

Non-erosive reflux disease (NERD) — acid reflux and symptom patterns

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SUMMARY

Background: Recent reports suggest that patients with non-erosive reflux disease (NERD) treated with anti-reflux medications show lower symptom improvement rates than patients with erosive oesophagitis treated with the same medications.

Aim: To determine the acid reflux and symptom patterns of patients with NERD in comparison with those with erosive oesophagitis and Barrett's oesophagus, and to identify different NERD subgroups.

Methods: One hundred and forty-nine consecutive patients seen for classic heartburn symptoms were evaluated for the study. Oesophageal mucosal injury was assessed by upper endoscopy and classified by Hetzel–Dent criteria. Patients with Hetzel–Dent grades 0–1 were considered to have NERD. The extent of oesophageal acid exposure was determined by ambulatory 24-h oesophageal pH monitoring.

Results: Seventy-one patients were found to have NERD, 36 erosive oesophagitis and 42 Barrett's oesophagus. Compared with patients with erosive oesophagitis (75%) and Barrett's oesophagus (93%), those with NERD (45%)

were significantly less likely to have an abnormal pH test ($P = 0.0001$). Patients with Barrett's oesophagus had the highest mean number of acid reflux events (210 ± 17.7), compared with those with erosive oesophagitis (139.7 ± 15.2) and NERD (95.3 ± 9.4) ($P = 0.0001$); however, the rate of perceived acid reflux events was similar and very low in all groups (NERD, 3.6%; erosive oesophagitis, 2.9%; Barrett's oesophagus, 2.17%). NERD-positive patients (abnormal pH test) had a similar extent of oesophageal acid exposure to those with erosive oesophagitis. NERD-positive patients were more likely to demonstrate a symptom index greater than 75% than NERD-negative patients (normal pH test) (61.9% vs. 10.5%; $P = 0.0001$). In the NERD-negative group, those with a negative symptom index reported having heartburn at pH < 4 only 12.7% of the time, compared with 70.7% of the time in those with a positive symptom index, despite a similar mean number of heartburn episodes.

Conclusions: Patients with NERD commonly demonstrate a negative pH test. Acid reflux characteristics and symptom patterns suggest a heterogeneous group of patients.

INTRODUCTION

Symptoms of heartburn and acid regurgitation are common amongst the US adult population, affecting up to 40% monthly, 20% weekly and 7% daily.^{1–3} It is

estimated that up to 70% of patients with typical symptoms of gastro-oesophageal reflux disease (GERD) have normal oesophageal mucosa on upper endoscopy [non-erosive reflux disease (NERD) or endoscopy-negative reflux disease].^{4–6} For decades, NERD has been considered a mild form of GERD, and thus has been treated conservatively with lifestyle modifications, over-the-counter H₂-blockers or standard-dose H₂-blockers. However, most studies have shown that patients with NERD are less likely to respond to anti-reflux therapy

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compared with those with erosive oesophagitis. When treated with omeprazole, 20 mg daily, only 46–57% of NERD patients showed complete remission of heartburn after 4 weeks of therapy.^{5, 7} Patients with acid exposure within the normal limits in the distal oesophagus were the least likely to respond to anti-reflux treatment.⁵ In another study, treatment with lansoprazole, 15 mg and 30 mg, provided symptomatic relief in only 45% and 39% of NERD patients, respectively.⁸ Consequently, a significant number of NERD patients will continue to experience heartburn that is unresponsive to standard-dose proton pump inhibitor, suggesting a heterogeneous group of patients with an 'unpredictable' response to anti-reflux therapy.

In most studies, the definition of NERD has included all patients with typical GERD symptoms (heartburn and acid regurgitation) and normal upper endoscopy. However, it is estimated that 37–60% of patients with NERD will have normal ambulatory 24-h oesophageal pH monitoring.^{5, 9} This group of patients is described as suffering from functional heartburn by the Rome II criteria.¹⁰ In one study evaluating 771 patients with symptoms related to GERD, 60% were found to have a normal pH test, and only in 12.5% was there a statistically significant association between symptoms and acid reflux episodes.⁹ These findings suggest that patients with functional heartburn are likely to be a heterogeneous group, with different characteristics on 24-h oesophageal pH monitoring. Further studies evaluating the temporal relationship between heartburn and acid reflux events may provide us with a new insight into why proton pump inhibitors are less efficacious in patients with NERD.

The aims of this study were to evaluate the different acid reflux and symptom patterns of patients with NERD compared with those with erosive oesophagitis or Barrett's oesophagus, and to determine whether there were identifiable potential subgroups of NERD patients suggesting a heterogeneous disorder.

MATERIALS AND METHODS

One hundred and forty-nine consecutive patients with typical heartburn symptoms (a burning feeling rising from the stomach or lower chest up towards the neck), presenting to the Southern Arizona VA Health Care System, Primary Care and Gastrointestinal Clinics, as well as the Gastrointestinal Laboratory, were enrolled in the study.

All subjects who agreed to participate signed an informed consent. Subsequently, subjects underwent an upper endoscopy to assess the presence of oesophageal mucosal injury. Thereafter, ambulatory 24-h oesophageal pH monitoring was carried out to quantify the extent of acid exposure in the distal oesophagus. Based on the results of the upper endoscopy and pH testing, patients were divided into three major groups: Barrett's oesophagus, erosive oesophagitis and NERD. NERD was defined as proposed previously by the Genval Workshop.¹¹ Further partition of the latter group was based on the results of 24-h oesophageal pH testing. Those with an abnormal test were considered to be NERD-positive and those with values within the normal range were considered to be NERD-negative. Patients were excluded if they: were unable to complete 24-h oesophageal pH monitoring; were using prescription non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin; had already been treated with a proton pump inhibitor (patients receiving H₂-blockers were allowed to participate if treatment was discontinued 14 days prior to the initial evaluation); had a peptic stricture or duodenal and/or gastric ulcer on upper endoscopy; had a history of upper gastrointestinal surgery; had scleroderma, diabetes mellitus, autonomic or peripheral neuropathy, myopathy, functional bowel disorder or any underlying disease or medication that might affect the lower oesophageal sphincter pressure or increase the acid clearance time; were unable or unwilling to fully complete all stages of the study and were unable or unwilling to provide informed consent.

The Human Subjects Committee of the University of Arizona approved this study.

Upper endoscopy

After an overnight fast, patients were placed in the left lateral position. Sedation was achieved with a combination of midazolam (Roche, Nutley, NJ, USA) and meperidine (Sanofi Winthrop, New York, USA). The endoscope (Olympus GIF 100) was inserted via the mouth and into the oesophagus. The distal portion of the oesophagus was carefully evaluated to determine the presence of mucosal injury. The stomach and duodenum were also inspected to exclude possible ulcers. The extent of oesophageal mucosal damage was assessed using the Hetzel–Dent grading system:¹² 0, normal mucosa (no abnormalities); 1, erythema, hyperaemia and/or friability present (no visible macroscopic

erosions); 2, superficial ulcer or erosion involving less than 10% of the mucosal surface area of the last 5 cm of the oesophageal squamous mucosa; 3, superficial ulcer or erosion involving $\geq 10\%$ but less than 50% of the mucosal surface area of the last 5 cm of the oesophageal squamous mucosa; 4, deep ulcer anywhere in the oesophagus, or confluent erosions of more than 50% of the mucosal surface area of the last 5 cm of the oesophageal squamous mucosa; 5, stricture, which is defined as narrowing of the oesophagus that does not allow easy passage of the endoscope without dilation. Grades 0–1 were considered to be diagnostic of NERD and grades 2–4 of erosive oesophagitis. Patients with grade 5 were excluded from the study.

The distal portion of the oesophagus was carefully evaluated to determine the presence of Barrett's oesophagus: red colour and velvet-like texture extending into the oesophagus and/or mucosal injury. Barrett's oesophagus was defined as the presence of intestinal metaplasia on biopsy. Measurement of Barrett's length was performed from the proximal margin of continuous Barrett's epithelium to the end of the tubular oesophagus or the proximal margin of hiatal hernia folds.¹³ In patients with suspected Barrett's epithelium, multiple biopsies were obtained from a short segment (< 3 cm), and four quadrant biopsies every 2 cm, starting from the distal end, in a long segment (≥ 3 cm), to identify intestinal metaplasia and to exclude dysplasia.

All specimens were placed immediately in 10% buffered formalin solution, embedded in paraffin and stained with haematoxylin and eosin combined with alcian blue at pH 2.5. A designated pathologist reviewed the specimens to determine if intestinal metaplasia was present.

Ambulatory 24-h oesophageal pH monitoring

After an overnight fast, a pH probe with lower oesophageal sphincter identifier (Digitrapper MK III, Medtronic, Minneapolis, MN, USA) was inserted through the nostril and into the stomach. The probe was positioned 5 cm above the upper margin of the lower oesophageal sphincter and connected to a digital portable recorder. A reference electrode was attached to the upper chest. Patients were instructed to keep a diary recording meal times, position changes and the time and type of their symptoms. Patients were encouraged to pursue their normal daily activities and maintain their usual diet. At the beginning and end of the study, the electrode and the

system were calibrated in standard solutions of pH 1 and pH 7. Reflux was defined as pH < 4, and the reflux time as the interval until pH > 4. The 24-h pH test was considered to be positive when the percentage total time pH < 4 was greater than 4.2%.¹⁴ Analysis of the recorded data was performed using standard, commercially available computer software (Medtronic).

Symptom index and perceived acid reflux events

The 24-h oesophageal pH strips were closely evaluated for symptoms and their relationship to acid reflux events. The symptom index was calculated as the percentage of heartburn symptoms that occurred during an acid reflux event (pH < 4). The symptom index (SI) was considered to be positive if the correlation between heartburn and acid reflux was $\geq 50\%$.¹⁵

$$SI\% = (\text{No. of heartburn episodes at pH} < 4) / (\text{Total no. of heartburn episodes}) \times 100$$

In addition to the traditional symptom index, heartburn episodes at pH 5 and pH 6 were also calculated. Furthermore, the assessment of the percentage perceived acid reflux events was calculated using the following formula:

$$(\text{No. of heartburn episodes at pH} < 4) / (\text{Total no. of acid reflux events}) \times 100$$

Statistical analysis

For all the continuous variables, the mean and standard error were presented. For the number of acid reflux events and the percentage time spent at pH < 4, the analysis of variance (ANOVA) was used to analyse the difference between the groups. For multiple comparisons, Bonferroni's correction was applied. In the analysis, the Poisson regression model was employed to test the difference in the number of heartburn episodes between groups. Chi-squared test was used to compare the proportion of patients with symptoms, the proportion of patients with a symptom index $\geq 50\%$ and the distribution of gender and ethnicity between the groups. All statistical tests utilized a significance level of 0.05.

RESULTS

One hundred and forty-nine patients with typical symptoms of heartburn were evaluated for this study:

71 were found to have NERD, 36 erosive oesophagitis and 42 Barrett's oesophagus. The demographics of the patients in each group are presented in Table 1.

Thirty-two NERD patients (45.1%) demonstrated an abnormal 24-h pH test (NERD-positive), in comparison with 27 (75%) with erosive oesophagitis and 39 (93%) with Barrett's oesophagus (Figure 1). Patients with NERD were significantly less likely to have an abnormal pH test than those with erosive oesophagitis and Barrett's oesophagus ($P = 0.0012$).

Patients with erosive oesophagitis more commonly reported heartburn symptoms during pH testing (72.2%) than those with NERD (56.3%) and Barrett's oesophagus (57.1%), although the difference was not statistically significant ($P = 0.249$). In addition, of those reporting symptoms during the pH test, patients with erosive oesophagitis and Barrett's oesophagus more commonly demonstrated a positive symptom index (73.1% and 75%, respectively) than those with NERD (57.5%), but this was not statistically significant either ($P = 0.254$). Patients with Barrett's oesophagus had the highest mean number of acid reflux events (210.3 ± 17.7), compared with those with erosive oesophagitis (139.7 ± 15.2) and NERD (95.3 ± 9.4) ($P = 0.0001$). Furthermore, patients with Barrett's oesophagus and erosive oesophagitis were significantly less likely to report heartburn symptoms at pH > 4 (24.4% and 30.4%, respectively) than those with NERD (45.5%) ($P = 0.01$). Interestingly, the average percentage of perceived acid reflux events of the different GERD groups was relatively similar and very low (NERD, 3.6%; erosive oesophagitis, 2.9%; Barrett's oesophagus, 2.17%). Table 2 provides a comparison of the acid

Table 1. Demographics of the patients with gastro-oesophageal reflux disease

	NERD	EO	BO
<i>n</i>	71	36	42
Gender (male/female)	58/13	33/3	40/2
Mean age (years)	54.4 ± 1.8	56.1 ± 2.0	63.5 ± 2.0
Age range (years)	19–81	26–81	33–83
Ethnicity			
Caucasian	52	28	35
Hispanic	10	5	4
African-American	7	2	0
Other	2	0	0
Unknown	0	1	3

BO, Barrett's oesophagus; EO, erosive oesophagitis; NERD, non-erosive reflux disease.

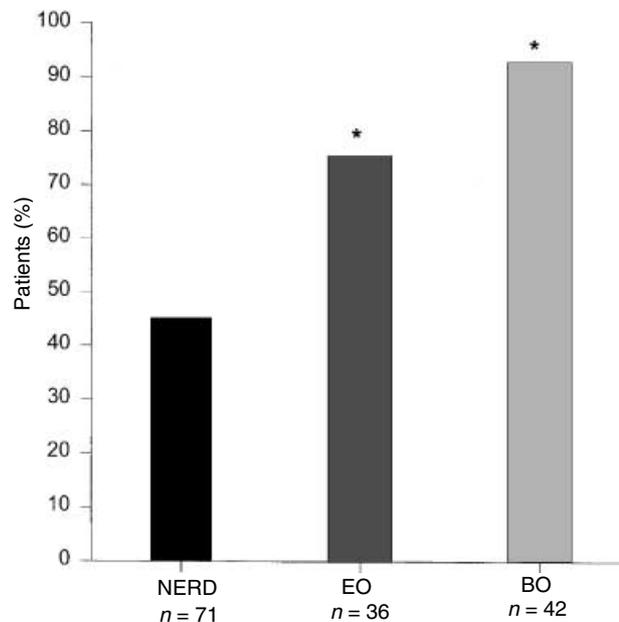


Figure 1. Distribution of abnormal oesophageal pH testing amongst the three different gastro-oesophageal reflux disease groups. In comparison with patients with erosive oesophagitis (EO) and Barrett's oesophagus (BO), those with non-erosive reflux disease (NERD) were significantly less likely to have an abnormal pH test. * $P = 0.0012$.

reflux characteristics and symptom patterns of the three different GERD groups.

NERD-positive patients demonstrated a similar degree of oesophageal acid exposure to those with erosive oesophagitis, regardless of the patient's position and the percentage total time pH < 4 (Table 3). In contrast, patients with Barrett's oesophagus had the highest oesophageal acid exposure in the erect ($P = 0.02$) and supine ($P = 0.006$) positions and over the total time ($P = 0.09$). Patients with Barrett's oesophagus were less likely to report GERD symptoms during the pH test (57%) than those with erosive oesophagitis (72.2%) and those who were NERD-positive (65.6%), but the difference was not statistically significant ($P = 0.4$). Moreover, the mean number of acid reflux events and the symptom index were similar amongst the different groups (Table 3).

Thirty-nine NERD patients (54.9%) had a negative pH test (NERD-negative). NERD-positive patients had a higher mean percentage time pH < 4 in all positions than NERD-negative patients (total, 11.5 ± 1.5 vs. 1.6 ± 0.2 ; supine, 9.7 ± 2.4 vs. 0.9 ± 0.2 ; erect, 11.4 ± 1.6 vs. 1.9 ± 0.3 ; $P < 0.0003$, $P < 0.03$, $P < 0.0003$, respectively).

Table 2. Comparison of acid reflux patterns and gastro-oesophageal reflux disease symptoms in patients with non-erosive reflux disease (NERD), erosive oesophagitis (EO) and Barrett's oesophagus (BO) undergoing pH testing

24-h pH test	NERD	EO	BO	P value
<i>n</i>	71	36	42	
Abnormal pH test	32 (45.1%)	27 (75%)	39 (93%)	0.0012
No. of patients reporting heartburn during the test	40 (56.3%)	26 (72.2%)	24 (57.1%)	0.249
No. with SI \geq 50% (% of those reporting symptoms)	23 (57.5%)	19 (73.1%)	18 (75%)	0.254
Mean time pH < 4 (%)				
Total	6.0 \pm 0.9	11.4 \pm 1.5	18.8	0.0001
Erect	6.2 \pm 0.9	13.4 \pm 1.7	18.2	0.0001
Supine	4.9 \pm 1.2	9.3 \pm 2.1	19.4	0.0001
Mean no. of acid reflux events	95.3 \pm 9.4	139.7 \pm 15.2	210.3 \pm 17.7	0.0001
Heartburn episodes (%)				
pH < 4	54.5	69.3	75.6	0.1813
pH 4–5	8.7	17.6	2.8	0.0429
pH 5–6	19.9	10.0	9.8	0.2296
pH > 6	16.9	3.1	11.8	0.0981
Average perceived acid reflux events (%)	3.61	2.93	2.17	0.5564

Using chi-squared test and analysis of variance. SI, symptom index.

Table 3. Comparison of acid reflux patterns and gastro-oesophageal reflux disease (GERD) symptoms in non-erosive reflux disease-positive (NERD+) patients and those with erosive oesophagitis (EO) and Barrett's oesophagus (BO) undergoing pH testing

24-h pH test	NERD+*	EO	BO	P value
<i>n</i>	32	36	42	
Abnormal pH test (%)	32 (100%)	27 (75%)	39 (93%)	
No. of patients reporting heartburn during pH test (%)	21 (65.6)	26 (72.2)	24 (57.1)	0.4
No. with positive SI \geq 50% (%)	16 (50.0)	19 (53.0)	18 (43%)	0.511
Mean total time pH < 4 (%)	11.4 \pm 1.5	11.4 \pm 1.5	18.8 \pm 2.3	EO vs. NERD+: 0.9 BO vs. NERD+: 0.09
Mean erect time pH < 4 (%)	11.4 \pm 1.6	13.4 \pm 1.7	18.2 \pm 2.2	EO vs. NERD+: 0.34 BO vs. NERD+: 0.02
Mean supine time pH < 4 (%)	9.7 \pm 2.4	9.3 \pm 2.1	19.4 \pm 2.9	EO vs. NERD+: 0.95 BO vs. NERD+: 0.006
Mean no. of acid reflux events	158.1 \pm 13.4	139.7 \pm 15.2	210.3 \pm 17.7	EO vs. NERD+: 0.3 BO vs. NERD+: 0.3

Using chi-squared test and analysis of variance. SI, symptom index.

* Patients with typical symptoms of GERD, normal upper endoscopy and abnormal pH testing.

NERD patients

Of the NERD patients, 19 (48.7%) NERD-negative subjects and 21 (65.6%) NERD-positive subjects had symptoms of heartburn during the pH test ($P = 0.2292$). Of these, 17.95% of the NERD-negative patients and 50% of the NERD-positive patients had a positive symptom index ($\geq 50%$) ($P = 0.004$). Therefore, the majority of NERD-negative subjects (82.05%) had heartburn unrelated to acid reflux (SI < 50%). The symptom index was < 25% in 42.1% of NERD-negative patients, compared to 9.5% of NERD-positive patients

($P < 0.0281$). NERD-positive patients were more likely to have a symptom index > 75% than NERD-negative patients (61.9% vs. 10.5%; $P = 0.0001$) (Figure 2). Overall, by using probability analysis, NERD-positive patients had a 50% chance of having a positive symptom index, compared to 17.95% in NERD-negative patients ($P = 0.004$).

NERD-negative group

Of the NERD-negative patients who experienced symptoms during pH testing, seven (36.8%) had a positive

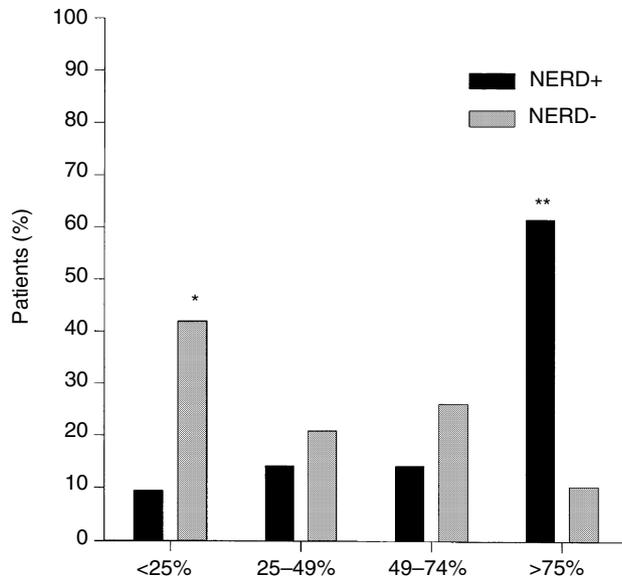


Figure 2. Comparison of the percentage of heartburn symptoms that occurred during an acid reflux event (symptom index) between non-erosive reflux disease-positive (NERD+) (with abnormal pH test) and NERD-negative (NERD-) (with normal pH test) patients. * $P = 0.0281$. ** $P = 0.0001$.

symptom index (NE-SI+) and 12 (63.2%) had a negative symptom index (NE-SI-). The demographics of these two subgroups are compared with those of symptomatic NERD-positive patients with a positive symptom index (NE+SI+) in Table 4. Table 5 summarizes the temporal relationship between symptoms and

Table 4. Demographics of the different potential subgroups of non-erosive reflux disease (NERD) patients who reported symptoms during pH testing

	NE-SI-	NE-SI+	NE+SI+
<i>n</i>	12	7	21
Gender (male/female)	11/1	4/3	17/4
Mean age (years)	62.2 ± 4.4	48.9 ± 4.6	53.6 ± 3.1
Age range (years)	18-81	36-72	25-81
Ethnicity			
Caucasian	11	5	19
Hispanic	0	2	1
Other	1	0	1

NE-SI-, NERD patients with a pH test within the normal range and negative (< 50%) symptom index; NE-SI+, NERD patients with a pH test within the normal range and positive (≥ 50%) symptom index; NE+SI+, NERD patients with an abnormal pH test and positive (≥ 50%) symptom index.

acid reflux events in all three subgroups of NERD (NE-SI-, NE-SI+ and NE+SI+).

The mean number of acid reflux events during 24-h pH testing was significantly higher in the NE+SI+ and NE-SI+ groups than in the NE-SI- group. However, there was no statistically significant difference in the average percentage of perceived acid reflux events amongst the three groups ($P = 0.1$).

Despite the fact that NERD-negative patients demonstrated less oesophageal acid exposure than NERD-positive patients, there was no statistical difference in the mean number of reported heartburn symptoms amongst the subgroups during the pH test. However,

Table 5. Temporal relationship between symptoms and acid reflux events in patients from the different potential subgroups of non-erosive reflux disease (NERD)

	NE-SI- (<i>n</i> = 12)	NE-SI+ (<i>n</i> = 7)	NE+SI+ (<i>n</i> = 21)	<i>P</i> value
Mean no. of reported heartburn episodes	3.8 ± 0.9	4.7 ± 1.8	4.6 ± 4.9	0.8
Heartburn episodes (%)				
pH < 4	12.7	70.7	73.0	
pH 4-5	11.0	10.0	6.85	
pH 5-6	34.1	6.4	16.3	
pH > 6	42.2	12.9	3.87	
Mean no. of acid reflux events	27.5 ± 5.1	70.7 ± 12.1	162.9 ± 10.1	0.0001
Average perceived acid reflux events (%)	2.1	5.8	3.7	0.1
Mean time pH < 4 (%)				
Total	1.2 ± 0.3%	2.6 ± 0.4%	10.5 ± 1.4%	
Erect	2.0 ± 0.6%	2.8 ± 0.6%	11.2 ± 1.5%	
Supine	0.7 ± 0.2%	1.0 ± 0.5%	9.1 ± 2.3%	

Using chi-squared test and analysis of variance.

NE-SI-, NERD patients with a pH test within the normal range and negative (< 50%) symptom index; NE-SI+, NERD patients with a pH test within the normal range and positive (≥ 50%) symptom index; NE+SI+, NERD patients with an abnormal pH test and positive (≥ 50%) symptom index.

the mean percentage of heartburn symptoms that occurred at pH < 4 was significantly lower in the NE-SI- group (12.7%) than in the NE+SI+ (73%) and NE-SI+ (70.7%) groups ($P = 0.001$). In addition, the percentages of heartburn complaints that occurred at pH > 6 in each subgroup were 42.2% in NE-SI-, 12.9% in NE-SI+ and 3.87% in NE+SI+ ($P = 0.001$).

DISCUSSION

Proposed definitions of NERD do not attest to the complexity of the disease. The Genval Workshop Report suggests that a diagnosis of endoscopy-negative reflux disease should be reserved for individuals who satisfy the definition of GERD, but who do not have either Barrett's oesophagus or definite oesophageal mucosal breaks.¹¹ Fass *et al.* defined NERD as the presence of typical symptoms of GERD caused by intra-oesophageal acid in the absence of visible oesophageal mucosal injury.¹⁶ The latter definition is less inclusive than the former, but it emphasizes the need to further tighten the relationship between GERD symptoms and acid reflux events when using the term 'reflux disease'. Regardless of the definition of NERD, for decades investigators have presumed, based on physiological studies, that this group of GERD patients has a mild form of the disease.¹⁷ Consequently, a much more conservative therapeutic approach has been suggested to be adequate for these patients.¹⁸ However, therapeutic trials in patients with NERD have consistently demonstrated lower efficacy in symptom control than what has been achieved in patients with erosive oesophagitis.^{5, 7} This unexpected response to therapy of NERD patients, that is also observed for proton pump inhibitors, is likely to be due to the diversity of patients who meet the broad definition of NERD.

Unlike patients with erosive oesophagitis and Barrett's oesophagus, NERD patients with normal ambulatory 24-h oesophageal pH monitoring may not represent a false negative test. In our study, approximately 55% of NERD patients had a pH test within normal limits. Other investigators have reported similar results, suggesting that NERD patients include a large subgroup with pH values that fall within the normal range.^{19, 20} Interestingly, in this study, the pH test was abnormal in 93% of Barrett's oesophagus, 75% of erosive oesophagitis and 45% of NERD patients. It appears that the greater the duration of abnormal oesophageal acid exposure in the distal oesophagus in the different GERD groups, the

higher the likelihood that the pH probe will record an acid reflux event. In addition, as a group, patients with NERD demonstrated a significantly lower degree of oesophageal acid exposure, regardless of patient position, as well as a lower mean number of acid reflux events, when compared with those with erosive oesophagitis and Barrett's oesophagus. However, when only NERD-positive patients were compared with the other GERD groups, the degree of acid exposure in the different positions and the number of acid reflux events were similar to those of patients with erosive oesophagitis. Moreover, the calculated symptom index matched that of the erosive oesophagitis group. These results suggest that the NERD group represents a mixture of two main types of patient: those with abnormal acid reflux and symptom patterns similar to those of patients with erosive oesophagitis, who fit the more classic form of GERD, and those with acid reflux patterns that fall within the physiological range. The lack of oesophageal mucosal breaks in NERD-positive patients is probably due to the preservation of local mucosal defensive mechanisms, as well as other factors that have been shown to play an important role in preventing mucosal damage.^{21, 22}

An important finding of this study was the very low percentage of perceived acid reflux events, which was found to be similar amongst the three GERD groups (NERD, 3.61%; erosive oesophagitis, 2.93%; Barrett's oesophagus, 2.17%). It has been pointed out in the past that most acid reflux events that occur during a 24-h pH recording are not sensed and thus never perceived.²³ However, our study demonstrated for the first time that, regardless of the GERD group and thus pH exposure, sensed reflux events were essentially an uncommon phenomenon. It is yet to be elucidated what factors determine the perception of intra-oesophageal stimuli. Is it the actual hydrogen ion concentration, the summation of several short reflux events or the increased number or duration of acid reflux events? Others have speculated that central factors, such as anxiety, depression and stress, may modulate oesophageal perception and cause patients to perceive low-intensity oesophageal stimuli as being painful.²⁴⁻²⁹ Peripheral factors, such as fat and other nutrients, have recently been shown to significantly shorten latency to onset of heartburn and intensify the perception of acid-induced heartburn.³⁰

The larger number of patients with NERD and normal 24-h oesophageal pH monitoring have been diagnosed

as having 'functional heartburn'. The Rome II Committee for Functional Oesophageal Disorders defined functional heartburn as an episodic retrosternal burning in the absence of pathological gastro-oesophageal reflux, pathology-based motility disorders or structural explanations.¹⁰ This definition is vague and provides very little information about the mechanisms that lead to heartburn symptoms in NERD-negative patients.

Other investigators have already shown that NERD-positive patients are more likely to report symptoms during pH testing than NERD-negative patients.³¹ We found that 65.6% of NERD-positive and 48.7% of NERD-negative patients reported symptoms during the pH test. NERD-positive patients were more likely to have a high symptom index (50%) than were NERD-negative patients. The latter may suggest that some NERD-negative patients experience heartburn that is not related to acid reflux. When the NERD-negative group was further stratified on the basis of their calculated symptom indices, those with a negative symptom index reported having heartburn at pH < 4 only 12.7% of the time, compared with 70.7% of the time in those with a positive symptom index, despite a similar mean number of heartburn episodes. These data further support the concept that NERD patients with a negative symptom index are likely to include a group with heartburn that is not due to acid reflux. There is a growing body of literature demonstrating non-acid-related stimuli that cause classic heartburn. Oesophageal balloon distension, non-acidic reflux, motor events and others result in heartburn in normal subjects and patients with GERD.^{32–35} NERD-negative patients with a positive symptom index appear to have a similar percentage of heartburn episodes at pH < 4 as NERD-positive patients with a positive symptom index (70.7% and 73.0%, respectively). They also demonstrate the highest rate of perceived acid reflux events amongst the three NERD subgroups. These results suggest that NERD-negative patients with a positive symptom index may represent a potential group with increased oesophageal chemosensitivity to acid. In further support of the role of acid in triggering symptoms in this group of patients, Watson *et al.* have demonstrated that doubling the standard dose of omeprazole in patients with NERD and a normal pH test resulted in symptom improvement in 4 weeks of, almost exclusively, patients with a positive symptom index.³⁶ Future studies are needed to further explore this specific group of patients.

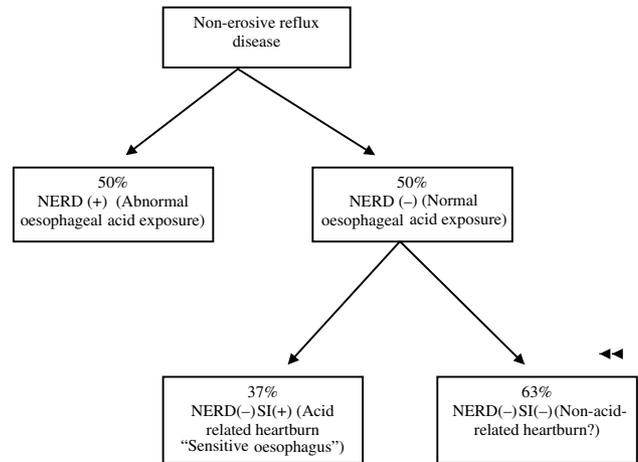


Figure 3. Stratification of the patients with non-erosive reflux disease (NERD) to the different subgroups. SI, symptom index.

In summary, this study evaluated the acid reflux characteristics and symptom patterns of patients with NERD, compared with those of patients with erosive oesophagitis and Barrett's oesophagus. Further exploration of the NERD group revealed the potential for several subgroups with different underlying mechanisms for heartburn symptoms (Figure 3). The heterogeneous character of NERD may explain the results of recent physiological, clinical and therapeutic studies that have addressed this group of patients. Our study included a relatively small number of patients from the different subgroups of NERD due to the strict inclusion of only patients who reported heartburn symptoms during the pH test. Future studies are needed to further define the different subgroups of patients who meet the broad definition of NERD. Such information may force us to rethink our current definitions of NERD and improve our understanding of the pathophysiology and therapy of this disorder.

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