Characteristics of Reflux Episodes and Symptom Association in Patients With Erosive Esophagitis and Nonerosive Reflux Disease: Study Using Combined Impedance–pH Off Therapy

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OBJECTIVES: **We sought to compare reflux and symptom association patterns in patients with nonerosive reflux disease (NERD), erosive esophagitis (EE), and in healthy volunteers (HVs).**

METHODS: **Patients with EE and NERD underwent combined impedance–pH monitoring. Normal values were defined on the basis of previously collected data from 48 HVs. We evaluated distal esophageal acid exposure time (AET), number and type of reflux episodes (acid, nonacid), acid and bolus clearance times, proximal extension of reflux episodes, and symptom association probability (SAP).**

RESULTS: **Distal AET (percentage time, pH<4) was higher ($P<0.01$) in 58 EE patients (median 7.4%, 25–75th percentile 4.2–9.9%) compared with 168 NERD patients (4.2% (1.2–6.4%)) and 48 HVs (0.7% (0.2–1.4%)). Patients with EE and NERD had a higher ($P<0.01$) number of acid reflux episodes compared with HVs (51 (37–66) vs. 34 (22–51) vs. 17 (8–31); $P<0.05$), but a similar number of nonacid reflux episodes (22 (15–39) vs. 23 (15–38) vs. 18 (14–26); P=NS). The percentage of reflux episodes reaching the proximal esophagus was higher ($P<0.01$) in EE patients (57% (45–73%)) than in NERD patients (45% (36–60%)) and HVs (33% (19–46%)). A positive SAP for heartburn or regurgitation was found in 161 of 168 (96%) NERD and 54 of 58 (93%) EE patients (P=NS).**

CONCLUSIONS: **Acid reflux episodes, volume, and acid clearance are important factors in the pathogenesis of reflux-induced lesions. Nonacid reflux contributes less to esophageal mucosa damage, but is involved in the development of reflux symptoms in both NERD and EE patients.**

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most common chronic gastrointestinal diseases in Western countries, notable for its prevalence, variety of clinical presentations, underrecognized morbidity, and substantial economic consequences (1). Nonerosive reflux disease (NERD) and erosive esophagitis (EE) represent the most common phenotypic presentations of GERD (2). In particular, NERD, defined as the presence of typical symptoms of GERD caused by intraesophageal reflux, in the absence of visible esophageal mucosal injury at endoscopy, is estimated to affect between 50 and 70% of the whole GERD population (3,4). Thus, NERD represents the most frequently encountered form of GERD and previous studies have shown that NERD patients, as a whole population, have lower esophageal acid exposure than patients with reflux esophagitis and Barrett's esophagus. However, NERD patients can suffer from symptoms as severe as those with EE and the impact on quality of life can be at least as disabling (5).

Studies evaluating differences between NERD and EE patients found that patients with NERD tend to have normal lower esophageal sphincter (LES) pressure, minimal esophageal body motility abnormalities, low esophageal acid exposure profile,

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low prevalence of hiatal hernia, and minimal nighttime esophageal exposure (6–8). Compared with patients with EE, NERD patients have a lower incidence of acid reflux events and a more homogeneous distribution of acid reflux along the esophagus (9,10).

In recent years, the addition of impedance channels to conventional pH catheters offered the ability to detect and monitor liquid and air movement within the esophagus and to distinguish between acid and nonacid refluxes (11–13). It has been recently shown that combined pH–impedance monitoring is more accurate than pH alone for the detection of both acid and weakly acidic refluxes (14). Nevertheless, there are limited data on patterns of acid and nonacid refluxes in patients with EE and NERD (15). Moreover, the use of this novel technique has allowed us to distinguish various subgroups of patients with NERD (14) and to identify with more precision the subset of functional heartburn (FH), that, according to Rome III criteria (16), must be no more included in the realm of GERD.

The aim of this study was to compare the characteristics of reflux episodes in patients with EE and NERD, subtracting from the latter group those with FH, using combined esophageal impedance–pH monitoring.

METHODS

Subjects

Between June 2004 and June 2009, patients with typical GERD symptoms (e.g., heartburn and regurgitation) lasting for more than 6 months and occurring at least three times weekly, presenting to the motility center at the University Hospital of Genoa, were prospectively enrolled in the study. Exclusion criteria were history of thoracic, esophageal, or gastric surgery; primary or secondary severe esophageal motility disorders (e.g., achalasia, scleroderma, diabetes mellitus, autonomic or peripheral neuropathy, myopathy); history of alcohol or drug abuse; and evidence of EE at previous (5 years) endoscopy in case of patients with NERD. In women of childbearing age, pregnancy was excluded by urine analysis. Patients were asked to discontinue any medication that would influence esophageal motor function at least 1 week before performing tests of esophageal function.

For comparisons, a group of 48 healthy volunteers (HVs, 22 men; mean age 44 years, range 22–77 years; mean body mass index 23 $kg\,m^{-2}$, range 16–34 $kg\,m^{-2}$) without any type of digestive and systemic symptoms were enrolled in the study.

The study protocol was approved by the local ethics committees and performed according to the Declaration of Helsinki Principles. All patients gave written informed consent before the start of the study.

Esophageal impedance and pH monitoring

Esophageal impedance–pH monitoring was performed using an ambulatory multichannel intraluminal impedance and pH monitoring system (Sleuth; Sandhill Scientific, Highland Ranch, CO). The system included a portable data logger with impedance–pH amplifiers and a catheter with one antimony pH electrode and eight impedance electrodes at 2, 4, 6, 8, 10, 14, 16, and 18 cm from the tip of the catheter. Each pair of adjacent electrodes represented an impedance-measuring segment (2 cm length) corresponding to one recording channel. The six impedance and one pH signals were recorded at 50 Hz on a 128 MB CompactFlash (SanDisk, Milpitas, CA).

Study protocol

All subjects who agreed to participate in our investigation underwent a careful physical and clinical examination into their medical history (including current medication, height and weight, tobacco use, alcohol and coffee consumption), an upper gastrointestinal endoscopy to assess the presence of esophageal mucosal injury, a routine biochemistry, and an upper abdominal ultrasound. Patients treated with antisecretory drugs were asked to discontinue acid suppressive therapy at least 30 days before the endoscopic examination. During the washout period, patients were allowed to use an oral antacid or alginate on as-needed basis for the relief of heartburn. On the basis of the results of the upper endoscopy, patients were subdivided into three major groups: Barrett's esophagus, EE, and NERD. EE was defined as the presence of esophageal mucosal injury with international criteria (17). Patients were considered to have NERD in case of an absence of visible esophageal mucosal injury during upper endoscopy, along with an abnormal esophageal acid exposure time (AET) and/or a positive symptom association probability (SAP, >95%) to acid and/or nonacid refluxes during impedance–pH monitoring (18,19). Patients with FH, defined as those with a normal esophagoscopy result, a normal pH testing result, and a negative result in symptom association analysis, were ruled out from the whole group of NERD patients. Patients with Barrett's esophagus were not included in this study. Within 1–5 days (median 3 days) of upper endoscopy, all patients underwent ambulatory multichannel intraluminal impedance–pH monitoring.

Thereafter, EE and NERD patients underwent a stationary esophageal manometry to locate the LES. After stationary manometry, the combined pH–impedance assembly was passed through the nose under topical anesthesia and positioned with the proximal pH electrode at 5 cm above the LES. In this position, the midpoints of the impedance recording segments were located at 3, 5, 7, 9, 15, and 17 cm proximal to the LES. During the 24 h study, patients were asked to remain in an upright position during the day and they were allowed to move freely and to have one recumbent period. Each subject consumed three standard meals during the examination period (breakfast at 08:00 hours, lunch at noon, and dinner at 18:00 hours), the composition of which has been previously reported (20). Patients were instructed to fill out a diary indicating the start and end of meals, changes in body position from upright to recumbent and *vice versa*, and record reflux symptoms during the monitoring period. Data recording was concluded after 24 h, when patients returned to our hospital service.

Data analysis

Data stored on the CompactFlash card were downloaded into a personal computer and analyzed using a semiautomated reflux detection algorithm (Autoscan; Sandhill Scientific). Accuracy of reflux detection was verified manually by an expert reader blinded to the condition of the patients (ES). Meal periods (three periods of approximately 20 min each) were excluded from the analysis.

Definitions of reflux episodes. Liquid reflux was defined as a retrograde 50% drop in impedance, starting distally (at the level of the LES) and propagating to at least the next two more proximal impedance-measuring segments. Gas reflux was defined as a rapid ($3\,k\Omega\,s^{-1}$) increase in impedance $>5{,}000\,\Omega$, occurring simultaneously in at least two esophageal measuring segments, in the absence of swallowing. Mixed liquid–gas reflux was defined as gas reflux occurring immediately before or during a liquid reflux.

Simultaneously recorded pH data were used to classify reflux episodes as acid, weakly acidic, or weakly alkaline according to the previously reported criteria (13): (i) acid reflux: impedance-detected reflux episodes with a nadir pH less than 4; (ii) weakly acidic reflux: impedance-detected reflux episodes with a nadir pH between 4 and 7; and (iii) weakly alkaline reflux: impedance-detected reflux episodes with a nadir pH above 7. For symptom analysis, weakly acidic and weakly alkaline refluxes were grouped together as nonacid reflux episodes (nadir pH >4).

Gastroesophageal reflux parameters. Impedance and pH data were used to define the number and type of reflux episodes, acid exposure (refluxate presence time (min) and refluxate percent time), proximal extent (number and percent of reflux episodes reaching 15 cm above LES), and median bolus clearance time and mean acid clearance time. Parameters were reported separately for upright and recumbent periods. Meals were excluded for the analysis.

Total 24 h esophageal acid exposure (%) was defined as the total time at pH below 4 divided by the time of monitoring. Total distal esophageal acid exposure (i.e., percent time pH <4) less than 4.2% over 24 h was considered normal (19,20).

For comparisons, normal values were obtained from 48 HVs studied in ambulatory conditions consuming the same standardized meals. The 95th percentile values obtained in this series were considered to be the upper limit of normal values.

Symptom–reflux association analysis. In each patient, we calculated the SAP for typical esophageal symptoms. In the analysis, we separated symptoms associated with acid reflux from those associated with nonacid reflux (including weakly acidic and weakly alkaline refluxes as a whole) and symptoms occurring independently of reflux episodes. Separate analysis was performed for each individual symptom if patients recorded different types of symptoms.

The SAP was calculated for both acid and nonacid refluxes using a custom-made Excel macrofunction (RT), by means of the algorithm described by Bredenoord *et al.* (21), and was considered positive if >95%.

A positive SAP for acid only was declared when SAP was ≥95% for acid refluxes and negative for nonacid refluxes; a positive SAP for nonacid only was declared when SAP was ≥95% for nonacid refluxes and negative for acid refluxes; a positive SAP for both acid and nonacid refluxes was declared when SAP was ≥95% for acid refluxes and ≥95% for nonacid refluxes or when SAP was negative for acid refluxes and nonacid refluxes separately, but was ≥95% considering both refluxes as a whole.

Statistical analysis

Differences in proportions were compared using the χ^2- or Fisher's exact test, depending on the sample size. Unless otherwise specified, data are presented as median and percentile values (25th, 75th, 95th percentile). Because data were not normally distributed, differences between groups were compared using Kruskal–Wallis and/or Mann–Whitney tests. Differences were considered statistically significant when $P<0.05$.

RESULTS

A total of 300 consecutive patients (139 men, mean age 49 years, range 18–80 years) with typical symptoms of GERD (i.e., heartburn and regurgitation) met the enrolment criteria and entered the study. During upper endoscopy, EE was identified in 58 patients (35 men, mean age 48 years, range 22–80 years), Barrett's esophagus was histologically confirmed in 18 patients (11 men, mean age 54 years, range 30–74 years), and no mucosal breaks were found in 224 patients (91 men, mean age 49 years, range 18–80 years). In the EE group, 34 patients had grade A, 13 had grade B, 9 had grade C, and 2 had grade D esophagitis. Patients with Barrett's esophagus were excluded from the study. During the impedance–pH monitoring period, 272 patients (87 men, mean age 49 years, range 18–80 years) reported at least one type of typical gastroesophageal reflux symptom (i.e., heartburn and regurgitation) and were included in the final analysis. Among the 214 patients with no mucosal injury at upper endoscopy and reporting typical reflux symptoms during impedance–pH testing, 168 were classified as having NERD (67 men, mean age 49 years, range 20–78 years), whereas 46 patients were identified as having FH and were excluded from the study.

Detailed demographic data of EE and NERD patients are shown in **Table 1**. Patients with EE were more frequently male (35 (60.3%) vs. 67 (39.9%); $P<0.01$) and had a higher mean body mass index ($27\,kg\,m^{-2}$ (range 18–$41\,kg\,m^{-2}$) vs. $25\,kg\,m^{-2}$ (range 18–$41\,kg\,m^{-2}$); $P<0.01$) compared with patients with NERD. The prevalence of hiatal hernia tended to be higher in EE than in NERD patients, but the difference was not significant (44 (75.9%) vs. 104 (61.9%); P = NS). No differences between these two groups were found with regard to mean age, smoking, alcohol, and coffee consumption.

The examination was well tolerated by all subjects and no important technical failure occurred. The median total recording time was 23.4 (22.9–23.6) h.

Table 1. Demographic and clinical characteristics of EE and NERD patients (*n*=226)

Demographic/clinical parameter	EE	NERD	*P* value
Patients, *n*	58	168	
Male patients, *n*	35	67	<0.01
Mean age	48 (23–80)	49 (20–78)	NS
Mean BMI	27 (18–41)	25 (18–41)	<0.01
Tobacco use, %	25.9	19	NS
Alcohol consumption, %	44.8	40.5	NS
Coffee consumption, %	70.7	78.6	NS
Prevalence of hiatal hernia, %	75.9	61.9	NS
Patients having previously received PPIs, *n* (%)	14 (24.1)	116 (69)	<0.01
Positive (>50%) symptom response, *n* (%)	8 (57.1)	83 (71.6)	NS

BMI, body mass index; EE, erosive esophagitis; NERD, nonerosive reflux disease; NS, not significant; PPI, proton pump inhibitor.

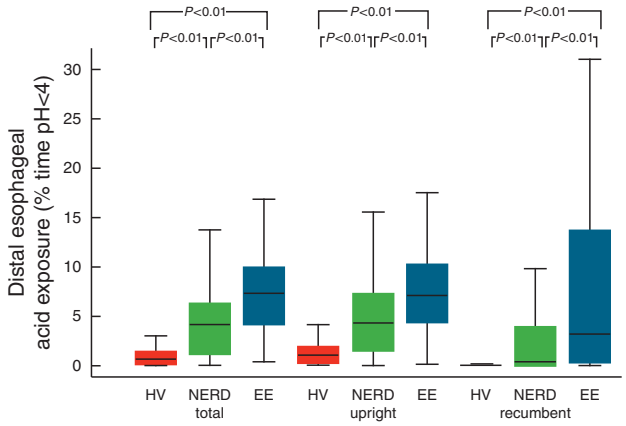

Figure 1. Median values of esophageal acid exposure time in erosive esophagitis (EE) patients (*n*=58), nonerosive reflux disease (NERD) patients (*n*=168), and healthy volunteers (HVs; *n*=48). Bars indicate median values.

pH–metry data

In all, 47 (81%) patients with EE and 90 (55%) patients with NERD had abnormal distal acid exposure ($P<0.01$). Patients with EE and NERD had significantly longer distal esophageal AETs compared with HVs (7.4 (4.2–9.9; 24) vs. 4.2 (1.2–6.4; 16) vs. 0.7 (0.2–1.4; 4.2), respectively; $P<0.01$). Distal esophageal acid exposure was longer ($P<0.01$) in EE patients than in NERD patients. This was true for both upright and recumbent body positions ($P<0.01$; **Figure 1**).

The mean acid clearance time was 96 (67–213; 438) s in EE patients and was significantly higher compared with that in NERD patients (72 (38–138; 311) s; $P<0.01$) and HVs (32 (16–50; 85) s; $P<0.01$). Moreover, NERD patients had a mean acid clearance time that was significantly longer than that of HVs ($P<0.01$).

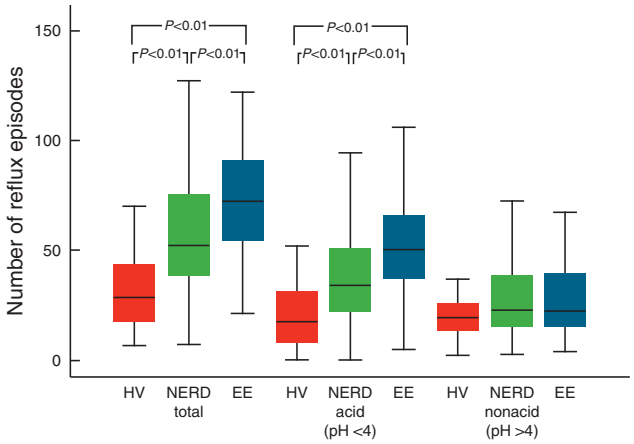

Figure 2. Numbers of total, acid, and nonacid reflux episodes in erosive esophagitis (EE) patients (*n*=58), nonerosive reflux disease (NERD) patients (*n*=168), and healthy volunteers (HVs; *n*=48).

Impedance data

The numbers of gastroesophageal reflux episodes (total, acid, and nonacid) detected during the pH–impedance studies are indicated in **Figure 2**. The median total number of reflux episodes (73 (54–91; 173)) and the median number of acid reflux events (51 (37–66; 157)) were significantly higher in EE patients than in NERD patients (52 (39–75; 136) and 34 (22–51; 91), respectively; $P<0.01$) and HVs (32 (18–43; 54) and 17 (8–31; 45), respectively; $P<0.01$). This was also true when NERD patients were compared with HVs ($P<0.01$). EE patients, NERD patients, and HVs had a similar median number of nonacid reflux episodes (22 (15–39; 66) vs. 23 (15–38; 78) vs. 18 (14–26; 45) (P=NS)).

With regard to the physical properties of the refluxate, patients with EE had a higher median number of liquid (30 (15–48; 103)) and gas-containing reflux episodes (43 (31–53; 65)) compared with NERD patients (20 (10–35; 88) and 32 (20–45; 61), respectively; $P<0.01$) and HVs (15 (8–20; 31) and 16 (6.5–23; 37.5), respectively; $P<0.01$). This was true for both upright and recumbent body positions ($P<0.01$). Moreover, NERD patients showed a higher incidence of gas-containing reflux episodes compared with HVs ($P<0.01$), but there was no difference in terms of liquid reflux episodes (P=NS; **Figure 3a** and **b**).

The median bolus clearance time (seconds) of EE patients (17 (13–23; 31)) was significantly different compared with that of NERD patients (14 (11–19; 30); $P<0.01$) and HVs (12 (8–15; 20); $P<0.01$). Conversely, no difference was found between NERD patients and HVs (P=NS).

More reflux episodes reached the proximal esophagus (44 (29–60; 109)) in EE patients than in NERD patients (24 (14–41; 77); $P<0.01$) and HVs (9 (4–17; 30); $P<0.01$). Moreover, the percentage of total reflux episodes reaching the proximal measuring site was higher in EE patients than in NERD (57 vs. 45%; $P<0.01$) patients and HVs (57 vs. 33%; $P<0.01$), as shown in **Figure 4**. The

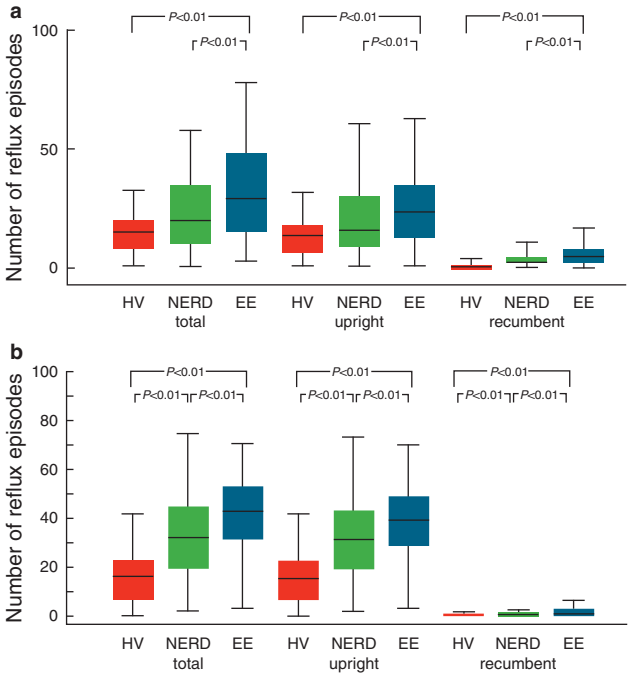

Figure 3. Number of liquid (**a**) and mixed (**b**) reflux episodes in erosive esophagitis (EE) patients ($n=58$), nonerosive reflux disease (NERD) patients ($n=168$), and healthy volunteers (HVs; $n=48$). (**a**) Liquid reflux episodes. (**b**) Mixed reflux episodes.

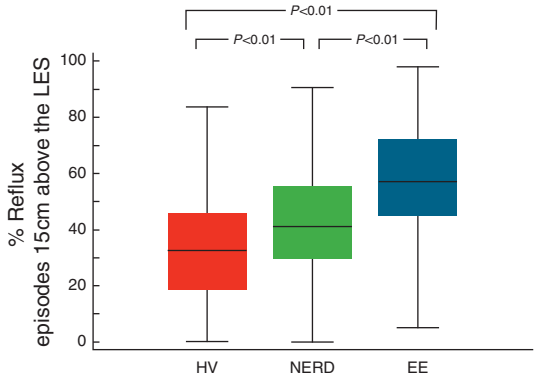

Figure 4. Percentage of reflux episodes reaching the proximal measuring site (15 cm above the lower esophageal sphincter (LES)) in erosive esophagitis (EE) patients ($n=58$), nonerosive reflux disease (NERD) patients ($n=168$), and healthy volunteers (HVs; $n=48$).

differences between NERD patients and HVs were also statistically significant ($P<0.01$).

Symptom–reflux association

The total number of symptoms reported by EE and NERD patients was 2,654 (6 (3–14; 38), range 1–137). Patients reported 1,669 heartburn (4 (2–11; 31), range 1–76) and 985 regurgitation events (3 (1–7; 32), range 1–69). No difference was found between EE and NERD patients considering the mean frequency of reported reflux symptoms, both heartburn (6 (3–13; 26) vs. 4 (2–11; 31); $P=$NS) and regurgitation (5 (2–7; 24) vs. 3 (1–8; 36); $P=$NS).

The SAP with acid and nonacid reflux in EE and NERD patients is shown in **Figure 5a** and **b**. Among the 58 EE patients, we found an abnormal AET in 47 (81%) patients, and 44 (76%) of them had a positive SAP (≥95%). In all, 35 (60%) patients had a positive SAP for acid reflux only, 4 (7%) individuals for nonacid reflux only, and 5 (9%) for both. Eleven patients (19%) had a normal AET (percent time pH <4 less than 4.2%), out of whom 10 (17%) had a positive SAP. Four (7%) patients had a positive SAP for nonacid reflux only, three (5%) for acid reflux only, and three (5%) for both. Among the 168 NERD patients, we found an abnormal AET in 90 (53%) patients, and 83 (49%) of them had a positive SAP. A total of 63 (37%) patients had a positive SAP for acid reflux only, 10 (6%) for nonacid reflux only, and 10 (6%) for both. In all, 78 (47%) patients had a normal AET with a positive SAP. Twenty-six (16%) patients had a positive SAP for nonacid reflux only, 27 (16%) for acid reflux only, and 25 (15%) for both.

DISCUSSION

Our study collected 24 h ambulatory impedance–pH monitoring data in a large group of unselected EE and NERD patients who were off medication. Owing to the application of impedance–pH monitoring, we excluded from the whole group of patients with NERD those who responded to the objective criteria of FH and, for the first time, we were able to compare reflux characteristics between EE and "real" NERD patients in agreement with the Rome III criteria (16). We showed a higher AET, a higher median number of total and acid-only refluxes, a higher rate of liquid and gas-containing reflux episodes, more prolonged mean acid clearance time and median bolus clearance time, and, finally, a higher percentage of proximal migration of the refluxate in patients with EE compared with patients with NERD and HVs. Conversely, NERD patients had a higher AET, a higher median number of total and acid-only refluxes, a higher rate of gas-containing reflux episodes, more prolonged mean acid clearance time, and finally, a higher percentage of proximal migration of the refluxate than controls. As to nonacid reflux episodes, impedance recordings detected a similar number in EE and NERD patients, as well as in HVs. These results suggest that acid reflux episodes, volume, and acid clearance are important factors in the pathogenesis of reflux-induced mucosal lesions, whereas nonacid reflux contributes less to esophageal mucosal damage. Conversely, nonacid reflux is relevant toward inducing reflux symptoms in both EE and NERD patients, as indicated by previous studies (14).

In our investigation, EE patients had higher AETs compared with NERD patients, who, in turn, presented a higher AET than did HVs, both in upright and supine positions. Previously, Frazzoni *et al.* (22) in a study evaluating a large number of patients with different forms of GERD reported a greater supine nocturnal acid reflux time in EE patients compared with NERD patients. On the basis of these findings, they concluded that nocturnal acid reflux occurring in the recumbent position had the highest probability of damaging the esophageal mucosa, as the

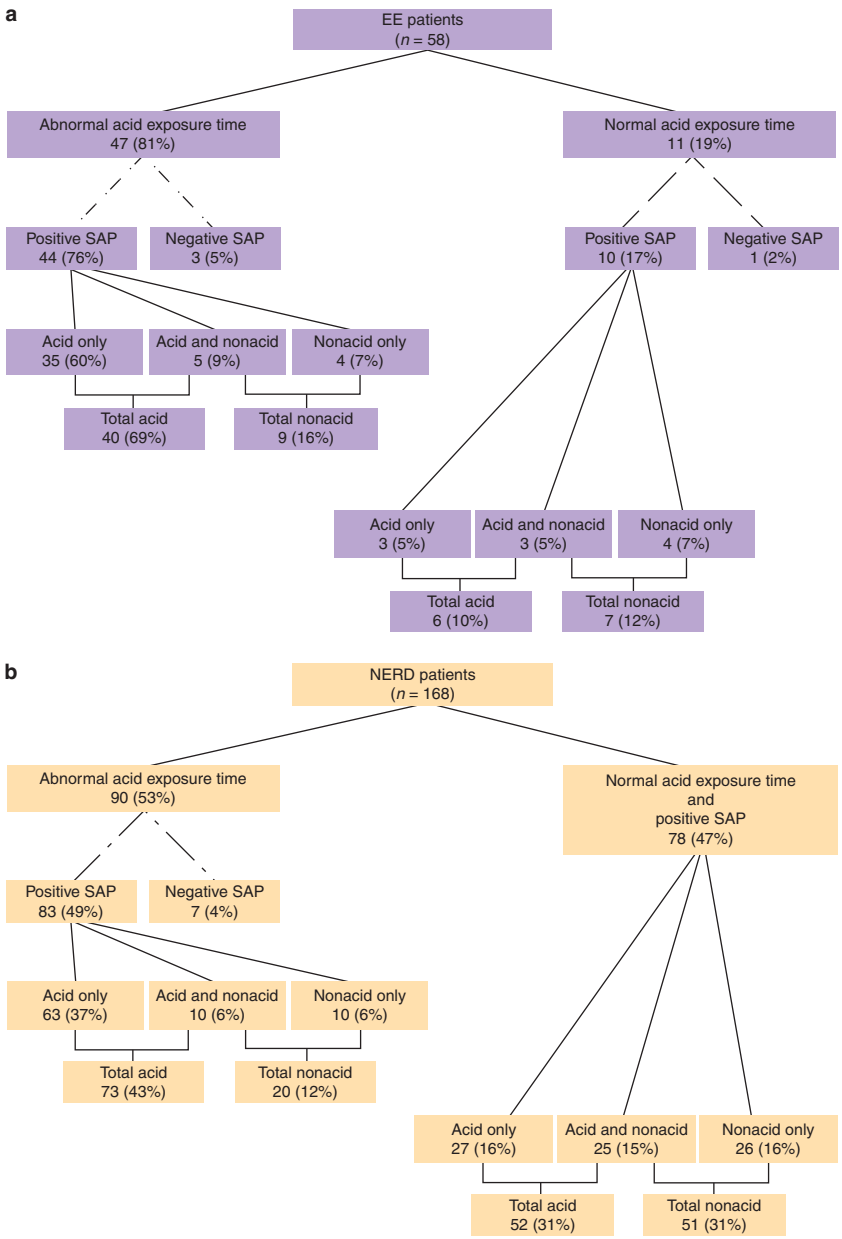

Figure 5. (**a**) Stratification of erosive esophagitis (EE) patients on the basis of distal esophageal acid exposure and symptom association probability (SAP). (**b**) Stratification of nonerosive reflux disease (NERD) patients on the basis of distal esophageal acid exposure and SAP.

absence of gravity coupled with reduced primary peristalsis and salivation during sleep leads to impaired bolus clearance. However, in our investigation, we observed a significantly longer AET in upright periods as well. A possible explanation for this could be the increased prevalence of hiatal hernia in our EE patients, as this factor has been shown to have a major role in promoting acid refluxes (23,24) and in determining the best proton pump inhibitor dosage for optimal treatment of GERD (25). Moreover, the higher mean body mass index value of EE patients compared with NERD patients and HVs could explain this difference, as overweight increases the propensity to have reflux and consequently to higher AET (26). In addition, Martinez *et al.* (9) reported a higher prevalence of abnormal AET in EE compared with NERD patients. It is worth noting, however, that this difference could be because of the presence, under the same NERD population, of patients affected by distinct subsets with normal AET, such as FH and hypersensitive esophagus, as we have shown in a recent study (14). Indeed, Martinez *et al.* (9) observed that only NERD-positive patients (abnormal pH test) had the same degree of acid exposure in different positions and the same number of acid reflux events as patients with EE. Finally, the more prolonged acid and volume clearances we observed in EE patients compared with NERD and HVs further corroborate our findings. These results, together with current data, emphasize that not only the presence of acid but also its amount and the reduced clearing capacity of the esophagus have an important role in causing erosive lesions.

Similar to previous studies (9,22), we noted that the number of total and acid reflux episodes and liquid- and gas-containing events were higher in patients with EE compared with NERD patients and HVs. Sifrim *et al.* (27) using pH-impedance testing over 24 h for the first time suggested that acid reflux and, in particular, liquid episodes were more likely to damage the esophageal mucosa. This important concept is confirmed in our investigation in which, unlike the above study, we compared not only EE patients with controls but also EE patients with NERD patients who, by definition, have a reflux disease without endoscopic signs of mucosal damage, despite an abnormal AET and/or positive symptom association. Indeed, in our study, we observed that EE patients had more liquid reflux episodes when compared to NERD patients and HVs. This difference is not seen in NERD patients when compared with HVs, revealing another piece in the puzzle of understanding the role of the physical properties of reflux episodes in causing esophageal damage.

As reported initially by Sifrim *et al.* (27) and more recently by Conchillo *et al.*, (15) we did not find an increased number of nonacid reflux episodes in EE patients compared with NERD and HVs, thus confirming that monitoring for nonacid reflux is of little help in differentiating between NERD and EE patients and implying that nonacid reflux most likely has a marginal role in the pathogenesis of esophageal mucosal injury. However, it is relevant to note that the above two studies differ from ours because they were performed on smaller groups of patients in different experimental conditions and with other primary aims. Indeed, Sifrim *et al.* (27) compared the reflux patterns collected from a group of 30 complicated GERD patients, including those with EE and Barrett's esophagus in the same population, with patterns collected from a group of 28 HVs, thereby excluding patients with NERD from their study. Moreover, unlike our investigation, they enrolled GERD patients who were referred to their center with both typical and atypical reflux symptoms and performed impedance–pH studies using three standardized liquid meals during the testing day to promote homogeneous mixing of gastric contents and to reduce the well-known influence of a different diet on the results. Conversely, Conchillo *et al.* (15) compared a small sample of 13 EE and 13 NERD patients, and they failed to find any relevant difference between them regarding not only the prevalence of nonacid reflux but also the majority of impedance–pH variables; it is quite possible that their negative results were a consequence of a type II error. At variance with the above two studies, we enrolled a large number of EE and NERD patients and this allowed us to prove that relevant differences between these two populations exist by taking into account the majority of impedance–pH data and they may explain, at least in part, the presence of esophageal mucosal injury in EE compared with NERD patients.

Several studies have revealed the role of nonacid reflux in the pathogenesis of symptoms in GERD patients, in particular while on acid suppressive therapy. Vela *et al.* (28) showed that, although the total number of postprandial reflux episodes did not change significantly after acid suppressive treatment, reflux episodes with pH > 4 were associated with typical reflux symptoms. In a recent study, Mainie *et al.* (29) evaluated patients with persistent symptoms despite acid suppressive therapy and found that nonacid reflux was the main type of reflux associated with typical GERD symptoms in them. To the best of our knowledge, this is the first study aimed at comparing SAP with acid and nonacid refluxes recorded using multichannel intraluminal impedance–pH in such a large population of GERD patients. It is worth noting that we analyzed SAP in EE and NERD patients off medication to investigate the role of nonacid in inducing symptoms in these two GERD subpopulations. The present results indicate that nonacid reflux is associated with typical reflux symptoms in 7 and 6% of EE and NERD patients with abnormal AET, respectively, and in 7 and 16% of EE and NERD patients with a normal AET. Although at first glance, the proportion of patients with a positive symptom association with nonacid reflux seems to be small, this finding is relevant because it indicates that components other than acid in the gastroesophageal refluxate have a role in symptom development in both the erosive and nonerosive form of GERD. These results emphasize that nonacid reflux induces symptoms even in patients with EE not treated with acid suppressive medications. A positive symptom association with nonacid argues for gastroesophageal reflux causing symptoms, thus reducing the need to look for causes other than reflux to explain the lesions and symptoms in these patients. As to the clinical relevance of these findings, we can speculate that these patients are more likely to belong to the group of those in whom symptoms fail to respond to acid suppressive medications (30). Finally, the increased percentage of NERD patients whose symptoms are related to nonacid reflux in the population with normal AET could explain the lower response rate of NERD patients compared with EE patients to acid suppressive therapy. Conversely, this proton pump inhibitor failure could be because of the higher sensitivity of NERD patients to stimuli other than acid, as proposed by others (4,31–36).

The percentage of reflux episodes reaching the proximal esophagus was higher in patients with EE compared with NERD patients and HVs and in NERD patients compared with HVs. These data confirm previous results by Bredenoord *et al.* (37) documenting that in symptomatic GERD patients without excessive esophageal acid exposure, a higher proportion of reflux episodes reaches the proximal esophagus. Unfortunately, because of the small sample size in their study, they could not subdivide GERD patients into EE or NERD to evaluate differences among these two subgroups of patients. The increased prevalence of gas-containing reflux episodes that we found in both symptomatic EE and NERD patients is in agreement with a recent study by Emerenziani *et al.*, (38) showing the role of gas as an enhancer of symptom perception. In contrast with our findings, Cicala *et al.* (39) reported that NERD patients are characterized by a significantly higher proportion of proximal acid refluxes compared with patients with esophagitis. This discrepancy could be because of methodological reasons, as

Cicala *et al.*, using pH monitoring only, focused primarily on acid reflux, whereas in our study, the use of impedance–pH monitoring helped us to identify the proximal extent of non-acid reflux as well.

This study certainly has limitations, as it was designed to primarily compare the reflux patterns in EE and NERD patients off therapy. In fact, only retrospective data are available on the response to proton pump inhibitor therapy in the two patient groups; therefore, it remains unclear whether patients with EE and with NERD respond differently to medication and those with abnormal AET and positive symptom association with acid and/or nonacid reflux respond differently from those with normal AET and positive symptom association with acid and/or nonacid reflux. Evaluating patients on a Mediterranean diet could also be regarded as a shortcoming of this study, with the argument that it was not refluxogenic enough to induce symptoms. The decision to use a Mediterranean diet was based on the fact that this diet is common in Italy and to allow us to compare the results obtained from EE and NERD patients with those from healthy Italian volunteers. It is noteworthy that that the number of typical reflux symptoms reported by our patients during the monitoring period did not differ from those observed in other studies in which the diet was not controlled (38).

In conclusion, comparing reflux patterns in patients with erosive and nonerosive (devoid of the FH subgroup) GERD with HVs suggests that the number of acid reflux episodes, volume and acid clearance, liquid reflux events, and proximal migration of the refluxate are important factors in the development of esophageal mucosal lesions. Nonacid reflux seems to be less damaging to esophageal mucosa. However, monitoring for both acid and nonacid reflux is important while evaluating the causes of symptoms in patients with both EE and NERD.

CONFLICT OF INTEREST

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Specific author contributions: Edoardo Savarino: design of the study, data collection and analysis, writing of the paper, and approving final version; Radu Tutuian: data analysis, writing of the paper, and approving final version; Patrizia Zentilin: design of the study, data collection and analysis, writing of the paper, and approving final version; Pietro Dulbecco: data collection and approving final version; Daniel Pohl: data analysis, writing of the paper, and approving final version; Elisa Marabotto: data collection and analysis and approving final version; Andrea Parodi: data collection and approving final version; Giorgio Sammito: data collection and analysis and approving final version; Lorenzo Gemignani: data collection and analysis and approving final version; Giorgia Bodini: data collection and approving final version; Vincenzo Savarino: design of the study, data collection and analysis, writing of the paper, and approving final version.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Gastroesophageal reflux disease (GERD) is one of the most common chronic gastrointestinal diseases in Western countries. Nonerosive reflux disease (NERD) and erosive esophagitis (EE) are the most frequent phenotypic presentations of GERD.
- ✓ The use of 24 h esophageal pH monitoring has been used to distinguish GERD patients with normal and abnormal esophageal acid exposure.
- ✓ In recent years, the combination of traditional pH monitoring and esophageal intraluminal electrical impedance has offered the potential to detect all kinds of reflux patterns in GERD patients.

WHAT IS NEW HERE

- ✓ The number of acid reflux episodes, refluxate and acid clearance, liquid reflux events, and proximal migration of the refluxate are important in the pathogenesis of esophageal mucosal damage.
- ✓ Nonacid reflux seems less damaging to the esophageal mucosa; however, it is involved in the perception of reflux symptoms.
- ✓ Monitoring for acid and nonacid reflux is clinically relevant in both erosive and nonerosive GERD.

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