

## Non-erosive and uncomplicated erosive reflux diseases: Difference in physiopathological and symptom pattern

Vittorio Bresadola, Gian Luigi Adani, Francesco Londero, Cosimo Alex Leo, Vittorio Cherchi, Dario Lorenzin, Anna Rossetto, Gianmatteo Vit, Umberto Baccarani, Giovanni Terrosu, Dino De Anna

Vittorio Bresadola, Gian Luigi Adani, Francesco Londero, Cosimo Alex Leo, Vittorio Cherchi, Dario Lorenzin, Anna Rossetto, Gianmatteo Vit, Umberto Baccarani, Giovanni Terrosu, Dino De Anna, Department of Surgery and Transplantation, University Hospital of Udine, P.le S.M. della Misericordia, Udine 33100, Italy

Author contributions: Vittorio Bresadola designed the research, analyzed the data and wrote the paper. Gian Luigi Adani designed the research and wrote the paper. Francesco Londero, Cimo Alex Leo, Vittorio Cherchi and Gianmatteo Vit performed the research. Anna Rossetto wrote the paper. Dario Lorenzin, Umberto Baccarani and Giovanni Terrosu analyzed the data. Dino De Anna revised manuscript.

Correspondence to: Gian Luigi Adani, MD, PhD, Clinica Chirurgica e Centro Trapianti Fegato, Rene e Pancreas, AOUD, P.le S.M. della Misericordia, Udine 33100, Italy. [adanigl@hotmail.com](mailto:adanigl@hotmail.com)  
Telephone: +39-0432-559902 Fax: +39-0432-559552

Received: December 9, 2010 Revised: January 31, 2011

Accepted: April 7, 2011

Published online: June 15, 2011

### Abstract

**AIM:** To investigate differences in the physiopathological findings (manometry and pH monitoring) and symptoms between cases of non-erosive reflux disease (NERD) and erosive reflux disease (ERD) found positive at 24 h pH monitoring.

**METHODS:** For a total of 670 patients who underwent 24 h pH monitoring, esophageal manometry and upper endoscopy were retrospectively evaluated, assessing the reflux symptoms, manometric characteristics of the lower esophageal sphincter (LES) and esophageal body and the presence or absence of esophagitis and hiatal hernia. Typical and atypical symptoms were also evaluated. For inclusion in the study, patients had to have NERD or ERD and be found positive on pH monitoring (NERD+). Patients with Gastroesophageal reflux disease (GERD)

complicated by stenosis, ulcers or Barrett's esophagus were ruled out.

**RESULTS:** 214 patients were involved in the study, i.e. 107 cases of NERD+ and 107 of ERD. There were no significant gender- or age-related differences between the two groups. The ERD group had more cases of hiatal hernia ( $P = 0.02$ ) and more acid reflux, both in terms of number of reflux episodes ( $P = 0.01$ ) and as a percentage of the total time with a pH < 4 ( $P = 0.00$ ), when upright ( $P = 0.007$ ) and supine ( $P = 0.00$ ). The NERD+ cases had more reflux episodes while upright ( $P = 0.02$ ) and the ERD cases while supine ( $P = 0.01$ ). The LES pressure was higher in cases of NERD+ ( $P = 0.03$ ) while the amplitude and duration of their esophageal peristaltic waves tended to be better than in the ERD group ( $P > 0.05$ ). The NERD+ patients presented more often with atypical symptoms ( $P = 0.01$ ).

**CONCLUSION:** The NERD+ patients' fewer reflux episodes and the fact that they occurred mainly while in the upright position (unlike the cases of ERD) may be two factors that do not favor the onset of esophagitis. The frequently atypical symptoms seen in patients with NERD+ need to be accurately evaluated for therapeutic purposes because patients with GERD and atypical symptoms generally respond only partially to medical and surgical treatments.

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**Key words:** Gastroesophageal reflux disease; Non-erosive reflux disease; Erosive reflux disease; Barrett's esophagus; Reflux symptoms

**Peer reviewers:** Fernando Fornari, Professor, Department of Gastroenterology, Faculdade de Medicina-Universidade de Passo Fundo, Rua Teixeira Soares, 817, Centro, Passo Fundo-RS 99010080, Brazil; Jing-Bo Zhao, Associate Professor, Mech-Sense, Research House, AalborgHospital, Adr. Skovvej 15, Aalborg 9000, Denmark

Bresadola V, Adani GL, Londero F, Leo CA, Cherchi V, Lorenzin D, Rossetto A, Vit G, Baccarani U, Terrosu G, De Anna D. Non-erosive and uncomplicated erosive reflux diseases: Difference in physiopathological and symptom pattern. *World J Gastrointest Pathophysiol* 2011; 2(3): 42-48 Available from: URL: <http://www.wjgnet.com/2150-5330/full/v2/i3/42.htm> DOI: <http://dx.doi.org/10.4291/wjgp.v2.i3.42>

## INTRODUCTION

Gastroesophageal reflux disease (GERD) develops when the contents of the stomach flow back into the esophagus, causing troublesome symptoms and sometimes damaging the mucosa and leading to complications<sup>[1]</sup>. This definition actually covers different conditions, ranging from non-erosive reflux disease (NERD) to erosive reflux disease (ERD), to forms of GERD complicated by ulcers or stenosis and Barrett's esophagus (BE). These various forms of GERD are often interpreted on the strength of a "spectrum model", on the assumption that the disease progresses in steps to a more severe form and may occasionally regress to a less severe form. NERD, ERD and BE are thus usually configured as different stages of the same disease<sup>[2,3]</sup>. On the other hand, these features of GERD are sometimes seen as three different categories of patients in which it is rare to see a patient's transition from one group to another<sup>[4,5]</sup>. From the clinical standpoint, 50%-75% of individuals with GERD have an intact esophageal mucosa<sup>[4,6]</sup>. These NERD patients are also the cases that respond the least and the least predictably to medical therapy<sup>[7]</sup>. In recent years, various researchers have attempted to characterize the various ways in which GERD can become manifest from the physiopathological, symptomatic and anatomopathological standpoints, often with contradictory results<sup>[8]</sup>.

The aim of this study was to investigate a cohort of patients with NERD found positive on pH monitoring (NERD+) as compared with a cohort of patients with uncomplicated erosive reflux disease and ascertained ERD. These two groups of patients can be seen as closely juxtaposed in the "spectrum" model but very different from the categorical standpoint. Our main aim was to evaluate whether differences exist between NERD+ and ERD patients in terms of their manometric variables detectable in the lower esophageal sphincter (LES) and esophageal body and the outcome of their pH monitoring. The second endpoint of this study was to see whether there was any difference between the two groups in the clinical presentation of their symptoms.

## MATERIALS AND METHODS

### Type of study

We performed a retrospective clinical assessment.

### Study population and inclusion criteria

We considered all the reports on patients referred to the digestive physiopathology laboratory at the Surgery De-

partment at the University of Udine from 1998 to 2010 who underwent esophageal manometry and 24 h pH monitoring.

To be included in the study, patients had to fulfill the following criteria:

**They were positive on 24 h pH monitoring (DeMeester score > 14.8) and consequently diagnosed with GERD:** pH monitoring was done with a pH catheter with an antimony electrode (Zinectics 24; Medtronic) positioned 5 cm from the upper margin of the LES (previously identified by manometry). The data collected over 24 h were recorded in a portable data logger (Digitrapper MkIII, Synectics Medical) and subsequently processed using the manufacturer's software.

**They had undergone esophageal manometry:** Stationary esophageal manometry was completed before pH monitoring using an 8 channel catheter perfused with water to establish the site and features of the LES. Peristalsis and the related pressures on a level with the esophageal body were assessed in 10 wet swallows. All data were processed using the Polygram for Windows software by Medtronic.

**They had undergone esophagogastroduodenoscopy:** NERD+ patients were not to have been taking any medical therapy prior to the test.

**ERD patients' esophagitis had to be classifiable as grade 1-2 according to the Los Angeles classification:** Severe or complicated esophagitis or Barrett's esophagus were considered exclusion criteria.

### Data collection

Data were collected on the following:

**Demographic:** Gender and age.

**Endoscopic:** Presence/absence of uncomplicated esophagitis (ERD/NERD) and hiatal hernia (judged to be present when the distance between the diaphragmatic pinchcock and the gastro esophageal junction was > 2 cm).

**Manometric:** Mean pressure, total and abdominal lengths of the LES; mean proximal and distal wave amplitude and duration in the esophageal body; effective of peristalsis (i.e. absence of specific motor anomalies or aspecific motor disorders, defined as peristaltic waves with an amplitude < 30 mmHg on a level with the distal esophagus or pathological waves with no contractions or with double or triple peaks in > 30% of 10 wet swallows during manometry of the esophageal body).

**pH monitoring:** Total number of reflux episodes, number of reflux episodes persisting more than 5 min, percentage of the total time with pH < 4, in a supine or upright position, DeMeester score.

**Table 1** Description of the study population *n*(%)

Population	NERD +	ERD	<i>P</i> value
Gender			
Males	39 (36.5)	35 (32.8)	NS
Females	68 (63.5)	72 (67.2)	
Age			
mean $\pm$ SD	52.08 $\pm$ 13	52.8 $\pm$ 14	NS
Median	55	54	
Hiatal hernia	53 (43.4)	69 (56.6)	0.02

NERD+: Non-erosive reflux disease positive on pH monitoring; ERD: Erosive reflux disease; NS: Non-statistically significant.

**Symptoms:** Symptoms were reported as typical (heartburn, regurgitation) or atypical (respiratory, otorhinolaryngological, cardiac symptoms).

### Statistical analysis

The data were described using means, medians and standard deviations (SD). The frequencies were also described using percentages where applicable. Continuous variables were compared using Student's *t*-test for data with a normal distribution and the Mann-Whitney test in the remaining cases. Proportions were compared using the chi square test. Odds ratios were calculated for 95% confidence intervals. The value of the single tests was considered significant where  $P < 0.05$ . The data analysis was conducted using the SPSS, rel. 18 (Chicago, IL, USA).

## RESULTS

### Study population

From 1998 to 2010, a total of 670 patients were assessed at our surgical physiopathology laboratory; 214 of them met all the previously-stated inclusion criteria and were included in the study. There were 107 (50%) cases with evidence of esophagitis (ERD) and 107 (50%) with no esophageal lesions (NERD+).

### Demographic characteristics

Of the 214 patients considered, 74 (34.6%) were female and 140 (65.4%) were male. In the two patient groups, NERD+ and ERD, there were 39/107 (36.5%) and 35/107 (32.8%) women respectively and 68/107 (63.5%) and 72/107 (67.2%) men. The mean age of the study population was  $52.49 \pm 14$  years (median 54.50); it was  $52.08 \pm 13$  (median 55) in the NERD+ group and  $52.8 \pm 14$  (median 54) in the ERD group.

The two groups were judged to be homogeneous for both the demographic variables considered ( $P < 0.05$ ) (Table 1).

### Hiatal hernia

Hiatal hernia was found in 122 (57%) patients, i.e. in 53 cases of NERD+ (43.4%) and 69 cases of ERD (56.6%). The cases of ERD were therefore more frequently associated with hiatal hernia ( $P = 0.02$ ).

### Physiopathological patterns

**Esophageal body manometric characteristics:** The peristalsis assessment in the study population as a whole identified distal waves with a mean amplitude of  $77.97 \pm 42$  mmHg and a mean duration of  $3.61 \pm 0.9$  s; at proximal level, the mean values were  $50.68 \pm 21$  mmHg and  $2.87 \pm 0.6$  s respectively. In the NERD+ group, the mean wave amplitude was  $80.38 \pm 45$  at distal level and  $50.61 \pm 20$  mmHg at proximal level, while the waves' duration was  $3.58 \pm 1$  and  $2.83 \pm 1$  s respectively. In the ERD group, the mean distal and proximal wave amplitude was  $75.55 \pm 40$  and  $50.74 \pm 21$  mmHg respectively and their duration was  $3.64 \pm 0.9$  and  $2.92 \pm 0.6$  s.

No significant differences emerged on comparing the amplitude and duration of the distal and proximal peristaltic waves. The two groups of patients were also similar as regards the efficacy of peristalsis variable, i.e. 41 NERD+ patients (47.7%) and 45 ERD patients (52.3%) had an ineffectual peristalsis ( $P = NS$ ).

### Lower esophageal sphincter manometric characteristics:

For the study population as a whole, manometry of the LES identified a mean pressure of  $10.33 \pm 6$  mmHg, a mean total length of the LES of  $2.51 \pm 0.8$  cm and a mean abdominal length of  $1.09 \pm 0.9$  cm. In the two patient groups, NERD+ and ERD, the mean values were respectively:  $11.18 \pm 6.5$  and  $9.4 \pm 5.3$  mmHg for the pressure;  $2.57 \pm 0.7$  and  $2.44 \pm 0.8$  cm for the total length of the LES; and  $1.13 \pm 0.8$  and  $1.05 \pm 0.9$  cm for its abdominal length.

NERD+ patients had a significantly more severe pressure insufficiency than ERD patients ( $P = 0.037$ ). On the other hand, the length of the LES was not dissimilar in the two groups ( $P < 0.05$ ) (Table 2).

**pH monitoring characteristics:** For the study population as a whole, the mean number of reflux episodes was  $144.3 \pm 106.2$  and the episodes lasting  $> 5$  min amounted to a mean  $6.3 \pm 6.78$ . The NERD+ patients had a mean  $125.67 \pm 74.49$  reflux episodes and those lasting  $> 5$  min amounted to a mean  $4.42 \pm 4.9$ . In the ERD group, the figures were  $162.93 \pm 128.15$  and  $8.19 \pm 7.78$  respectively so these patients with endoscopic findings positive for esophagitis had significantly more and more persistent reflux episodes than the patients without esophagitis (respectively  $P = 0.01$ ;  $P = 0.00$ ). In the study population as a whole, we recorded a total percentage of the time with a pH  $< 4$  of  $12.5 \pm 11.8$ , with  $12.2 \pm 10.9$  for the upright position and  $12.9 \pm 17.7$  for the supine position. In the NERD+ group, the percentage of the total time with a pH  $< 4$  and the corresponding percentages for the upright and supine positions were respectively:  $9.24 \pm 8.1$ ,  $10.2 \pm 7.9$  and  $7.6 \pm 12.2$ . In the ERD group, the three values were:  $15.8 \pm 14$ ,  $14.2 \pm 13$  and  $18.2 \pm 20.6$ . The proportion of time with a pH  $< 4$  was significantly higher in the ERD group than in the NERD+ group, both for the period as a whole ( $P = 0.000$ ) and after distinguishing between the two positions, upright ( $P = 0.007$ ) and supine ( $P = 0.000$ ).

**Table 2 NERD+ vs ERD: manometry study**

Manometry	NERD+	ERD	P value
LES			
Pressure (mmHg)			
mean ± SD	11.18 ± 6.5	9.4 ± 5.3	0.03
Median	9.33	8.5	
Total length (cm)			
mean ± SD	2.57 ± 0.7	2.44 ± 0.8	NS
Median	3	3	
Abdominal length (cm)			
mean ± SD	1.13 ± 0.8	1.05 ± 0.9	NS
Median	1	1	
Esophageal body			
Distal wave amplitude (mmHg)			
mean ± SD	80.38 ± 45	75.55 ± 40	NS
Median	70.2	68.3	
Proximal wave amplitude (mmHg)			
mean ± SD	50.61 ± 20	50.74 ± 21	NS
Median	50	48.65	
Distal wave duration (s)			
mean ± SD	3.58 ± 1	3.64 ± 0.9	NS
Median	3.45	3.4	
Proximal wave duration (s)			
mean ± SD	2.83 ± 1	2.92 ± 0.6	NS
Median	2.75	2.75	
Effective peristalsis (%)	41 (47.7%)	45 (52.3%)	NS

LES: Lower esophageal sphincter; NERD+: Non-erosive reflux disease positive on pH monitoring; ERD: Erosive reflux disease; NS: Non-statistically significant.

In the ERD patients, the percentage of the time with a pH < 4 was longer in the supine position ( $P = 0.01$ ) than when upright; vice versa, in the NERD+ patients reflux was more prevalent when patients were upright ( $P = 0.024$ ).

The analysis of the DeMeester scores indicated a mean value for the total population of  $50.3 \pm 43.38$ . For the NERD+ patients, the mean DeMeester score was  $37.24 \pm 32.63$  while the ERD patients had a significantly higher mean score of  $63.38 \pm 48.70$  ( $P = 0.00$ ) (Table 3).

**Symptom pattern:** On the whole, 128 patients (67.4%) had typical esophageal symptoms while 62 (32.6%) reported typical and atypical, or only atypical symptoms. No data regarding symptoms were available in the clinical records of 24 patients (11.2%; 5 ERD and 19 NERD+) so these cases were not considered for this parameter. In the NERD+ group, 52/88 patients (59.1%) had typical symptoms while the other 36 (40.9%) had a typical and atypical, or entirely atypical symptom pattern. Conversely, the patients with typical symptoms in the ERD group amounted to 76 (74.5%) while 26 (25.5%) reported atypical symptoms. Patients with esophagitis thus presented a typical symptom pattern far more frequently than those with NERD+ ( $P = 0.01$ ). The latter have a high probability of developing atypical symptoms with an odds ratio of 2.02 (95% CI, 1.05-3.93) (Table 4).

## DISCUSSION

### General considerations: study population

The noteworthy feature of this study lies in that we con-

**Table 3 NERD+ vs ERD: pH monitoring**

24 h pH monitoring	NERD+	ERD	P value
Number of reflux episodes			
Total			
mean ± SD	125.67 ± 74.49	162.93 ± 128.1	0.01
Median	118	131	
Lasting > 5 min			
mean ± SD	4.42 ± 4.9	8.19 ± 7.7	0
Median	3	6	
pH < 4			
Total time (%)			
mean ± SD	9.24 ± 8.1	15.80 ± 14	0
Median	6.8	11	
Upright time (%)			
mean ± SD	10.20 ± 7.9 <sup>a</sup>	14.20 ± 13 <sup>b</sup>	0.007
Median	7.8	10.7	
Supine time (%)			
mean ± SD	7.6 ± 12.2 <sup>a</sup>	18.20 ± 20.6 <sup>b</sup>	0
Median	4.1	11.1	
DeMeester score			
mean ± SD	37.24 ± 32.63	63.38 ± 48.70	0
Median	30.4	48.7	

NERD+: Non-erosive reflux disease positive on pH monitoring; ERD: Erosive reflux disease; NS: Non-statistically significant; <sup>a</sup>NERD+: Upright vs supine ( $P = 0.02$ ); <sup>b</sup>ERD Supine vs upright ( $P = 0.01$ ).

**Table 4 Clinical presentation of NERD+ and ERD patients n(%)**

Clinical presentation	NERD+ (88/107)	ERD (102/107)	P value
Typical symptoms only	52 (59.1)	76 (74.5)	0.01
Typical and atypical symptoms	36 (40.9)	26 (25.5)	0.01

NERD+: Non erosive reflux disease positive on pH monitoring; ERD: Erosive reflux disease.

figured two groups of patients, each of which was particularly homogeneous. The NERD+ group only included patients with ascertained pathological reflux, disregarding any cases with symptoms but no confirmed pathological reflux (NERD-), which are associated with a hypersensitive esophagus, functional heartburn or non-acid reflux<sup>[9,10]</sup>, all controversial physiopathological explanations that are often difficult to demonstrate<sup>[8]</sup>. Assessing heterogeneous groups of NERD patients (NERD+ and NERD-) or with a diagnosis of NERD based exclusively on symptoms and endoscopic evidence (as some researchers have done) can trigger a cascade of biases affecting the interpretation of the results<sup>[11]</sup>. Bearing this in mind, our study has one of the most numerous cohorts of NERD+ cases to have been investigated in the literature from the physiopathological standpoint.

Another important aspect of our study lies in the lack of any differences between our two groups of patients regarding their demographic characteristics. In particular, the fact that the mean age of the ERD group was similar to that of the NERD+ patients (around 50 years old in both cases) seems to contradict the claim that patients with-

out esophagitis tend to be younger and can be expected to progress towards a picture of full-blown esophagitis as they grow older<sup>[12,13]</sup>. Other authors reported individuals with complicated reflux disease being older than patients with NERD+, although the latter were actually much the same age as the group with ERD, as in our population<sup>[14]</sup>.

We also found no gender-related differences in our two patient groups despite the literature reporting a tendency to find more females among NERD patients than among cases of esophagitis<sup>[12,15,16]</sup>.

In our study population, the presence of hiatal hernia was associated more frequently with a picture of reflux with esophagitis. Hiatal hernia is currently assumed to be one of the physiopathological factors contributing to the onset of GERD by reducing LES competence and interfering with esophageal clearance<sup>[17,18]</sup>. Hiatal hernia is apparently a dominant predictor of erosive esophagitis<sup>[19]</sup> but it has been little studied in patients with NERD who are less likely to have hiatal hernias than patients with esophagitis<sup>[14,5,20]</sup>.

### Physiopathological pattern

Resting LES pressure was found to be higher in our patients with NERD+ while the other two sphincter competence variables considered (total and abdominal length) were similar in the two groups. A tendency for NERD+ patients to have a higher mean LES pressure than ERD patients has also been reported in other studies, although the difference failed to reach statistical significance<sup>[14,20]</sup>.

Findings for esophageal body motility did not differ significantly between patients with NERD+ and those with ERD, apart from a slight tendency for the distal wave amplitude to be greater in the first group. Much the same can be said of the efficacy of peristalsis since the NERD+ patients tended less to have an ineffective peristalsis. If we consider distal wave amplitude and efficacy of peristalsis as important parameters in the process of esophageal clearance, we could say that NERD+ patients tend to have a better esophageal clearance but not to any significant degree. That NERD+ patients have distal esophageal waves with a higher mean amplitude than patients with esophagitis has also been reported by other researchers<sup>[14]</sup>.

NERD+ patients were found to have less severe reflux than ERD patients in terms of both the total number of reflux episodes and the percentage of the time with a pH < 4 in the upright position and when supine at night; this situation was confirmed by the former having a lower DeMeester score. Patients with NERD+ have more reflux when upright in the daytime than at night whereas reflux is more common at night in the group with esophagitis; this finding is certainly worth noting because night-time reflux is known to be more harmful to the esophageal mucosa<sup>[21]</sup>. It would therefore seem from this study that, in addition to NERD+ and ERD patients experiencing a different number of reflux episodes, the timing of their reflux episodes is also different (when upright during the day or supine at night) and this could explain the presence or absence of lesions affecting the esophageal mucosa. In the few studies conducted on this issue, findings have been

contradictory and often supported by a small number of patients.

The results of our study are consistent with Frazzoni's demonstration of a higher percentage of total and night-time reflux in ERD than in NERD patients. That a different reflux pattern exists between NERD and ERD has also been suggested in other studies<sup>[22,23]</sup>. On the other hand, a study conducted by Martinez (on 36 ERD patients and 71 NERD patients, the latter including cases both positive and negative on pH monitoring) reported NERD having a lower acid exposure, but with the 39 NERD- patients we disregarded, the 32 NERD+ patients no longer differed from those with ERD<sup>[24]</sup>. Unlike the situation seen in our study, excluding patients with functional heartburn seems to make the NERD+ and ERD cases overlap in terms of severity of acid reflux<sup>[15,25,26]</sup>. In NERD patients, therefore, the progression towards esophagitis might correlate more with the duration of their disease than with any greater quantity of acid reflux<sup>[27]</sup>.

### Symptom patterns

There is no evidence in the literature of symptom patterns (nature and severity of the symptoms) differing between cases of ERD and NERD when the latter types of patient include NERD+ and NERD- cases<sup>[16]</sup>.

In our study, however, the clinical presentation of patients with NERD+ differed significantly from those with esophagitis, i.e. the former presented more frequently with atypical symptoms. Quantitative differences in patients' reflux episodes might be seen to support the "spectrum model", based on the assumption that NERD+ patients will become ERD cases with time due to their reflux episodes increasing secondary, for instance, to a further impairment of LES competence and esophageal clearance. Conversely, the different prevalent symptom patterns in the two populations (typical symptoms in ERD and atypical symptoms in NERD+) seem instead to support the categorial view<sup>[28]</sup> since it is difficult to imagine patients with mainly atypical symptoms progressing with time towards a different symptom pattern in which typical symptoms prevail.

In conclusion, our study demonstrates that NERD+ patients are not very dissimilar from cases of ERD from the functional standpoint, despite a lower acid exposure, a better sphincter competence and a tendency to have a better esophageal clearance. On the other hand, the two patient groups reveal a different prevalence of symptoms, more typical in ERD and atypical in NERD+. For the latter patients, pH monitoring plays a fundamental part in distinguishing patients with a normal acid exposure (NERD- from those with an abnormal contact time (NERD+). This is fundamental, particularly when dealing with NERD patients failing to respond to medical therapy with proton pump inhibitors (PPI) or when considering surgery for such patients<sup>[29]</sup>. In fact, NERD+ patients respond better than NERD- to medical therapy with standard-dose PPI<sup>[30]</sup> while the finding of a pathological reflux on pH monitoring in patients with reflux symptoms is a positive predictor of the success of surgery<sup>[31]</sup>.

As regards symptoms, patients with NERD+ can be further divided into two subpopulations with or without atypical symptoms. NERD+ patients with atypical symptoms are more difficult to treat from both the medical and the surgical standpoint, being those least responsive to treatment with PPI or surgical anti-reflux procedures<sup>[32,33,34]</sup>.

## COMMENTS

### Background

Gastro esophageal reflux disease (GERD) has approached as a spectrum of disease, ranging from non-erosive reflux disease (NERD) to erosive reflux disease (ERD), to form of GERD complicated. In literature NERD population is poorly defined as for physiopathology and related symptoms. The current article investigates physiopathological findings and symptoms between NERD and ERD population

### Research frontiers

Important areas in these fields are to better understand which are the best diagnostic studies and the best therapeutic treatments in NERD patients with atypical symptoms.

### Innovations and breakthroughs

The physiopathological study in the NERD population with reflux showed a different outcome if compared to ERD population; in the first group, the reflux episodes are fewer and occurred mainly in upright position. Moreover NERD patients have frequently atypical symptoms.

### Applications

This study demonstrates that in the clinical practice, patients without esophagitis but with ERD symptoms could benefit of the physiopathological study for a better definition of their disease.

### Peer review

The study provides evidences that the NERD+ patients have fewer reflux episodes and frequently atypical symptoms compared with ERD patients. It is good for the readership of this journal, especially for the gastroenterologist and GERD patients, even relevant for the normal population.

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