

Thresholds of gastroesophageal reflux for diagnosis of esophageal reflux diseases

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Abstract

AIM: To establish the optimal thresholds of pH variation (pH fluctuations and reflux episodes) for separating physiological and pathological gastroesophageal reflux (GER), and to evaluate their significance for GER diagnosis.

METHODS: Twenty-four hour intraesophageal pH monitoring and endoscopy were performed in 400 patients with GER symptoms and in 100 healthy controls.

RESULTS: The percentages of the time with pH fluctuations in patients with and without esophagitis, and in healthy controls were, on average, 12.65%, 9.5% and 2.76% in 24 h, respectively, and the respective percentages of the time with reflux episodes in the same groups in 24 h were, on average, 3.12%, 2.04% and 0.18%, respectively. Using a receiver-operating-characteristic curve analysis, < 6.7% of the time with pH fluctuations and 0.1% of the time with reflux episodes were defined as the combined thresholds for physiological versus pathological reflux. The sensitivity of the combined thresholds for the detection of GER in patients with and without esophagitis was 96.7% and 90.0%, respectively, and the specificity for the diagnosis of patients with abnormal GER disease was 100%.

CONCLUSION: pH fluctuations and reflux episodes, when evaluated together, are more useful for classifying patients with GER; the combined thresholds yield higher diagnostic accuracy for assessing patients with GER disease.

Key words: Gastroesophageal reflux/diagnosis; Esophagitis/diagnosis; Hydrogen-ion concentration

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INTRODUCTION

Twenty-four hour intraesophageal pH monitoring is the technique of choice for measuring gastroesophageal reflux (GER)^[1-5]. Most studies have suggested a certain percentage of the recording time with pH below 4 to be set as a threshold of normality^[6,7]. In these studies, only episodes of pH changes > 2 units (e.g. from around pH 6 to 4) have been considered. However, reflux events that do not fulfill the above criteria have been ignored when evaluating the contributions of some pathogenic factors to the development of esophagitis. The aims of the present study were to establish the optimal thresholds for both reflux episode and pH fluctuations, and to assess their value in the diagnosis of GER disease.

MATERIALS AND METHODS

Materials

Four-hundred patients (280 men, 120 women) were enrolled in the study. All patients had experienced the GER symptoms of regurgitation, heartburn and/or chest pain for at least 1 year (Table 1). None of these patients had undergone previous upper gastrointestinal surgery and none had taken H₂-blockers or H-/K+ATPase (proton-pump) blockers during the 2 wk prior to endoscopy and pH-metry. The control group consisted of 100 (60 men, 40 women) healthy subjects aged 20-year-old to 72-year-old, with a mean age of 49-year-old. None of the controls had experienced any GER symptoms, such as chest pain, dysphagia and heartburn. A few subjects had experienced occasional regurgitation. This study was conducted in accordance with the Declaration of Helsinki and was approved by the participating hospitals.

Methods

Twenty-four hour esophageal pH monitoring was carried out in accordance with the method described elsewhere^[8,9]. Briefly, subjects were advised to take a standard meal of approximately 9199.5 KJ (2200 kcal) during 24 h intraesophageal pH monitoring. A glass pH electrode with an incorporated potassium chloride reference (In gold electrode, No 440) was introduced *via* the naso-esophageal route and positioned with the tip at 5 cm above the gastroesophageal junction that had been identified by the pH meter. The output from the pH probe was recorded on a solid-state recorder (Autroni-

Table 1 Anamnestic data and endoscopic findings

Parameter	Gastroesophageal reflux patients with esophagitis (n = 228)	Gastroesophageal reflux patients without esophagitis (n = 172)	Healthy controls (n = 100)
Age, yr	52 ± 18.3	46 ± 7.5	48 ± 9.4
Sex, male/female	158/70	122/50	60/40
Duration, yr	12.4 ± 3.2	8.1 ± 3.8	
GER symptoms, %	100	100	0
Smoker, %	54.3	44.2	35
Alcohol consumer, %	25	20.3	22
Hiatal hernia, %	18.4	11.0	2.0
Grade of esophagitis, %			
I - II	72.3	0	0
III - IV	27.7	0	0

Table 2 Reflux episodes and pH fluctuations in gastroesophageal reflux patients ($\bar{x} \pm s$)

Group	pH fluctuations			Reflux episodes		
	n	Duration, min	Time, % 24 h	n	Duration, min	Time, % 24 h
Gastroesophageal reflux patients with Esophagitis						
Total	67 ± 46	191.7 ± 118.9	12.7 ± 6.5 ^b	22 ± 31	45.4 ± 110.6	3.1 ± 7.5 ^b
Day	55 ± 34	124.0 ± 97.5	8.2 ± 4.6 ^b	15 ± 13	19.1 ± 58.7	1.3 ± 2.7 ^b
Night	12 ± 8	50.1 ± 35.4	3.3 ± 4.5 ^b	7 ± 10	22.8 ± 64.7	1.5 ± 4.8 ^b
GER patients without Esophagitis						
Total	50 ± 18	130.4 ± 57.5	9.5 ± 2.8 ^b	14 ± 14	27.4 ± 68.3	2.0 ± 5.0 ^b
Day	41 ± 14	94.0 ± 35.7	6.8 ± 3.5 ^b	11 ± 7	18.8 ± 45.2	1.4 ± 12.9 ^b
Night	9 ± 8	36.3 ± 26.4	2.6 ± 3.1 ^b	3 ± 6	8.6 ± 24.7	0.6 ± 2.2 ^b
Healthy controls						
Total	23 ± 16	41.3 ± 30.7	2.7 ± 2.0	3 ± 3	3.0 ± 5.7	0.2 ± 0.4
Day	20 ± 11	37.3 ± 24.1	2.5 ± 1.9	2 ± 2	2.0 ± 2.4	0.1 ± 0.2
Night	3 ± 5	4.1 ± 3.9	0.3 ± 0.4	1 ± 1	1.0 ± 2.1	0.1 ± 0.1

^bP < 0.01 vs healthy controls.

Table 3 Correlations between the percentages of the time with pH fluctuations/reflux episodes and the total duration and numbers of episodes

Group	Total duration		Total number	
	r	P	r	P
Gastroesophageal reflux patients with esophagitis				
Time (%) with pH fluctuations	0.92	< 0.01	0.53	< 0.01
Time (%) with reflux episodes	0.67	< 0.01	0.65	< 0.01
GER patients without esophagitis				
Time (%) with pH fluctuations	0.88	< 0.01	0.29	> 0.05
Time (%) with reflux episodes	0.42	< 0.05	0.45	< 0.01
Controls				
Time (%) with pH fluctuations	0.98	< 0.01	0.82	< 0.01
Time (%) with reflux episodes	0.62	< 0.01	0.46	< 0.05

^{*}Total duration: Duration of pH fluctuations + duration of reflux episodes; Total numbers: Numbers of pH fluctuations + numbers of reflux episodes.

cord CM 18), which the patients carried on a belt. Data were electronically analyzed by means of a self-designed computer program. The parameters recorded included the frequency and duration of the 24 h reflux episodes and pH fluctuations. The pH fluctuation was defined as a decrease from pH < 4 to pH 2 lasting more than 20 s, and the reflux episode was a decrease in pH < 2 lasting more than 20 s. All study subjects underwent upper gastrointestinal endoscopy during the week before pH-metry. Esophagitis was graded from I to IV according to Savary and Miller^[10]. Only a few patients presented with grades II and III, and therefore all patients were grouped as I and II or III and IV, respectively.

Statistical analysis

The Wilcoxon rank sum test was used to compare the percentages of the time with both types of pH variations (pH fluctuations and reflux episodes) for the three groups (*i.e.* I and II, III and IV, healthy controls). Spearman's rank correlation was used to analyze the relationships between total recording time and pH < 4 and the time (%) with both types of pH variations. Differences between GER patients with/without esophagitis and healthy controls in the distribution of pH fluctuations and reflux episodes were analyzed by means of the chi-square test. Using receiver operating characteristic (ROC) curves^[11,12], the optimal threshold values were identified for each parameter and combined parameters (pH fluctuations and reflux episodes). For these thresholds, the percentages of true-positive decisions (sensitivity) and false-positive decisions (100% minus specificity) were calculated and charted. The more the line curved towards the point of 100% true positivity and 0% false-positivity,

the better the diagnostic value of the test; therefore, lowering of the threshold decreased sensitivity but increased specificity, and vice versa.

RESULTS

Anamnestic data and endoscopic findings are presented in Table 1. Table 2 shows the frequency, duration and percentage of the time with pH fluctuations and reflux episodes in GER patients with and without esophagitis and in healthy controls. The percentages of the time with pH fluctuations in GER patients with and without esophagitis and in healthy controls were, on average, 12.7%, 9.5% and 2.7%, respectively, while percentages of the time with reflux episodes in the same groups were, on average, 3.1%, 2.0% and 0.2%, respectively. Both patients with and without esophagitis showed statistically significant differences compared to the healthy controls (*P* < 0.01). There was no significant difference between the patients with esophagitis and those without esophagitis for comparison of percentage of the time with pH fluctuations/reflux episodes; total duration and frequency of episodes are listed in Table 3.

The distribution of the duration and frequency of pH fluctuations and reflux episodes in GER patients with and without esophagitis and in healthy controls is shown in Figure 1. The duration of pH fluctuations in GER patients with and without esophagitis and in healthy controls was 80.8%, 82.6% and 93.2%, respectively, whereas the duration of reflux episodes in the same groups was 19.2%, 18.4% and 6.8%, respectively. There was a significant difference between the patients with/without esophagitis, and healthy controls (Figure

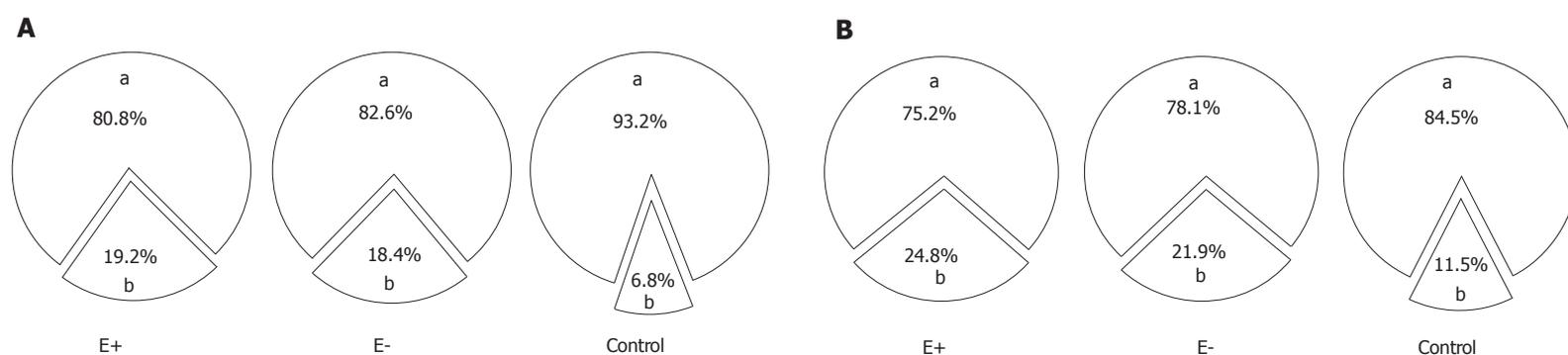


Figure 1 Distribution of the duration (A) and frequency (B) of pH fluctuations (a) and reflux episodes (b) in gastroesophageal reflux patients with (E+) and without (E-) esophagitis and in healthy controls.

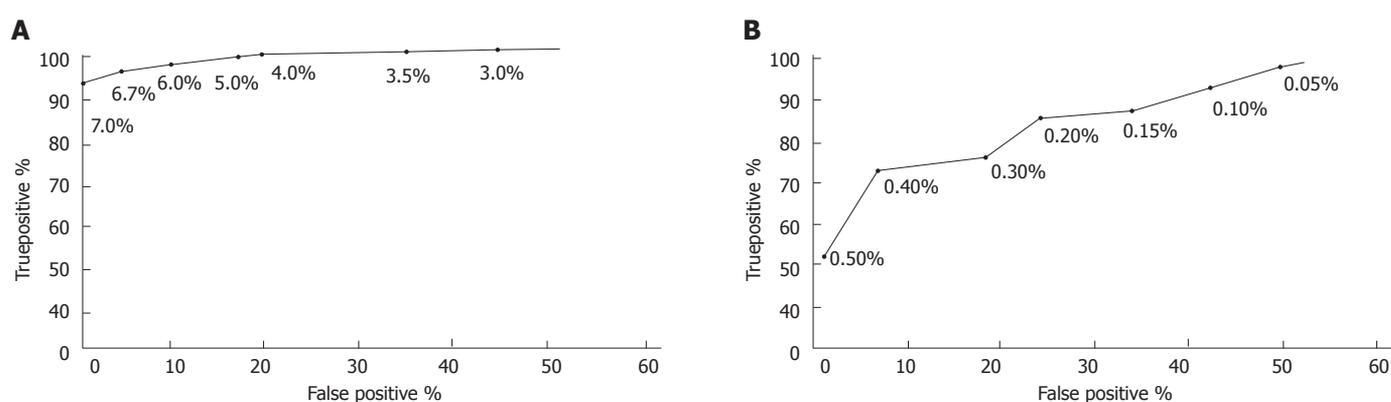


Figure 2 Receiver operating characteristic curve analysis for thresholds of pH fluctuations (A) and reflux episodes (B). The true- and false-positive rates for thresholds of pH fluctuations (A) and reflux episodes (B) are shown.

Table 4 Sensitivity and specificity of pH fluctuations and reflux episodes for the diagnosis of abnormal gastroesophageal reflux

Threshold, %	Sensitivity, %		Specificity, %
	gastroesophageal reflux patients with esophagitis	gastroesophageal reflux patients without esophagitis	
pH fluctuations < 6.7	93.7	93.3	97.7
Reflux episodes < 0.1	96.7	90.0	45.2
Combination	96.7	90.0	100

*Combination: pH fluctuation < 6.7% + reflux episode < 0.1%.

1A, $P < 0.01$). The frequencies of pH fluctuations and reflux episodes in the three groups are shown in Figure 1A. The difference between the patients with/without esophagitis and healthy controls was notable ($P < 0.01$).

Figure 2 shows the true- and false-positive rates for different thresholds of pH fluctuations and reflux episodes by means of ROC curve analysis. As shown in Table 4, if only < 0.1% of reflux episodes was used as the threshold, the sensitivity for diagnosis of abnormal GER was 96.7% in GER patients with esophagitis and 90.0% in GER patients without esophagitis, but the specificity was only 45.2%. Similarly, when < 6.7% of pH fluctuations was used as the threshold to define pathological reflux, the sensitivity was 93.7% in GER patients with esophagitis and 93.3% in GER patients without esophagitis; the specificity for diagnosing abnormal GER was 97.7%. When < 6.7% of pH fluctuations for 24 h was combined with < 0.1% of reflux episodes for 24 h as the combined thresholds to define pathological reflux, the sensitivity for diagnosing GER patients with and without esophagitis was 96.7% and 90.0%, respectively, and the specificity for the patients with GER disease increased to 100%.

DISCUSSION

Over the past few years, 24 h intraesophageal pH monitoring has been increasingly used to investigate suspected GER patients. Until now, though, thresholds for the detection of pathological GER have not been standardized. Having defined < 4.2% of time with pH < 4 during 24 h as a threshold between physiological and pathological GER, DeMeester *et al.*^[13] obtained a sensitivity for the detection

of acid reflux of 90.3% and a specificity for excluding acid reflux of 90%. The thresholds defined by Schindlbeck *et al.*^[14] were 10.5% of time with esophageal pH < 4 for the upright position and 6.0% for the supine position, and the sensitivity and specificity obtained were 93.3% and 92.9%, respectively.

The main problem is whether the sensitivity and specificity of 24 h intraesophageal pH monitoring for the diagnosis of abnormal GER can be further improved. It is evident that improving the sensitivity and specificity for the diagnosis of GER disease depends upon the ability to establish optimal thresholds between pathological and physiological reflux. The greater the difference between the patients with pathological reflux and the subjects with physiological reflux in distribution of the data, the better the sensitivity and specificity of the threshold. In our study, we found that reflux episodes, as characterized by a sudden, appreciable decrease in pH, accounted for 3.1%, 2.0% and 0.2 % of recording time, respectively, while in GER patients with and without esophagitis and in healthy controls, pH fluctuations, as characterized by smaller pH variations (*i.e.* ≤ 2 pH units below pH 4), accounted for 12.7%, 9.5% and 2.7% of recording time, respectively. There was a significant difference between GER patients with abnormal GER and healthy controls in percentages of time with reflux episodes and pH fluctuations. The pH fluctuations, in comparison with the reflux episodes, showed a better correlation with total duration of the pH fluctuations and reflux episodes. In addition, in the distribution of the duration and frequency of both types of pH variations, the rates of duration and frequency of reflux episodes in GER patients with and without esophagitis were significantly greater than in healthy controls, whereas the rates of duration and frequency of pH fluctuations were significantly smaller

than those in healthy controls. Thus, there may be a significant difference between patients with GER disease and healthy controls in the distribution of the pH fluctuation and reflux episode data. Thus, pH fluctuation and reflux episodes can be used to differentiate between pathological and physiological reflux.

Defining normal limits of the given data is important for establishing an optimal threshold to categorize pathological reflux. One approach is to take the mean value \pm 2 standard deviations of the control subjects. Analysis of the present data indicates that this method is not appropriate, as our data were not normally distributed. The means and standard deviations were created to describe normally distributed data. Another way to define normal limits is the ROC curve analysis. The ROC curve is not dependent on normal distribution. Using ROC curve analysis, we selected < 6.7% of pH fluctuations and < 0.1% of reflux episodes as the cut-off points between physiological and pathological reflux; thus, if both values were above the thresholds, the GER was defined as pathological. The results indicated that the combined thresholds of pH fluctuations and reflux episodes yield higher diagnostic accuracy in the evaluation of GER disease than when a single threshold is used; additionally, our results appear to be better in terms of both sensitivity and specificity than those obtained by other investigators^[13,14].

In conclusion, pH fluctuations and reflux episodes are two different kinds of esophageal pH variations. The use of both parameters, the thresholds of which are < 6.7% and < 0.1% of recording time, yields higher diagnostic accuracy in assessing patients with GER disease.

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