

# Reflux characteristics triggering post-reflux swallow-induced peristaltic wave (PSPW) in patients with GERD symptoms

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## Abstract

**Background:** Esophageal chemical clearance has been evaluated with the post-reflux swallow-induced peristaltic wave (PSPW) index. The factors triggering PSPW in Gastro-esophageal reflux disease (GERD) have not yet been investigated. This multi-center study was aimed at evaluating the characteristics of reflux episodes associated with PSPW occurrence in patients with typical GERD symptoms.

**Methods:** Impedance-pH tracings from patients with typical reflux symptoms were analyzed. Sixteen healthy subjects were included for comparison. Multivariate analysis was performed to determine predictors of PSPW events.

**Key results:** Impedance-pH tracings from 60 patients and 16 healthy subjects were evaluated. A total of 3454 refluxes were recorded. In patients, comparing reflux episodes followed with those not followed by a PSPW, significantly higher proportions of acid (79% vs. 74%,  $p$ : 0.02), mixed (47% vs. 32%,  $p$ : 0.0001) and proximal refluxes (34% vs. 20%,  $p$ : 0.0001) were observed. A multivariate analysis, acid (OR: 1.3, 95% CI: 1.05–1.6), mixed (OR: 2, 95% CI: 1.6–2.3), and proximal (OR: 2.1, 95% CI: 1.7–2.5) refluxes were independently associated with PSPWs. Reflux episodes followed by a PSPW were characterized by a significantly higher bolus clearing time [(mean  $\pm$  SD) 41 s  $\pm$  6 s vs. 30 s  $\pm$  5 s,  $p$  < 0.05] whereas nadir pH value of reflux events preceding PSPWs was tangentially but not significantly lower [(mean  $\pm$  SD) 2.61  $\pm$  1.22 vs. 2.74  $\pm$  1.26,  $p$ : 0.057].

**Conclusions and inferences:** Acid, mixed and proximal refluxes, and their duration are key factors in eliciting PSPWs. PSPW represents a response to reflux directly related to the potential harmfulness of reflux contents.

## KEYWORDS

GERD, PPI, PSPW

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## 1 | INTRODUCTION

Gastro-esophageal reflux disease (GERD) represents one of the most common gastrointestinal disorders, with an increasing worldwide prevalence.<sup>1-3</sup> GERD is a complex disease and is characterized by various symptom profiles as well as complex pathogenesis.

Esophageal clearance of refluxate represents, among all, a key factor in preventing the development of reflux disease and disease progression.<sup>4,5</sup> The clearance of reflux episodes is usually mediated by primary and secondary peristalsis, the latter elicited by local activation of mechanoreceptors removing the bulk of refluxate—volume clearance—and the former triggered by a vagal esophago-salivary reflex inducing salivary swallow and increasing esophageal pH—chemical clearance—.<sup>6-8</sup> Nevertheless, volume and chemical clearance do not always restore the esophageal pH preceding the reflux event.

Recently, the esophageal chemical clearance mechanism has been demonstrated with the post-reflux swallow-induced peristaltic wave (PSPW), that is, the impedance drops propagating from the proximal to the distal esophagus and occurring within 30 s after a reflux event and triggered by the esophago-salivary reflex.<sup>9</sup> Dividing the number of PSPWs by the number of reflux events a new multichannel intra-luminal impedance-pH (MII-pH) variable, namely the PSPW index, has been obtained.<sup>9</sup> It has been shown that patients with GERD present lower PSPW index values as compared to controls, being this variable also a potential diagnostic tool when other MII-pH parameters are inconclusive.<sup>10</sup> Moreover, PSPW index appears to be a promising variable in predicting response to acid-suppressive therapy,<sup>11</sup> as suggested by current international guidelines.<sup>12-14</sup> Very recently, it has been shown that PSPWs are associated with significantly higher pH increments in GERD patients responding to proton pump inhibitor (PPI) therapy compared to non-responders, thus confirming the defense role of the esophago-salivary reflex against reflux.<sup>15</sup>

Nowadays, it is still not completely understood why, in GERD patients, less than half of reflux episodes are followed by PSPW events. Recently, two studies were aimed at evaluating the potential factors triggering PSPWs. Zhang et al<sup>16</sup> have shown, in a large cohort of asymptomatic subjects, that reflux episodes followed by PSPWs were more frequently mixed, with a higher proximal extent, occurring while awake and associated with a shorter chemical clearance time. Furthermore, it has been shown in a small group of GERD patients that PSPWs were elicited more frequently by reflux episodes with a higher proximal extent whilst the role of the acid component of refluxate seemed not to be less important.<sup>17</sup>

Finally, it has recently been shown that patients with reflux symptoms and evidence of esophageal hypomotility as detected at high-resolution manometry (HRM) are characterized by significantly lower PSPW index values than patients with normal esophageal motility.<sup>18</sup>

In order to better elucidate the relationship between reflux properties and PSPW occurrence, we evaluated the characteristics of reflux episodes associated with PSPW occurrence in a large group of patients with typical GERD symptoms.

### Key points

- It has been shown that PSPWs are associated with remarkable increments of esophageal pH, higher in PPI-responsive than in PPI refractory GERD, revealing the occurrence of esophago-salivary reflex, and its clinical relevance as a neural-mediated defense mechanism against reflux.
- In the present study, we show that PSPWs are more frequently elicited by acid, mixed, and proximal refluxes as well as by prolonged reflux events.
- The present findings indicate that eliciting of PSPWs is directly related to the aggressive characteristics of refluxate.

## 2 | MATERIALS AND METHODS

### 2.1 | Patients

Ambulatory 24-h MII-pH tracings from consecutive adult patients (age > 18 years), assessed at six centers in Italy, were retrospectively evaluated. Inclusion criteria were the presence of dominant esophageal symptoms (heartburn, regurgitation, and non-cardiac chest pain)<sup>19</sup> unresponsive to acid-suppressive therapy or responsive but requiring reflux testing to confirm the need for long-term PPI therapy or to document pathologic reflux prior to anti-reflux surgery. A validated structured questionnaire, administered and in the presence of a senior investigator and based on a four-grade Likert-type scale, was used in each center to evaluate esophageal, dyspeptic and extra-esophageal reflux symptoms, (0 = none; 1 = mild/occasional; 2 = moderate/frequent; 3 = severe/constant).<sup>20</sup> Symptoms were considered troublesome when a score  $\geq 2$  was achieved. Inclusion in this study required ambulatory MII-pH studies, performed off acid-suppressive therapy (after at least 7 days pharmacological wash-out).<sup>21</sup> Individuals with inadequate evaluation (equipment malfunction, poor study quality and presence of artifacts), patients with evidence of erosive esophagitis and/or Barrett esophagus, presence of hiatal hernia >2 cm, connective tissue disease, psychiatric disease, history of neoplasia, and prior foregut surgery were excluded. MII-pH studies were always preceded by high-resolution esophageal manometry (HRM) for accurate location of the lower esophageal sphincter (LES) and exclusion of major motility disorders. All patients were treated, within the previous year, with at least 8 weeks of standard-dose PPI therapy (Esomeprazole 40 mg once daily [od], Pantoprazole 40 mg od, Lansoprazole 30 mg od, and Omeprazole 20 mg od). Patients were categorized as non-responders if symptom improvement while on therapy, using these scales, was <50% compared to symptom assessment off therapy.<sup>22</sup> Non-responder patients with normal findings at MII-pH study were excluded. Data were compared to those obtained from 16 asymptomatic healthy subjects evaluated with HRM and MII-pH monitoring.

The study was carried out in accordance with the Declaration of Helsinki and was approved by institutional review boards. Signed informed consent was obtained from all individuals before undergoing clinical investigations.

## 2.2 | 24-h MII-pH monitoring

Multichannel intra-luminal impedance-pH was recorded using a 2.3 mm diameter polyvinyl catheter assembly containing a series of impedance electrodes, each 4 mm in axial length, spaced at 2 cm intervals, and a distal antimony pH electrode (Sandhill Scientific Inc.). The pH electrodes were calibrated using pH 4.0 and pH 7.0 buffer solutions before MII-pH monitoring. Following esophageal manometry, the catheter was passed through the anesthetized nostril, and positioned with the pH electrode 5 cm above the LES, and impedance electrodes at 3, 5, 7, 9, 15, and 17 cm proximal to the LES. MII-pH was always preceded by HRM for accurate location of the LES and exclusion of major motility disorders according to guidelines.<sup>23</sup>

Event markers, corroborated with paper diaries, were used to record symptoms, meal times, and supine periods. Tracings were manually assessed with the aid of commercial software. Liquid and liquid-gas reflux events were distinguished into acid (nadir pH < 4.0), weakly acidic (nadir pH between 4.0 and 7.0), and weakly alkaline (nadir pH not below 7.0); meal times were excluded. Acid exposure time (AET) was defined as pathological if the time pH < 4 exceeded 6% of the total recording time.<sup>12</sup> Reflux-symptom association was assessed using symptom index (SI) and symptom association probability (SAP) for all reflux episodes using previously described methodology.<sup>24,25</sup> Bolus clearing time (BCT), that is, time-frame between reflux entry and exit, was calculated at 5 cm above LES.<sup>26</sup> PSPWs were defined as antigrade 50% drops in impedance, originating in the proximal esophagus and reaching the distal lumen within 30 s after reflux events. The PSPW index was calculated by dividing the number of PSPWs by the number of reflux events.<sup>9,27</sup> A reflux episode was defined as preceded by another reflux if the latter occurred in the preceding 5-min time-window frame. Refluxes followed by symptom recording and subsequently followed or not by a PSPW event, within a 30 s time window, were measured. Moreover, reflux episodes followed by a PSPW event and subsequently followed by a symptom (within a 2 min time window) were also measured.

## 2.3 | Statistical analysis

Data are presented as means and standard deviation (SD) unless otherwise indicated. Comparisons between groups were assessed using the Fisher's exact test and the Mann-Whitney *U* test when appropriate. Multivariate regression models were generated to evaluate the association between each reflux characteristic and PSPW events. Significance was achieved when the *p* value was <0.05. Statistical analysis was performed using SPSS version 16.0 software (SPSS Inc.).

## 3 | RESULTS

Multichannel intra-luminal impedance-pH tracings from 60 patients and 16 controls were evaluated. Demographics and MII-pH characteristics of patients and controls included in the study are reported in Table 1. In patients, the majority of cases were characterized by a pathological AET or a positive SAP and/or SI. Twelve patients (20%) were non-responders to previous PPI treatments; of these, 10 were characterized by a pathological AET and the remaining 2 by a positive SAP and/or SI. All controls displayed normal AET.

A total of 3096 reflux episodes were detected in GERD patients. The mean reflux number for each patient was 51.6 (SD: 29). Overall PSPW index was 21.5%. The majority of refluxes were acid, pure liquid, and not reaching the proximal esophagus. One-fourth of the total refluxes were preceded by a reflux episode in the previous 5-min time window. Mean BCT at 5 cm above LES for all reflux episodes was 28.6 s (SD: 76.1 s). Among control subjects, a total of 358 reflux episodes were detected. Mean reflux number for each healthy subject was 22.4 (SD: 10) (*p* < 0.01 vs. patients). Overall PSPW index was 70.1% (*p* < 0.01 vs. patients). Mean BCT at 5 cm above LES for all reflux episodes was 13.5 s (SD: 17.4 s), (*p* < 0.01 vs. patients). Reflux episodes followed by a PSPW were characterized by a significantly higher BCT at 5 cm above the LES compared with refluxes not followed by a PSPW [(mean ± SD); 18.1 ± 11.2 and 9.7 ± 8.6, *p* < 0.01].

Ineffective esophageal motility (IEM) was detected in 10 patients (two patients with 8–10 ineffective swallows). Overall PSPW index value in patients with normal motility and evidence of IEM was 24% and 21.3% (*p*: 0.34).

Table 2 summarizes the characteristics of reflux episodes associated or not to a PSPW event in patients. Among reflux episodes followed by a PSPW event, a significantly higher proportion of acid, mixed and proximal refluxes was observed when compared with the reflux episodes not followed by a PSPW. Proportion of refluxes

TABLE 1 Demographic and MII-pH characteristics of patients and controls included in the study

	Patients	Controls
Male gender ( <i>n</i> ) (%)	32 (53%)	8 (50%)
Age (years) (mean) (SD)	47 (18)	41 (15)
Abnormal AET ( <i>n</i> ) (%)	32 (53%)	0
Positive SAP/SI ( <i>n</i> ) (%)	37 (62%)	0
Total refluxes	3096	358
Refluxes followed by a PSPW ( <i>n</i> ) (%)	666 (21.5%)	251 (70.1%)
Acid refluxes ( <i>n</i> ) (%)	2343 (76%)	98 (27.3%)
Mixed refluxes ( <i>n</i> ) (%)	1091 (35%)	149 (41.6%)
Proximal refluxes	723 (23%)	131 (36.6%)
Refluxes preceded by a reflux episode (5 min) ( <i>n</i> ) (%)	776 (25%)	45 (12.6%)

	Refluxes followed by a PSPW (n.: 666)	Refluxes not followed by a PSPW (n.: 2430)	p Value
Acid refluxes (n) (%)	527 (79%)	1816 (74%)	$p < 0.02$
Mixed refluxes (n) (%)	315 (47%)	776 (32%)	$p < 0.001$
Proximal refluxes (n) (%)	228 (34%)	495 (20%)	$p < 0.001$
Refluxes preceded by a reflux episode (5 min) (n) (%)	161 (24%)	615 (25%)	$p: 0.3$

TABLE 2 Characteristics of reflux episodes associated and not associated to a PSPW event in patients

	Refluxes followed by a PSPW (n.: 251)	Refluxes not followed by a PSPW (n.: 107)	p Value
Acid refluxes (n) (%)	71 (28.3%)	27 (25.2%)	$p: 0.6$
Mixed refluxes (n) (%)	130 (51.8%)	19 (17.8%)	$p < 0.001$
Proximal refluxes (n) (%)	112 (44.6%)	19 (17.8%)	$p < 0.001$
Refluxes preceded by a reflux episode (5 min) (n) (%)	29 (11.6%)	16 (15%)	$p: 0.38$

TABLE 3 Characteristics of reflux episodes associated and not associated to a PSPW event in controls

preceded by a previous reflux episode, in the 5-min time window, were comparable between the two groups. In controls, among reflux episodes followed by a PSPW event, a significantly higher proportion of mixed and proximal refluxes was observed when compared with the reflux episodes not followed by a PSPW (Table 3).

In patients, reflux episodes followed by a PSPW were characterized by a significantly higher BCT at 5 cm above the LES compared with refluxes not followed by a PSPW (Figure 1). Reflux episodes followed by a PSPW event were characterized by lower nadir pH value when compared to refluxes not followed by PSPW, although this difference was not significant [(mean  $\pm$  SD);  $2.61 \pm 1.22$  and  $2.74 \pm 1.26$ ,  $p: 0.057$ ]. In healthy volunteers, reflux episodes followed by a PSPW event were characterized by similar nadir pH value when compared to refluxes not followed by PSPW [(mean  $\pm$  SD);  $3.51 \pm 0.81$  and  $3.72 \pm 0.92$ ,  $p: 0.42$ ].

A total of 207 over 3096 reflux episodes were followed by a symptom marker within 30 s. Of these, 41 reflux episodes (20%) were followed by a PSPW event within 30 s whilst the remaining 166 refluxes (80%) were not ( $p < 0.0001$ ). Thirty-two reflux episodes followed by a PSPW event were followed by symptom recording within a 2 min time window.

According to multivariate analysis, mixed liquid-gas and reflux reaching the proximal esophagus were characterized by a significantly higher probability to be associated to a PSPW event in controls whilst, in patients, acid, mixed liquid-gas and reflux reaching the proximal esophagus were characterized by a significantly higher probability to be associated to a PSPW event (Table 4). PSPW index values in patients with pathological AET (n.: 32), patients with only positive SAP/SI (n.: 18), and patients with normal AET and negative SAP/SI (n.: 10) were 18.7%, 23.6%, and 27.4%, respectively. Proportion of PSPW events associated with weakly

acidic refluxes were comparable between the three groups (21.3%, 22.6%, and 21.1%, respectively;  $p$ : not significant for all comparisons). According to multivariate analysis, in patients with only positive SAP and/or SI, acid, mixed liquid-gas, and proximal refluxes were characterized by a significantly higher probability to be associated with a PSPW event (Table 5). In patients with pathologic AET value and in those with both physiologic AET value and negative SAP and/or SI, mixed liquid-gas and proximal reflux episodes were characterized by a significantly higher probability to be associated with a PSPW (Table 5).

## 4 | DISCUSSION

To our knowledge, this is the first study evaluating the potential intra-esophageal factors associated with PSPW events, an important

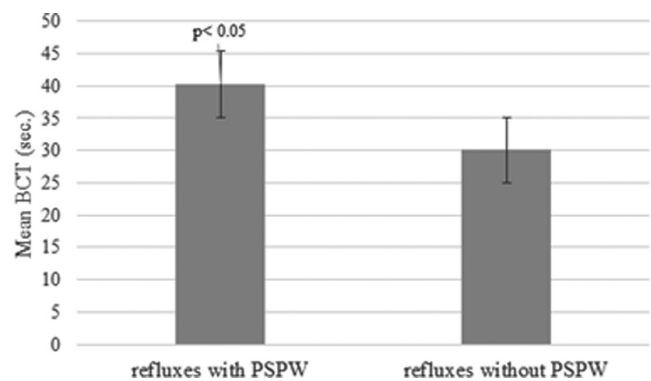


FIGURE 1 Mean ( $\pm$ SD) BCT values of refluxes associated and not associated to PSPW

**TABLE 4** Multivariate logistic regression analysis of predictors of PSPW events in patients and controls

	Patients		Controls	
	Odds Ratio (95% CI)	p Value	Odds Ratio (95% CI)	p Value
Acid refluxes	1.3 (1.05–1.6)	<i>p</i> < 0.05	0.8 (0.6–1.2)	<i>p</i> : 0.8
Mixed refluxes	2 (1.6–2.3)	<i>p</i> < 0.001	2.3 (1.8–2.6)	<i>p</i> < 0.001
Proximal refluxes	2.1 (1.7–2.5)	<i>p</i> < 0.001	1.9 (1.4–2.1)	<i>p</i> < 0.001
Refluxes preceded by a reflux episode (5 min)	0.9 (0.8–1.2)	<i>p</i> : 0.9	0.7 (0.6–1.1)	<i>p</i> : 0.7

**TABLE 5** Multivariate logistic regression analysis of predictors of PSPW events in patients according to the MII-pH profile

	AET+ (n.: 32)		AET-/SAP+/SI+ (n.: 18)		AET-/SAP-/SI- (n.: 10)	
	Odds Ratio (95% CI)	p Value	Odds Ratio (95% CI)	p value	Odds Ratio (95% CI)	p Value
Acid refluxes	0.5 (0.8–1.5)	<i>p</i> : 0.5	1.7 (1.1–2.6)	<i>p</i> : 0.016	0.8 (0.5–1.4)	<i>p</i> : 0.5
Mixed refluxes	1.6 (1.2–2)	<i>p</i> < 0.001	3.3 (2.2–4.7)	<i>p</i> < 0.001	2.6 (1.8–4)	<i>p</i> < 0.001
Proximal refluxes	2.3 (1.8–3)	<i>p</i> < 0.001	2.2 (1.5–3.2)	<i>p</i> < 0.001	1.6 (1.1–2.5)	<i>p</i> < 0.03
Refluxes preceded by a reflux episode (5 min)	1 (0.7–1.3)	<i>p</i> : 0.9	1.3 (0.9–2.0)	<i>p</i> : 0.16	1.1 (0.7–1.6)	<i>p</i> : 0.8

pre-epithelial defense mechanism, in a large group of patients with typical GERD symptoms. Indeed, studies addressing this issue have been carried out in healthy subjects<sup>16</sup> or focused on very small groups of GERD patients.<sup>17</sup>

The majority of our patients were responders to previous PPI trials and characterized by a pathological AET and a positive SAP and/or SI. Twelve patients (20%) were non-responders; however, all of these presenting a pathological AET and/or a positive SAP/SI.

A total of 358 reflux episodes were detected in controls; less than 50% of these were acidic, mixed liquid-gas and reaching the proximal esophagus. A total of 3096 reflux episodes were detected in patients; the majority of these were acid, pure liquid, and not reaching the proximal esophagus. In patients, about one-fourth of the total refluxes were preceded by a reflux episode in the previous 5-min time window. A total of 666 out of 3096 refluxes were followed by a PSPW event (overall PSPW index: 21.5%) in patients and 251 out of 358 refluxes were followed by a PSPW event (overall PSPW index: 70.1%) in controls (*p* < 0.01). In controls, among reflux episodes followed by a PSPW event, a significantly higher proportion of mixed liquid-gas and proximal refluxes was observed when compared with those not followed by a PSPW whilst in patients, among reflux episodes followed by a PSPW event, a significantly higher proportion of acid, mixed liquid-gas and proximal refluxes was observed when compared with those not followed by a PSPW. Proportion of refluxes preceded by a previous reflux episode, in the 5-min time window, were comparable between the two groups in both controls and patients. In controls, multivariate analysis showed that mixed liquid-gas and refluxes reaching the proximal esophagus were independently characterized by a significantly higher probability to be associated to a PSPW event. When patients were considered all together, multivariate analysis confirmed that acid, mixed

liquid-gas and refluxes reaching the proximal esophagus were independently characterized by a significantly higher probability to be associated with a PSPW event. In patients with a pathological AET, mixed liquid-gas, and refluxes reaching the proximal esophagus were characterized by a significantly higher probability to be associated with a PSPW event, while in patients with positive SAP/SI and normal AET acid refluxes were also characterized by a significantly higher probability to be associated with a PSPW event.

Our results further corroborate most of the currently available data on this topic. Zhang et al<sup>16</sup> have recently demonstrated, in healthy subjects, that reflux episodes with high proximal extent and containing gas play a relevant role in eliciting PSPWs, similarly to results obtained in our controls. In agreement with the study by Xu et al,<sup>17</sup> carried out in patients with reflux symptoms, our results show that refluxes reaching 15 cm above LES are strongly associated with PSPW occurrence.

Several mechanisms might explain the findings reported here-with in healthy subjects and patients. It is conceivable that acid reflux, as well as reflux with higher proximal extent or containing gas, may stimulate afferent nerves, through activation of esophageal chemoreceptors and mechanoreceptors, and, in turn, eliciting the esophago-salivary reflex as revealed by a PSPW event. It has been demonstrated that the proximal esophagus is characterized by a more superficial innervation compared to the distal esophagus. It is conceivable, therefore, that the proximal esophagus is more sensitive to intra-luminal stimuli, and thereby predisposed to trigger reflexes when stimulated.<sup>28,29</sup> Moreover, it is also known that refluxes reaching the proximal esophagus and containing gas are more likely to be perceived in GERD patients.<sup>30,31</sup>

We speculate that the acidic component of refluxate might contribute in eliciting PSPW via several mechanisms. It has been demonstrated



that esophageal acidification induces hyperalgesia and allodynia of esophageal mucosa,<sup>32,33</sup> thus enhancing the perception of various intra-luminal stimuli and, in turn, symptom-induced primary peristalsis. According to our results in both healthy subjects and patients, reflux episodes followed by a PSPW were characterized by a significantly higher BCT at 5 cm above LES compared with refluxes not followed by a PSPW. This finding is in agreement with data from the study by Xu et al,<sup>17</sup> whose results demonstrated that refluxes with higher volume clearance time and larger volume burden were more likely to trigger a PSPW event, and might further support the hypothesis that prolonged and high-volume reflux episodes, likely liquid-mixed refluxes, trigger esophageal peristalsis not only by a vagal esophago-salivary reflex but also by activating mechanoreceptors in the esophageal wall.

The present study does not elucidate why healthy subjects are characterized by a significantly higher PSPW index when compared to GERD patients. One possible explanation could be the greater number of reflux episodes observed in GERD patients, as confirmed by our results, which could induce some tolerance of the reflex response to reflux events as revealed by a PSPW. Since our findings confirm that proximal extension of refluxate increases symptom recording,<sup>34–36</sup> it may conceivably be assumed that reflux perception favors the PSPW event. However, in our series symptom recording was followed by a PSPW event in a minority of cases only, suggesting that reflux perception and symptom recording do not always match.

Symptom association probability and symptom index represent attempts to relate reflux perception with detected reflux episodes. Indeed, the diagnostic limits of SAP and SI have long been recognized<sup>37</sup> as well as those of AET<sup>38</sup> and do not explain why some patients with heartburn, normal AET and negative SAP/SI are responding to PPI therapy.<sup>39</sup> Moreover, PSPW occurs within 30 s after the end of a reflux episode while SAP and SI are calculated considering the 2-min post-reflux period, thus often occurring after a PSPW event. Finally, according to our results, SAP/SI was positive in 18 cases with normal AET and in 19 cases with pathologic AET, thus not all our patients had a positive symptoms association analysis despite a clear diagnosis of GERD, the latter finding confirming that symptom association analysis has suboptimal sensitivity and the above-mentioned reflux characteristics do not necessarily imply reflux episodes perception. Likewise, it is reasonable to hypothesize that PSPW elicitation could not be related always to reflux perception, particularly in those patients with negative SAP/SI and more variables should be investigated, including the impairment of motility.

Rogers et al<sup>18</sup> have recently demonstrated that PSPW index inversely correlates with impairment of esophageal motility and reflux burden, thus supporting the hypothesis that abnormal acid exposure is correlated with impairment of esophageal motility, the latter finding likely contributing to a lower PSPW index value. In contrast, in our series, the overall PSPW index in patients with or without IEM was comparable. However, it is important to note that our results are likely due to the very small number of patients with IEM and, in particular, with severe IEM, thus precluding further speculation on the association between PSPW and motility abnormalities.

Finally, Frazzoni et al<sup>5</sup> have previously hypothesized that the impairment of esophago-salivary reflux in patients with GERD could be genetic-based, predisposing them to develop reflux disease. Indeed, it has been shown that patients with GERD and an impairment of PSPW who are successfully treated with surgical fundoplication do not exhibit an improvement of their PSPW index,<sup>40</sup> thus reducing the role of reflux-induced esophageal inflammation.

As far as we know, this is the first multicenter study aimed at evaluating the potential factors involved in the elicitation of PSPW events in a large cohort of patients with GERD symptoms and in a group of controls. Some limitations could temper the strengths of our investigation. In particular, the retrospective patients evaluation and data analysis, although data collection was prospectively carried out for the whole study population. Moreover, MII-pH tracings were evaluated separately in each center involved in the study, although a satisfactory agreement between the same investigators has been achieved in previously published studies based on MII-pH tracings analysis.<sup>15,41</sup> Future outcome studies are needed to confirm the balance between aggressive factors and defense response in GERD.

In summary, our results demonstrate the relevance of acid and volume burden, mixed liquid-gas, proximal refluxes in eliciting PSPWs. Our findings corroborate the usefulness of performing MII-pH in the difficult management of patients with GERD symptoms and lead to the conclusion that PSPW, a key factor of epithelial protection, is correlated to reflux characteristics.

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## DISCLOSURES

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## AUTHOR CONTRIBUTIONS

Mentore Ribolsi, Marzio Frazzoni, Edoardo Savarino: study concept and design; collection, analysis, and interpretation of data; drafting of the manuscript. Nicola De Bortoli, Salvatore Tolone, Roberto Penagini, Michele Cicala: study concept; collection, analysis, and interpretation of data; critical revision of the manuscript. Elena Arsiè, Giovanni De Carlo, Lucia Mariani, Daria Maniero: collection, analysis, and interpretation of data; critical revision of the manuscript.

## DATA AVAILABILITY STATEMENT

Data of the individuals included in the present study are registered in a database saved in the online server of Campus Bio Medico University

of Rome, Italy. The Italian law does not allow to share individual data on a public server. Any consultation request of the included data from other institutes must be approved by our Ethics Committee.

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