

# Role of Mixed Reflux and Hypomotility with Delayed Reflux Clearance in Patients with Non-cardiac Chest Pain

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## Background/Aims

Gastroesophageal reflux disease (GERD) is the most common cause of non-cardiac chest pain (NCCP). Currently available data reveal a weak relationship between NCCP and dysmotility. Moreover, it is unclear why some refluxes are perceived as heartburn and others as NCCP. We aimed to evaluate the role of the reflux pattern and the esophageal motility in patients with NCCP.

## Methods

Forty-eight patients with NCCP (Group 1) and 50 only typical GERD symptoms (Group 2) were included and underwent high-resolution manometry (HRM) and multichannel intraluminal impedance-pH monitoring.

## Results

Impaired peristalsis was found in 60% of patients with NCCP and in 24% of patients with typical symptoms ( $P < 0.05$ ). In patients belonging to Group 1, the majority of reflux episodes associated with chest pain were acid and mixed. The proportion of mixed refluxes was higher than that in Group 2. In Group 1, the reflux clearing time at 5, 9, and 15 cm, measured in reflux episodes associated to NCCP was longer than in reflux episodes associated to typical symptoms (mean  $\pm$  95% CI:  $27.2 \pm 5.6$ ,  $23.3 \pm 4.4$ , and  $14.6 \pm 2.3$  seconds vs  $18.3 \pm 3.5$ ,  $13.3 \pm 2.2$ , and  $11.1 \pm 1.8$  seconds;  $P < 0.01$ ).

## Conclusions

The presence of gas in the refluxate seems to be associated with NCCP. The impaired motility observed in NCCP patients may play a relevant role in delaying reflux clearing, hence increasing the time of contact between refluxate and esophageal mucosa.

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## Key Words

Gastroesophageal reflux; High-resolution manometry; Ineffective esophageal motility; Non-cardiac chest pain; Non-erosive reflux disease

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## Introduction

Non-cardiac chest pain (NCCP), defined as a recurrent, angina-like pain without evidence of cardiac disease, is a common disorder, with a prevalence of 25% in Western countries, accounting for a significant morbidity and impaired quality of life.<sup>1</sup> In clinical practice, patients presenting with NCCP are usually evaluated after an accurate work-up excluding cardiovascular conditions. In patients without evidence of cardiac disorders, gastroesophageal reflux disease (GERD) remains the most common cause responsible for symptoms.<sup>2</sup> The diagnosis of GERD in patients with NCCP is a real challenge. Locke et al<sup>3</sup> have demonstrated that NCCP episodes are more frequent in patients who also report heartburn than in those without typical GERD symptoms. It has been demonstrated that in NCCP patients the prevalence of erosive esophagitis and of Barrett's esophagus is lower than that observed in patients with only typical symptoms, therefore the sensitivity of upper endoscopy appears very poor.<sup>4,5</sup> Ambulatory 24-hour pH studies have demonstrated that approximately 50% of NCCP patients present an abnormal acid exposure and/or pain episodes associated with reflux events.<sup>6,7</sup> Furthermore, in patients with NCCP and endoscopic or pH-metric evidence of GERD, the response of NCCP to proton pump inhibitors (PPIs) has been widely evaluated and considered as satisfactory, with a successful response ranging from 78% to 92%.<sup>8-10</sup> On the other hand, NCCP patients without evidence of reflux disease respond poorly to PPIs.<sup>11,12</sup>

The intraluminal mechanisms responsible for chest pain remain to be fully elucidated. Among of the various factors taken into consideration, duration of reflux episodes as well as the degree of acidity, esophageal hypersensitivity, and sustained contractions of the esophageal longitudinal muscle layer have been well investigated. However, it is still not clear why some reflux episodes are perceived as heartburn and others as NCCP in the same patients.<sup>13-16</sup>

Ambulatory 24-hour multichannel intraluminal impedance-pH (MII-pH) monitoring is currently considered the gold standard in evaluating gastroesophageal reflux. At present, studies using MII-pH to evaluate the reflux pattern in patients with proven GERD and reporting NCCP are still lacking. Moreover, all the above mentioned studies have evaluated GERD patients with presence of erosive esophagitis and/or pathological acid exposure, whilst no data are available on the group of patients with non-erosive reflux disease (NERD), including a large proportion of patients with a hypersensitive esophagus.

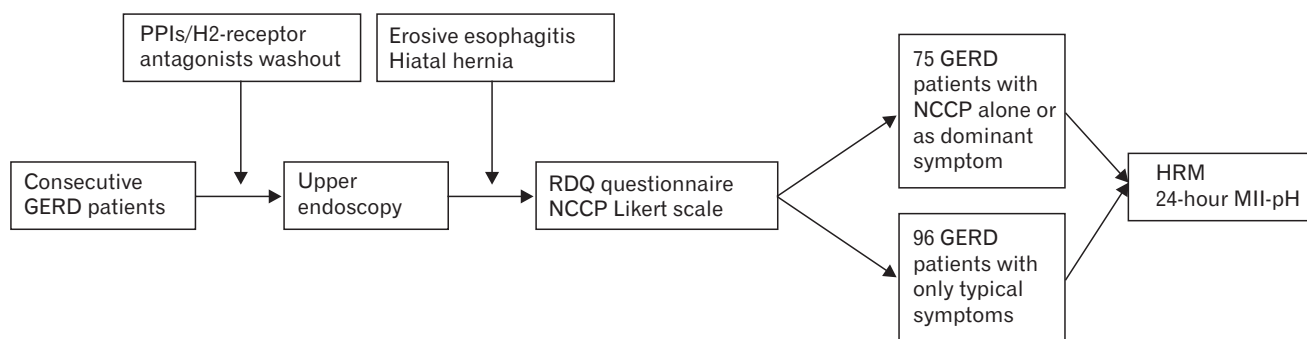
Currently available data reveal a weak relationship between

NCCP and esophageal motility disorders. It has been reported that only 30% of patients with NCCP are characterized by esophageal motor abnormalities, the most common motility disorders observed being the nutcracker esophagus and the hypotensive lower esophageal sphincter (LES).<sup>17,18</sup> However, in NCCP patients analyzed by means of combined manometry and pH monitoring, pain episodes were more frequently associated with acid reflux episodes than with motility abnormalities.<sup>19,20</sup> High-resolution manometry (HRM) has led to a better understanding of esophageal motility, however, this technology has not been used to explore esophageal motility in these patients yet.

The aim of the present study was to evaluate the role of the reflux pattern and of the esophageal motility, assessed by means of MII-pH monitoring and HRM, in the pathogenesis and perception of NCCP in a carefully selected population of NERD patients.

## Materials and Methods

GERD patients were prospectively recruited from those who had been referred to our outpatient unit between December 2013 and December 2014. Patients were selected on the basis of the presence of recurrent ( $\geq 2/\text{week}$ ) NCCP and/or typical GERD symptoms, ie, heartburn and regurgitation, lasting for  $\geq 6$  months and showing a satisfactory response to PPIs (esomeprazole 40 mg once a day and pantoprazole 40 mg once a day) given for at least 4 weeks (range, 4-8 weeks). All patients underwent upper endoscopy performed within 2 months before the interview and following a 2-week pharmacological washout from PPIs and/or histamine H<sub>2</sub> receptor antagonists. The presence of hiatal hernia and of esophageal erosions was carefully evaluated. Patients with evidence of erosive esophagitis and hiatal hernia were excluded. All patients had a negative cardiac evaluation prior to undergoing esophageal physiology testing. All patients filled out a standardized structured questionnaire (reflux disease questionnaire [RDQ]) for the assessment of typical symptoms.<sup>21</sup> Patients scored RDQ symptom intensity on a 4-point Likert scale from "none" to "severe". An ad-hoc questionnaire, recording frequency and severity of NCCP, was obtained from each patient, on 5-point Likert scales. Among the patients screened, 75 patients with NCCP alone or as dominant symptom, and 96 patients presenting only typical symptoms, underwent HRM followed by ambulatory 24-hour MII-pH, performed on the same day (Fig. 1). Forty-eight out of 75 patients with NCCP (17 female, mean age 44 years, range 29-58 years; Group 1) and 50 out of 96 patients with typical symptoms (24 female, mean age 48 years, range 31-64 years; Group 2), reporting symptoms during



**Figure 1.** Schematic representation of the study design. PPIs, proton pump inhibitors; H2, histamine-2; GERD, gastroesophageal reflux disease; RDQ, reflux disease questionnaire; NCCP, non-cardiac chest pain; HRM, high-resolution manometry; MII-pH, multichannel intraluminal impedance-pH.

the MII-pH study and presenting an abnormal acid exposure time (AET) and/or positive symptom association probability (SAP), were considered for the analysis. The study was approved by the Ethics Committee of the University Campus Bio Medico of Rome and written informed consent was obtained from all individuals.

## 24-hour Multichannel Intraluminal Impedance-pH Monitoring

The combined pH-impedance assembly (Sandhill Scientific, Highlands Ranch, CO, USA) was positioned with the proximal pH electrode 5 cm above the LES. In this position, impedance was measured at 3, 5, 7, 9, 15, and 17 cm above the LES. Patients were asked not to lie down during the daytime, but only at their usual bedtime and were instructed to have 3 standard meals and 2 beverages at fixed times. Event markers recorded the occurrence of symptoms, times of meals and changes in posture.

## High-resolution Manometry

A catheter with 36 circumferential solid state pressure sensors (MMS, Enschede, Netherlands), located at 1-cm intervals, was used. The catheter was inserted, following overnight fasting, through an anesthetized nostril. The HRM catheter was placed with at least 5 distal pressure sensors positioned across the LES. The manometric study was performed with a total of 10 saline (5 mL) swallows, at 30-second intervals, in each patient in a semi-recumbent position.

## Data Analysis

### 24-hour multichannel intraluminal impedance-pH

Reflux events were detected and classified as liquid, mixed liquid-gas, and pure gas reflux episodes according to previously

published criteria.<sup>22</sup> AET was defined as pathological if the time at pH < 4 exceeded 5% of the total recording time. The SAP for all reflux episodes was calculated according to formula previously described.<sup>23</sup> Reflux clearing time (RCT), ie, time-frame between reflux entry and exit, was calculated at 5, 9, and 15 cm above the LES using Bioview software, after a manual analysis of each MII-pH tracing. Heartburn and regurgitation were considered in the analysis of symptoms. Reflux episodes were classified as symptom-related if they occurred  $\leq 2$  minutes before the onset of the symptom.

### High-resolution manometry and multichannel intraluminal impedance

Data were stored and analyzed using dedicated software (MMS Database software). The mean resting LES pressure and the integrated relaxation pressure (4 seconds), as well as the distal contractile integral (DCI), contractile front velocity, and distal latency values were calculated according to formula described elsewhere.<sup>24</sup> Moreover, the presence of any motility disorder in each subject were assessed analyzing the tracings of HRM study with 10 saline swallows according to the Chicago classification 3.0.<sup>24</sup> The presence of a pathological number of large esophageal peristaltic breaks was carefully assessed in the 20 mmHg isobaric contour, according to previously described criteria.<sup>25</sup> The length of transition zone was considered pathological if > 2 cm in the 20 mmHg isobaric contour.

## Statistical Methods

Data are presented as mean  $\pm$  standard deviation (SD) or mean and range. Means between groups were compared using ANOVA. Fisher's exact test was used to compare differences between proportions. Multivariate analysis was used to assess the

relative risk of NCCP and heartburn perception. For this purpose, each reflux episode was considered independently. The dependent variable was the NCCP or heartburn perception while the potential predictors were the presence of acidic, mixed, or proximal reflux episodes.

Differences were judged statistically significant when  $P$  was  $< 0.05$ . The statistical analysis was performed using SPSS 16.0 software (SPSS Inc, Chicago, IL, USA).

## Results

### Patients

According to the findings from the questionnaire, 41/48 Group 1 patients were classified as having predominant NCCP and concomitant typical symptoms occurrence; the remaining 7 patients presented NCCP episodes alone. Demographic characteristics of the 2 groups are in Table 1. No differences were found in terms of body mass index, smoking and alcohol consumption.

### High-resolution Manometry

Twenty-nine out of the 48 (60%) patients belonging to Group 1 and 12 out of 50 (24%) belonging to Group 2 showed evidence of impaired peristalsis ( $P < 0.05$ ). Overall 14 of these 29 Group 1 patients showed ineffective esophageal motility (IEM), 9 fragmented peristalsis and 6 absent contractility. Of the 12 patients belonging to Group 2, seven showed IEM and 5 fragmented peristalsis (Fig. 2). Two patients of Group 1 and 4 of Group 2 showed findings of hypertensive peristalsis. Mean DCI value was significantly lower in Group 1. Mean integrated relaxation pressure, DL, and CFV values were comparable between the 2 groups (Table 2).

### Multichannel Intraluminal Impedance-pH Findings

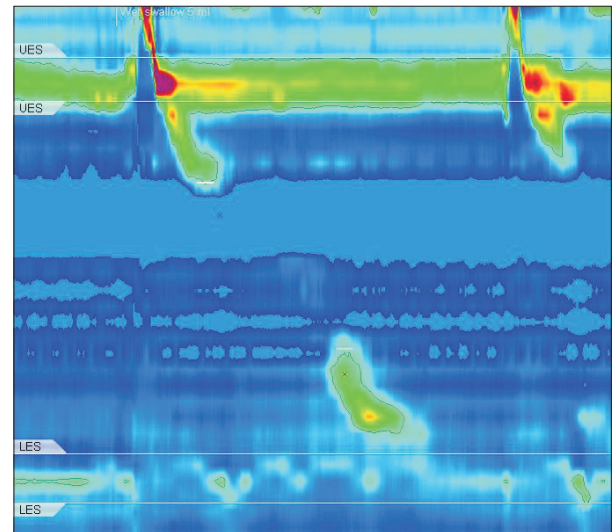
Of the 48 patients in Group 1, 22 showed a pathological AET (mean 8.5%, range 5.4-17.1%) and 26 showed a normal pH profile (mean 2.1%, range 0.6-4.2%). Of the 50 patients belonging to

Group 2, 24 showed a pathological AET (mean 7.7%, range 5.9-14.8%) and 26 showed a normal pH profile (mean 2.3%, range 0.9-43.9%). The proportion of patients with a pathological AET were similar between Groups 1 and 2 (54% vs 52%,  $P = NS$ ).

The reflux frequency and proportions of acid and proximal reflux episodes were comparable between Groups 1 and 2. Patients in Group 1 were characterized by a higher proportion of mixed reflux episodes compared to patients in Group 2 (Table 3).

### Symptom-reflux Association Analysis

A total of 302 NCCP episodes and 285 typical symptom episodes associated with refluxes (9.1% of all reflux events, range 3.8-12.7% and 10.2%, range 3.9-14.1%, respectively) were reported in Groups 1 and 2 during the 24 hours. The per patients frequency of



**Figure 2.** High-resolution manometry tracing showing the presence of a large defect of the peristalsis in a non-cardiac chest pain patient. UES, upper esophageal sphincter; LES, lower esophageal sphincter.

**Table 2.** Mean ( $\pm$  SD) Integrated Relaxation Pressure, Distal Latency, Contractile Front Velocity, and Distal Contractile Integral Values in Groups 1 and 2

	Group 1	Group 2
IRP 4 sec (mmHg)	9.3 $\pm$ 1.3	8.9 $\pm$ 2.2
DL (sec)	5.4 $\pm$ 1.1	6.2 $\pm$ 1.3
CFV (cm/sec)	4.2 $\pm$ 0.9	4.4 $\pm$ 1.2
DCI (mmHg·sec·cm)	956 $\pm$ 186	1649 $\pm$ 427 <sup>a</sup>

<sup>a</sup> $P = 0.005$ .

IRP, integrated relaxation pressure; DL, distal latency; CFV, contractile front velocity; DCI, distal contractile integral.

**Table 1.** Demographic Characteristics of the Groups 1 and 2

	Group 1 (n = 48)	Group 2 (n = 50)
Mean age (range), yr	44 (29-58)	48 (31-64)
Gender (M/F)	31/17	26/24
BMI (mean $\pm$ SD), kg/m <sup>2</sup>	21.2 $\pm$ 3.1	20.4 $\pm$ 2.3
Alcohol/coffee	3 (6.2%)/10 (21%)	2 (4%)/13 (26%)
Smokers	3 (6.2%)	4 (8%)

NCCP-associated reflux episodes was comparable to that of typical symptom-associated reflux episodes (mean  $\pm$  SD,  $5.9 \pm 2.7$  and  $5.7 \pm 2.8$ ). During the MII-pH monitoring, 41 out of 48 patients with NCCP also reported 126 typical symptoms associated to reflux episodes (mean  $\pm$  SD,  $3.1 \pm 1.1$ ).

Characteristics of symptomatic and asymptomatic reflux episodes in both groups are pointed out in Table 4. In Group 1, the majority of reflux episodes associated with chest pain were acid and mixed, whilst the majority of refluxes associated with typical symptoms were proximal. The proportion of mixed refluxes associated with NCCP was higher than the proportion of mixed refluxes associated with typical symptoms, both in Groups 1 and 2. In the multivariate model, in Group 1, a mixed reflux episode was most probably perceived as chest pain (OR, 2.2; 95% CI, 1.6-3.1) while a proximal reflux was most probably perceived as heartburn (OR, 1.9; 95% CI, 1.3-3.0).

In Group 1, the RCT of NCCP-associated refluxes, calculated at 5, 9, and 15 cm, was longer than that observed in typical symptoms-associated refluxes (mean  $\pm$  95% CI:  $27.2 \pm 5.6$ ,  $23.3 \pm 4.4$ , and  $14.6 \pm 2.3$  seconds vs  $18.3 \pm 3.5$ ,  $13.3 \pm 2.2$ , and  $11.1 \pm 1.8$  seconds;  $P < 0.01$ ). In Group 1, the RCT of NCCP-associated refluxes at each esophageal level was longer than that in asymptomatic refluxes ( $13.3 \pm 1.5$ ,  $12.3 \pm 1.2$ , and  $9.8 \pm 0.9$  seconds;  $P <$

**Table 3.** Multichannel Intraluminal Impedance-pH Findings in Groups 1 and 2. In Group 1, the Majority of Reflux Episodes Associated with Chest Pain Were Acid and Mixed, Whilst the Majority of Refluxes Associated with Typical Symptoms Were Proximal

	Group 1	Group 2
Total reflux episodes (mean $\pm$ SD)	62 $\pm$ 24	56 $\pm$ 31
Acid (%)	47 $\pm$ 11	51 $\pm$ 13
Mixed (%)	62 $\pm$ 13 <sup>a</sup>	41 $\pm$ 12
Proximal (%)	44 $\pm$ 9	47 $\pm$ 7

<sup>a</sup> $P = 0.004$ .

**Table 4.** Characteristics of Symptomatic and Asymptomatic Reflux Episodes in Groups 1 and 2

	Group 1			Group 2	
	NCCP associated refluxes (n = 302)	Typical symptoms associated refluxes (n = 126)	Asymptomatic refluxes (n = 2548)	Typical symptoms associated refluxes (n = 285)	Asymptomatic refluxes (n = 2515)
Acid refluxes	193 (64%)	74 (59%)	738 (29%)	177 (62%)	604 (24%)
Mixed refluxes	229 (76%) <sup>a</sup>	65 (52%)	1350 (53%)	134 (47%)	1157 (46%)
Proximal refluxes	124 (41%)	84 (67%) <sup>b</sup>	866 (34%)	168 (59%)	805 (32%)

<sup>a</sup> $P = 0.005$  vs typical symptoms associated refluxes.

<sup>b</sup> $P = 0.008$  vs non-cardiac chest pain (NCCP) associated refluxes.

0.01) as well as than that of typical symptoms-associated refluxes in Group 2 patients ( $17.1 \pm 2.5$ ,  $12.2 \pm 1.2$ , and  $12.1 \pm 1.4$  seconds;  $P < 0.01$ ).

### Analysis of Patient with Only Non-cardiac Chest Pain

Three out of the 7 Group 1 patients with only NCCP showed a pathological AET. Two of them showed evidence of impaired peristalsis. In patients belonging to this subgroup the majority of reflux episodes associated with chest pain were acid and mixed (61% and 73%, respectively), as well as in patients with both NCCP and typical symptoms.

## Discussion

NCCP is a common disorder with a considerable impact on the patients' quality of life and a high health-care cost, primarily on account of multiple clinic and emergency room visits as well as hospitalizations.<sup>26,27</sup> Nowadays, NCCP genesis is still not fully understood. In patients without cardiac diseases, GERD is considered the most common cause responsible for the genesis of chest pain episodes and esophageal dysmotility seems to play a limited role.

Esophageal HRM and ambulatory MII-pH are currently considered the gold standard in evaluating esophageal motor function and gastroesophageal reflux, respectively, although their contribution in understanding the relationship between GERD and NCCP has not been completely tested. Therefore, we aimed at evaluating the role of esophageal motility disorder and of the reflux pattern, assessed by HRM and ambulatory MII-pH monitoring, in the pathogenesis and perception of NCCP in NERD patients. Since the large majority of patients presenting a hypersensitive esophagus belong to the NERD category, we selected patients with a satisfactory PPI response and presenting a proven non-erosive disease, ie, presence of abnormal AET and/or positive SAP at MII-pH. Moreover, patients showing evidence of hiatal hernia >

2 cm were excluded. According to the presence of NCCP as the dominant symptom or only heartburn and regurgitation, NERD patients were divided into Group 1 and Group 2, respectively.

The results of the present study show that the majority of our patients with NCCP display evidence of hypomotility, due to the presence of IEM, failed peristalsis or an abnormal number of large peristaltic breaks. Moreover, the mean DCI observed in patients with NCCP was significantly lower than that observed in patients with only typical symptoms. Currently available data on selected GERD patients with NCCP evaluated with HRM are scarce. Results of the present investigation confirm that esophageal hypertensive disorders and hypotensive LES do not play a relevant role in NCCP elicitation. Moreover, our results reveal that hypotensive disorders in terms of peristaltic breaks, which are not recognizable with conventional manometry, are often found in patients with NCCP. The relationship between esophageal motility disorders and NCCP still remains controversial. One of the more relevant limitations of esophageal manometry, usually performed with 10 swallows of saline solution, is that patients rarely report pain episodes during the test, thus making it difficult to directly correlate motor findings with NCCP. Moreover, esophageal manometry cannot evaluate contraction of the longitudinal muscle layer, which has been reported to be also involved in the genesis of NCCP.<sup>16</sup>

Our findings show that the proportion of NERD patients with abnormal AET was similar in the group of patients with NCCP and that of patients with only typical symptoms. Moreover, the reflux frequency and proportion of acid and proximal reflux episodes were comparable between the 2 groups of patients, whilst NCCP patients were characterized by a higher proportion of mixed reflux episodes with respect to patients presenting only typical symptoms. According to our results, the majority of reflux episodes associated with chest pain were acidic and mixed, whilst the majority of refluxes were associated with typical symptoms reaching the proximal esophagus.

In the present series, the proportion of NCCP patients with a higher AET (approximately 50%) is similar to that reported in previous studies.<sup>6</sup> Although the measure of the AET does not discriminate NERD patients with NCCP from those with typical symptoms, our data show that chest pain episodes are frequently preceded (ie, associated) by acid refluxes. This finding confirms the relevant role of repeated acid exposures in the esophagus, not only for chest pain elicitation, but also for sensitization of mechanosensitive afferent pathways.<sup>13-15</sup> In the study by Hu et al,<sup>15</sup> performed on healthy subjects, the pain perception was evaluated during balloon distension, after short-lasting, repeated, and acid infusions. Hu

et al<sup>15</sup> found that acid perfusion reduced the perception and chest pain thresholds. Reasonably, NERD patients with NCCP display a lower esophageal pain threshold than healthy subjects and, following repeated acid exposures, their pain threshold further decreases.

In our series of NERD patients with NCCP, mixed reflux episodes were more probably perceived as chest pain whilst a proximal reflux was more likely perceived as heartburn. It is thought, although never directly demonstrated, that mixed refluxes are characterized by a higher volume than pure liquid reflux episodes, and it is conceivable that the activation of the mechanoreceptors, together with an esophageal pre-sensitization due to repeated acid refluxes, leads to the chest pain episodes.

On the other hand, in our series, weakly acidic refluxes do not appear to be relevant in pain perception. The finding that the majority of our patients with NCCP display evidence of hypomotility significantly favors the noxious contact of gastric refluxate with the esophageal mucosa, as confirmed by the RCT values. Indeed, the prolonged contact time of the gastric refluxate with the esophageal mucosa might sensitize the mucosa to subsequent stimuli. In this scenario, the manometric finding of hypomotility reported herewith, even if not being directly correlated with NCCP elicitation, could represent a key factor responsible for pain perception.

Nowadays, the esophageal manometry, performed either with HRM or conventional manometry, is still performed with 10 saline swallows which represents a limit of the present study. A manometric study using solid and/or repetitive swallows might unmask failure of peristalsis not revealed by conventional saline swallows. Another limitation of the present study could be the relatively small sample size of patients, although, to our knowledge, the present series is one of the largest investigated for pathophysiological purposes. It would be also of interest to evaluate NCCP patients with a more prolonged study, in order to detect any correlation between pain episodes and motility findings.

In conclusion, impaired peristalsis is more frequently observed in NERD patients with predominant NCCP. The impaired motility observed in patients with NCCP may play a relevant role in delaying reflux clearing, thus increasing the time of contact between the refluxate and the esophageal mucosa. The role of impaired esophageal motility on reflux clearing, shown in the majority of NCCP patients, supports the rationale of using prokinetic drugs in these patients.

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**Author contributions:** Mentore Ribolsi, Paola Balestrieri, and Michele Cicala: planning and conducting the study, collecting and interpreting data, drafting the manuscript; and Dario Biasutto and Sara Emerenziani: drafting the manuscript.

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