21	8
Males	26	7	15	4
Total	61	13	36	12

SAP — symptom association probability; SI — symptom index

Table 4. Comparison of the patient characteristics and pH monitoring results in patients with GERD and GERD-related chronic cough

	Patients with GERD-related chronic cough (n = 61)	Patients with GERD, but not GERD-related chronic cough (n = 74)
Age (years) Median and range	53 (22–80)	61.5 (27–81)
Gender (females/males)	36/25	48/26
Number of patients with symptoms other than cough	13 (21%)	23 (31%)
DeMeester score Median Number of patients with score > 14.7	 30.7* 55 (90%)	 23.8* 62 (84%)
Total fraction time when pH < 4.0 Median Number of patients > 4.2%	 6.6* 45 (74%)	 5.0* 46 (62%)
Upright fraction time when pH < 4.0 Median Number of patients > 6.3%	 10.9* 41 (67%)	 7.6* 45 (61%)
Supine fraction time when pH < 4.0 Median Number of patients > 1.2%	 4.4* 53 (87%)	 3.0* 56 (76%)

Data are given as medians; *$p < 0.05$

cance of weakly acidic and alkaline reflux in the aetiology of chronic cough [8, 9].

Diagnosing the reasons for chronic cough is difficult as it requires a multidisciplinary approach. GERD is one of the most common reasons for cough, but its diagnosis is challenging [4, 5]. The easiest way to confirm the diagnosis of GERD-related cough is empirical treatment, which results in cough disappearance or decrease in cough severity [4]. Treatment of GERD includes modification of diet and therapy with PPI. Unfortunately, failure of such therapy is often observed [8]. A meta-analysis of treatment efficacy with PPIs in patients with cough due to GERD failed to confirm their effectiveness [18]. If an empirical therapy is unsuccessful, diagnostic tests such as pH monitoring or intraluminal impedance monitoring (IIM) are necessary. The advantages of pH oesophageal monitoring include its simplicity and availability. However, IIM is more sensitive as it allows us to recognise weakly acidic and alkaline reflux as a reason for chronic cough [8, 9, 19]. Combined pH and IIM monitoring is useful in diagnosing reflux refractory to any therapy [8].

GERD may result in some changes observed in the laryngeal mucosa (redness and oedema of the posterior part of the larynx). The presence of such changes found at laryngological examination or on videolaryngoscopy may also suggest GERD [20]. However, they are not specific for GERD and cannot be treated as a definite method of identifying GERD as the reason of cough [21].

There are some limitations to our study. Firstly, the specificity and diagnostic accuracy pH monitoring could not be assessed as no reference method for diagnosing GERD (such as IIM) had been simultaneously performed. We were unable to perform IMM as we did not have the appropriate equipment. Secondly, pH monitoring was performed during hospitalisation, which may have affected its results. Thirdly, the patients noted cough episodes subjectively, and no cough monitor was used (no cough monitor was available in our institution). Moreover, a lack of manometry resulted in placing electrodes by pH "step up" method, which can result in reflux episode overdiagnosis [22]. Despite these limitations, the results of the study confirm the usefulness of pH oesophageal monitoring in diagnosing GERD as a reason for cough. It is worth mentioning that differentiation between GERD and GERD-related cough is important. Diagnosing GERD-related cough implies the introduction of anti-reflux therapy, while diagnosing GERD in patients with chronic cough should imply further diagnostic procedures.

In conclusion, oesophageal pH monitoring is a sensitive method to diagnose both GERD and GERD-related cough in patients with chronic cough. GERD was diagnosed twice as often as GERD-related cough. SAP index is more sensitive than SI for the diagnosis of GERD-related cough.

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Conflict of interest

The authors declare no conflict of interest.

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