

## Reflux characteristics of 113 GERD patients with abnormal 24-h multichannel intraluminal impedance-pH tests

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**Abstract:** Objective: To analyze reflux parameters by means of combined multichannel intraluminal impedance and pH (MII-pH) monitoring in patients with gastroesophageal reflux disease (GERD) symptoms off medication, and to find the reflux characteristics of Chinese GERD patients and the influences of gender, age, body posture, and body mass index (BMI) on gastroesophageal reflux (GER). Methods: Between Dec. 2008 and May 2014, 125 patients with typical GERD symptoms were subjected to 24-h MII-pH monitoring. Twelve patients with normal MII-pH profiles were not considered for analysis. The reflux parameters of 113 GERD patients with abnormal MII-pH results were analyzed. Results: (1) DeMeester scores were above the normal range in 46.90% (53/113) of GERD patients. Weakly acidic refluxes were prevalent in GERD patients, and the frequency of abnormal weakly acidic reflux was 75.22% (85/113). The frequencies of abnormal symptom index (SI) and symptom association probability (SAP) were 19.47% (22/113) and 14.16% (16/113), respectively. (2) The frequencies of DeMeester scores, the %time at pH<4, and the numbers of reflux episodes and of long reflux episodes >5 min were significantly higher in male patients than in female patients. (3) The %time at pH<4 was much higher during upright periods than during supine periods. During supine periods, 31.86% (36/113) of GERD patients had delayed bolus clearance time, compared with 19.47% (22/113) during upright periods. (4) The number of abnormal DeMeester scores, %time at pH<4, and the number of acid refluxes during upright periods were significantly higher in obese GERD patients than in GERD patients with a normal BMI. Overweight GERD patients also had many more acid refluxes during upright periods than GERD patients with a normal BMI. Conclusions: Weakly acidic refluxes were prevalent in Chinese GERD patients. The factors male, gender, upright position, obesity (BMI≥25), but not age, may increase the frequency and severity of GER.

**Key words:** Gastroesophageal reflux disease (GERD), Multichannel intraluminal impedance-pH (MII-pH), Reflux characteristics, Off medication

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### 1 Introduction

Gastroesophageal reflux disease (GERD) is one of the most common digestive diseases, with a high prevalence and a variety of clinical symptoms and complications. The incidence of GERD has been increasing in China recently. At present, proton pump inhibitors (PPIs) are the first-line medication for the treatment of GERD. However, this treatment may not be suitable for some symptoms of GERD patients,

and it has uncertain effect in preventing Barrett's esophagus (BE), intestinal metaplasia (IM) and adenocarcinoma (American Gastroenterological Association, 2011; Fitzgerald *et al.*, 2014). GERD patients with different symptoms may have different reflux profiles and should be given different treatments. For example, weakly acidic refluxes are more frequent than acid refluxes in patients with atypical symptoms of GERD, whereas acid refluxes still represent the most common phenomenon in GERD patients with typical symptoms (Grossi *et al.*, 2013).

Combined multichannel intraluminal impedance and pH (MII-pH) monitoring is considered the most sensitive tool for gastroesophageal reflux (GER)

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assessment in GERD patients as it can detect all types of reflux (gas, liquid, acid, weakly acidic and weakly alkaline reflux).

Our aim was to analyze reflux parameters by means of MII-pH monitoring in patients with typical GERD symptoms off medication, to find the reflux characteristics of Chinese GERD patients, and to determine the influences of gender, age, body posture, and body mass index (BMI) on GER.

## 2 Subjects and methods

### 2.1 Subjects

Inclusion criteria: GERD patients with typical symptoms (heartburn and/or reflux) lasting for more than three months and age  $\geq 20$  years. Patients were asked to discontinue any medication that would influence esophageal motor function or gastric fluid acidity at least seven days before performing MII-pH monitoring.

Exclusion criteria: history of thoracic, esophageal or gastric surgery, or underlying psychiatric illness.

### 2.2 MII-pH monitoring

MII-pH monitoring was performed using an MII-pH monitoring system (MMS, Enschede, the Netherlands), with a data logger and a combined impedance-pH catheter, which has one pH electrode and six impedance electrodes. After calibration, the impedance-pH catheter was inserted trans-nasally into the esophagus until the lower tip reached the gastric cavity. Then, the catheter was adopted and fixed, allowing monitoring of changes in intraluminal pH at 5 and impedance at 3, 5, 7, 9, 15, and 17 cm above the lower esophageal sphincter. Subjects were discharged and asked to maintain normal activities and sleep schedules, to eat their usual meals at their normal time, and to record symptoms, meal time, and posture changes. Impedance and pH data were collected on a compact flash card for 24 h, then downloaded onto a computer and analyzed using a dedicated software program. The definitions of reflux episodes are shown in Table 1.

**Table 1** Definitions of reflux episodes

Reflux episode	Definition
Acid reflux	Reflux with nadir pH<4
Weakly acidic reflux	Reflux with nadir $4 \leq \text{pH} < 7$
Weakly alkaline reflux	Reflux with nadir pH $\geq 7$

Twenty-four-hour MII-pH monitoring results were defined as abnormal when either the DeMeester score, acid reflux, weakly acidic reflux, weakly alkaline reflux, symptom index (SI), or symptom association probability (SAP) was above the upper normal limit. The normal values of the MMS MII-pH system were reported by Zerbib *et al.* (2005).

### 2.3 Statistical analysis

Data are presented as mean $\pm$ standard error or median and interquartile range (M (IQR)). Differences between groups were compared using the Chi-square or Mann-Whitney test depending on the data, and considered to be significantly different when *P* values were  $< 0.05$ .

## 3 Results

### 3.1 Demographic data

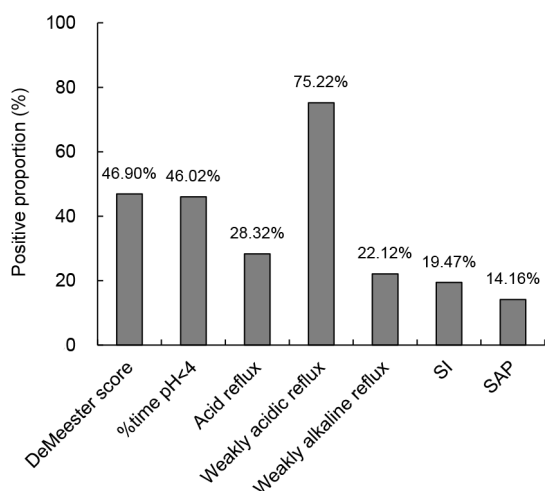
Between Dec. 2008 and May 2014, 125 patients with typical GERD symptoms were subjected to 24-h MII-pH monitoring. Twelve patients with normal MII-pH profiles were not considered for analysis. Abnormal results were found in 90.4% (113/125) of patients. The demographic data of the 113 GERD patients are shown in Table 2.

**Table 2** Demographic data of the 113 GERD patients

Parameter	Number
Gender (male/female)	48/65
Age distribution	
Group A (20–39 years)	14
Group B (40–49 years)	31
Group C (50–59 years)	41
Group D ( $\geq 60$ years)	27
BMI distribution	
Lean body mass (BMI<18.5)	13
Normal ( $18.5 \leq \text{BMI} < 22.9$ )	45
Overweight ( $23.0 \leq \text{BMI} < 24.9$ )	24
Obesity (BMI $\geq 25.0$ )	21

The patients aged (52.69 $\pm$ 12.73) years (range 21–93 years)

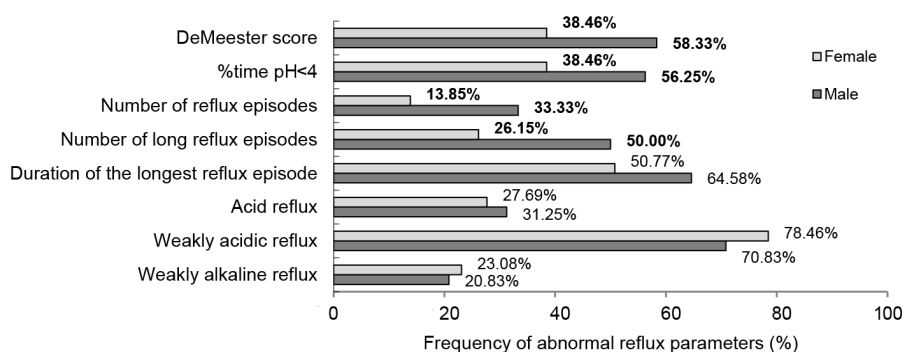
DeMeester scores were above the normal range in 46.90% (53/113) of GERD patients (Fig. 1). Weakly acidic refluxes were prevalent in GERD patients. The frequency of abnormal weakly acidic reflux was 75.22% (85/113), and frequencies of abnormal SI and SAP were 19.47% (22/113) and 14.16% (16/113), respectively.



**Fig. 1** Frequencies of abnormal results for reflux parameters in the 113 GERD patients

### 3.2 Influences of gender and age on GER

Patients were subgrouped according their genders. The frequencies of abnormal reflux parameters in male and female patients are reported in Fig. 2. The frequencies of abnormal DeMeester scores, %time at pH<4, number of reflux episodes, and number of long reflux episodes were significantly higher in male than in female patients (58.33% vs. 38.46%, 56.25% vs. 38.46%, 33.33% vs. 13.85%, and 50.00% vs. 38.46%, 50.77% vs. 27.69%, and 70.83% vs. 23.08%, and 78.46% vs. 20.83%,



**Fig. 2** Frequencies of abnormal reflux parameters in male and female GERD patients  
Frequencies associated with significant differences ( $P<0.05$ ) are shown in bold

**Table 3** Numbers or frequencies of abnormal reflux parameters during upright and supine periods in GERD patients

Period	%time at pH<4*	Frequency of abnormal reflux parameters (%)			
		Acid reflux	Weakly acidic reflux	Weakly alkaline reflux	Bolus clearance time*
Upright	3.8 (0.8, 13.05)	14.16	56.64	20.35	19.47
Supine	1.5 (0, 11.4)	22.12	64.60	10.62	31.86

Data for %time at pH<4 are presented as M (IQR) ( $n=113$ ), data of other parameters are presented as percentages of abnormal data.  
\*  $P<0.05$ , significant difference between upright and supine periods in GERD patients

respectively). The frequencies of abnormal acid refluxes, weakly acidic refluxes, and weakly alkaline refluxes were not significantly different between males and females.

The 113 GERD patients were subdivided into four groups according to their ages: Group A (20–39 years), Group B (40–49 years), Group C (50–59 years), and Group D ( $\geq 60$  years). There were no significant differences among the four age groups for reflux parameters.

### 3.3 Influence of body posture on GER

The %time at pH<4 was much higher during upright periods than during supine periods (Table 3). During supine periods, 31.86% (36/113) of GERD patients had delayed bolus clearance time, compared with 19.47% (22/113) during upright periods. Other reflux parameters showed no statistically significant differences in relation to body posture.

### 3.4 Influence of BMI on GER

Among 113 GERD patients, 103 patients had BMI information, and they were subgrouped into four groups according to their BMI values: 13 patients with lean body mass ( $BMI<18.5$ ), 45 patients with normal BMI ( $18.5\leq BMI<22.9$ ), 24 patients with overweight ( $23.0\leq BMI<24.9$ ), and 21 obese patients

**Table 4 Incidence of BMI on reflux parameters in GERD patients**

Group	DeMeester score	%time at pH<4	Acid reflux		Weakly acidic reflux		Weakly alkaline reflux	
			Up	Su	Up	Su	Up	Su
Lean body mass (n=13)	11.25 (8.68, 62.17)	2.80 (2.10, 20.50)	3.20 (0, 18.15)	1.00 (0, 9.85)	12.20 (3.05, 45.85)	2.10 (1.00, 7.80)	0 (0, 1.55)	0 (0, 0)
Normal (n=45)	6.66 (1.44, 34.93)	1.65 (0.30, 10.15)	5.80 (1.85, 18.23)	1.00 (0, 3.20)	17.55 (3.95, 55.23)	4.50 (0.75, 12.15)	1.00 (0, 4.33)	0 (0, 0)
Overweight (n=24)	14.32 (3.37, 35.77)	4.15 (0.83, 12.33)	14.70 (2.38, 32.98)*	2.10 (0, 3.18)	19.50 (8.58, 77.45)	5.25 (1.68, 19.33)	1.05 (0, 2.18)	0 (0, 0.75)
Obese (n=21)	50.57 (4.24, 83.24)*	11.50 (1.10, 26.25)*	10.60 (4.65, 26.05)*	2.10 (0.50, 4.75)	25.60 (12.05, 60.75)	2.10 (1.10, 12.05)	0 (0, 4.75)	0 (0, 0)

Data are presented as M (IQR). Up: during upright periods; Su: during supine periods. \*  $P < 0.05$  compared with the normal control

( $BMI \geq 25.0$ ). The numbers of DeMeester scores, %time at pH<4, and acid refluxes during upright periods were significantly higher in obese GERD patients than in those with a normal BMI (50.57 (4.24, 83.24) vs. 6.66 (1.44, 34.93), 11.50 (1.10, 26.25) vs. 1.65 (0.30, 10.15), and 10.60 (4.65, 26.05) vs. 5.80 (1.85, 18.23), respectively, as shown in Table 4). In addition, overweight GERD patients also had much more acid refluxes during upright periods than GERD patients with normal BMI (14.70 (2.38, 32.98) vs. 5.80 (1.85, 18.23)).

#### 4 Discussion

GERD is a digestive disease with a variety of troublesome reflux symptoms and/or complications, such as reflux esophagitis (RE), BE, and adenocarcinoma. The incidence of GERD has been increasing recently, in relation to the financial stress and poor quality of life of patients (Vakil, 2010). In Asian countries, the prevalence of GERD has been increasing because of changing dietary patterns, obesity, and other factors.

Several procedures are used to identify GER. The most widely used clinical procedures include: GERD-questionnaire (GERD-Q), endoscopy, pH monitoring, MII-pH monitoring, esophageal manometry, and the PPI test. Among them, MII-pH monitoring is currently considered the most sensitive tool for GER detection in GERD patients.

Wang *et al.* (2011) and Frazzoni *et al.* (2009) reported that combined MII-pH monitoring increased overall diagnostic yields. In this study, we evaluated reflux parameters by 24-h MII-pH monitoring in GERD patients off medication. Of 113 GERD patients confirmed by MII-pH monitoring, only 46.90% had abnormal DeMeester scores. Schindlbeck *et al.*

(1987) reported that the DeMeester score was not necessarily superior to the %time at pH<4 in discriminating GER. Our study confirmed this opinion: the %time at pH<4 and DeMeester scores were above the normal range in 46.02% and 46.90% of GERD patients, respectively, and there was no significant difference between these two parameters in discriminating GER. Frequencies of abnormal SI and SAP were very low in this study. The reason may be that although patients complained about troublesome symptoms in their daily life, they may not have had these symptoms when undergoing MII-pH monitoring.

Guidelines recommend PPIs as the first line of treatment for GERD patients (Katz *et al.*, 2013), but a considerable proportion of patients does not respond to PPIs (Clayton *et al.*, 2012; Vela, 2014). Clayton *et al.* (2012) showed that PPI treatment can transform acid refluxes into weakly acidic refluxes, but can not decrease the total number of reflux events. In this study, weakly acidic refluxes were prevalent in GERD patients off medication. The number of weakly acidic refluxes was above the normal range in 75.22% of GERD patients, whereas the frequencies of abnormal acid refluxes and weakly alkaline refluxes were 28.32% and 22.12%, respectively. The finding of weakly acidic reflux as the major type of reflux was different from the results of previous studies (Xiao *et al.*, 2009). The reason is unclear. In a weakly acidic environment bile reflux can impair esophageal mucosal integrity and provoke dilated intercellular spaces (Farre *et al.*, 2008). With MII-pH monitoring, it has been established that weakly acidic reflux also plays a role in the pathogenesis and natural history of GERD. Weakly acidic refluxes are more frequent than acid refluxes in patients with atypical symptoms of GERD (Grossi *et al.*, 2013). Weakly acidic refluxes may be more important for BE and non-erosive reflux disease (NERD) patients than separate acid

reflux (Wang *et al.*, 2011), and are the major cause of persistent symptoms in patients with NERD, who are being treated with PPIs (Hiroshi *et al.*, 2012). Studies of weakly acidic reflux and BE showed that weakly acidic refluxes were more prevalent in long-segment BE and short-segment BE patients than in RE and normal volunteers. Weakly acidic reflux may play a role in the pathogenesis of BE (Gutschow *et al.*, 2008) and persistent intestinal metaplasia after ablation in patients with BE (Krishnan *et al.*, 2012).

In our study, the frequencies of abnormal DeMeester scores, %time at pH<4, and numbers of reflux episodes were much higher in male than in female GERD patients. This means that the frequency and severity of symptoms were higher in male than in female patients. Although the incidence of GERD in the male and female populations was similar, the incidence of complications, such as RE, BE, and adenocarcinoma, was much higher in the male than in female population.

Aging is one of the risk factors for GERD and its complications (El-Serag *et al.*, 2009; Fitzgerald *et al.*, 2014). When GERD patients were subdivided into four groups according their ages, there were no significant differences among the four groups for reflux parameters. We confirmed that the severity of symptoms was not higher in older than in younger GERD patients. Age was not directly associated with GERD and its complications. Older patients were inclined to have a longer duration of GERD, and that may be a risk factor for GERD complications.

Guidelines for the treatment of GERD recommend raising the head of the bed to reduce symptoms in GERD patients with nocturnal reflux. This implies that a supine position could aggravate reflux. However, Frazzoni *et al.* (2009) reported that refluxes were more prevalent when patients were in an upright position than when they were in a supine position. We compared the reflux parameters during supine and upright periods. Although bolus clearance time was delayed during supine periods, the %time at pH<4 was much higher during upright than during supine periods. The reasons for this phenomenon are still unclear, but may be related to meals or activities during upright periods.

Obese GERD patients had higher DeMeester scores and %time at pH<4, and more acid refluxes than patients with a normal BMI. This confirmed that

a BMI of  $\geq 25$  was related to GER in Chinese GERD patients, especially those with acid refluxes.

The main limitation of this study was that it was retrospective. This may have reduced the accuracy of the information. Also, we could not obtain endoscopic and manometric information. However, since all patients included in our study had reflux symptoms and abnormal refluxes confirmed by MII-pH, we are sure that we enrolled only GERD patients.

In conclusion, weakly acidic refluxes were prevalent in Chinese GERD patients; the factors male gender, upright position, obesity (BMI $\geq 25$ ), but not age, may increase the frequency and severity of GER.

### Compliance with ethics guidelines

Yuan-yuan NIAN, Cheng FENG, Fu-chun JING, Xue-qin WANG, and Jun ZHANG declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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## 中文概要

**题目:** 24 小时食管多通道腔内阻抗-pH 监测阳性的 113 例胃食管反流病 (GERD) 患者的胃食管反流特点

**目的:** 通过分析多通道腔内阻抗-pH 监测 (MII-pH) 阳性的胃食管反流病 (GERD) 患者的各项反流指标, 探讨我国 GERD 患者的胃食管反流特点, 以及性别、年龄、体位和体质指数 (BMI) 对反流的影响。

**创新点:** 入组患者均经 MII-pH 监测证实具有客观存在的胃食管反流, 分析体位和 BMI 对反流的影响, 并且发现我国 GERD 患者普遍存在弱酸反流。

**方法:** 有典型反流症状的疑诊 GERD 患者, 进行 24 h MII-pH 监测, 对监测结果阳性的患者纳入研究对象, 分析其各反流指标以及性别、年龄、体位和 BMI 对反流的影响。

**结论:** 我国 GERD 患者普遍存在弱酸反流, 男性、直立体位、肥胖 (BMI $\geq$ 25) 可促进胃食管反流的发生, 且年龄不是胃食管反流的危险因素。

**关键词:** 胃食管反流病 (GERD); 多通道腔内阻抗-pH 监测 (MII-pH); 反流特点