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Impaired Esophageal Mucosal Integrity May Play a Causative Role in Patients With Nongastroesophageal Reflux Disease–Related Noncardiac Chest Pain

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Abstract: Baseline impedance (BI) measurement can be used to evaluate the status of the esophageal mucosa integrity. We hypothesized that impaired esophageal mucosal integrity may play a causative role in patients with nongastroesophageal reflux disease (non-GERD)–related noncardiac chest pain (NCCP). This retrospective study analyzed 24-hour multichannel intraluminal impedance-pH testing data from 77 patients with NCCP and 5 healthy volunteers. BI was calculated at 3 cm (distal esophagus) and 17 cm (proximal esophagus) above the lower esophageal sphincter. GERD was defined by the presence of pathologic acid exposure or reflux esophagitis. Among the 77 patients with NCCP, 16 (20.8%) were classified into the GERD-related NCCP group and 61 (79.2%) into the non-GERD-related NCCP group. BI (median, interquartile range) of the non-GERD-related NCCP group was lower than the control group at the proximal esophagus (2507 Ω , 2156–3217 vs 3855 Ω , 3238–4182, $P=0.001$) but was similar at the distal esophagus. The GERD-related NCCP group showed lower BI than the control group at both the distal and proximal esophagus (2024 Ω , 1619–2308 vs 3203 Ω , 2366–3774, $P=0.007$ and 2272 Ω , 1896–2908 vs 3855 Ω , 3238–4182, $P=0.003$, respectively). At the distal esophagus, BI was lower in the GERD-related NCCP group than the non-GERD-related NCCP group ($P=0.002$), whereas it did not differ between the 2 groups at the proximal esophagus. In conclusion, the mucosal integrity is impaired at the proximal esophagus in patients with non-GERD-related NCCP, which might be the pathogenic mechanism of NCCP.

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Abbreviations: 24-hr MII-pH = 24-hour multichannel intraluminal impedance-pH testing, BI = baseline impedance, FH = functional heartburn, GERD = gastroesophageal reflux disease, HRIM = high-resolution impedance-manometry, IBT = impaired bolus transit, IQR = interquartile range, LES = lower esophageal sphincter, NCCP = noncardiac chest pain, PAE = pathologic acid exposure, PBE = pathologic bolus exposure, RE = reflux esophagitis.

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INTRODUCTION

Noncardiac chest pain (NCCP) is defined as recurrent episodes of substernal chest pain that does not originate from cardiac cause.¹ The prevalence of NCCP is reported as 19% to 33%,^{2–5} and it affects 23% of the population during lifetime.² Although NCCP has excellent long-term prognosis, most of the patients with NCCP suffer from their symptom persistently.⁶ However, determining the clear etiology for patients with NCCP remains a challenge.⁷

Several pathophysiological mechanisms have been suggested, including gastroesophageal reflux disease (GERD), esophageal motility disorder, esophageal visceral hypersensitivity, and psychological comorbidity.⁸ Among them, GERD is the most common cause of NCCP.^{3,9} It is present in up to 60% of patients with NCCP in Western countries and ~35% in Asia.^{10–12} Esophageal motility disorder can be considered as an etiology of NCCP especially in non-GERD-related NCCP.¹³ Approximately 30% of patients with non-GERD-related NCCP are diagnosed as an esophageal motility disorder through esophageal manometric evaluation.¹⁴ Nevertheless, the etiology of NCCP still remains unclear in a significant portion of patients with NCCP. Esophageal visceral hypersensitivity is regarded as the presumed remaining etiology.¹⁵ Indeed, visceral hypersensitivity has been one of the most important pathophysiologic mechanisms in functional gastrointestinal disorders.^{15,16}

Over the last decade, the impairment of the esophageal mucosa integrity has become apparent to play a role in symptom perception in nonerosive reflux disease (NERD).¹⁷ This has prompted the hypothesis that impaired esophageal mucosal integrity may also play a causative role in NCCP, especially in non-GERD-related cases. Recently, baseline impedance (BI) measurement at the esophageal mucosa using 24-hour multichannel intraluminal impedance-pH testing (24-hr MII-pH) has been used to evaluate the status of the esophageal mucosa integrity.¹⁸ Impaired esophageal mucosa integrity morphologically displays the dilated intercellular spaces, which are the consequence of acid-peptic injury.^{19,20} If the mucosa is more permeable to ionic flow due to dilated intercellular spaces, BI will be lower. Thus, to test our hypothesis, we evaluated BI in the patients with NCCP and controls, and compared clinical data regarding esophageal high-resolution impedance-manometry (HRIM), 24-hr MII-pH, and upper endoscopy in patients with NCCP and control groups.

METHODS

Subjects

We performed a retrospective review of patients who were diagnosed with NCCP at the Samsung Medical Center between June 2011 and December 2012. All the patients presented with angina-like chest pain and underwent a cardiologic evaluation

such as electrocardiogram, echocardiogram, exercise treadmill test, and stress thallium scan depending on the patient's condition. After cardiac disease had been ruled out, patients underwent esophageal workup including upper endoscopy, esophageal HRIM, and 24-hr MII-pH. The patients with peptic ulcer disease, infectious esophagitis, a history of gastrointestinal surgery, and psychiatric disorders (eg, depression, panic disorder, and anxiety disorder) with medication were excluded.

For control, 5 healthy volunteers (2 men, ages 28–31 years) were recruited. They denied any symptoms of gastrointestinal system and any history of medical disease. All the volunteers revealed normal results on upper endoscopy, esophageal HRIM, and 24-hr MII-pH. This study protocol was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of Samsung Medical Center, Seoul, Korea (no. 2014-11-038).

Esophageal High-Resolution Manometry Protocol

High-resolution manometry (HRM) was performed in the standard fashion with a series of 10 swallows of 5-mL normal saline each in a supine, using the HRIM system (Sandhill Scientific, Highlands Ranch, CO). The motility disorders and peristalsis abnormalities were defined by the Chicago classification version 3.0.²¹ All the measurements were analyzed by using BioVIEW Analysis software (Sandhill Scientific) and were also reviewed manually.

24-hr MII-pH Protocol

Patients were instructed to stop proton pump inhibitor (PPI) and H₂ receptor antagonist prior to the study ≥7 and 3 days, respectively. 24-hr MII-pH was performed after stationary HRM, using the ZepHr system (Sandhill Scientific). In this

system, the pH is measured at 5 cm above the lower esophageal sphincter (LES), and the impedance levels are measured at 3, 5, 7, 9, 15, and 17 cm above the LES. The BioVIEW Analysis software (Sandhill Scientific) was used for data analysis, and the process was also reviewed manually.

BI Measurement

BI was calculated at 3 cm (distal BI) and 17 cm (proximal BI) above the LES by K.C., who was blinded to the patient groups. The 24-hr full-traced impedance recording was divided into 4 periods according to meals and sleep (2 periods between meals and 2 periods before and during sleep). In each period, we selected 3 different 1-minute duration measures, that had a constantly stable impedance level, for impedance measurement. Impedance of each period was calculated by averaging these 3 impedance levels. Then, BI was calculated by averaging the 4 period impedance levels (Fig. 1).

Definitions

Pathologic acid exposure (PAE) and pathologic bolus exposure (PBE) were defined as an intraesophageal pH of <4 for >4.2% of the recording time and as refluxate in contact with distal impedance electrodes for >1.4% of the recording time, respectively.²² Impaired bolus transit (IBT) was defined as >20% of swallows with incomplete bolus transit.^{23,24} GERD was defined by the presence of PAE or reflux esophagitis (RE, at least grade A according to the Los Angeles classification²⁵) on the upper endoscopy.

Statistical Analysis

Shapiro–Wilk test was performed for normality. The statistical results were presented as median with interquartile

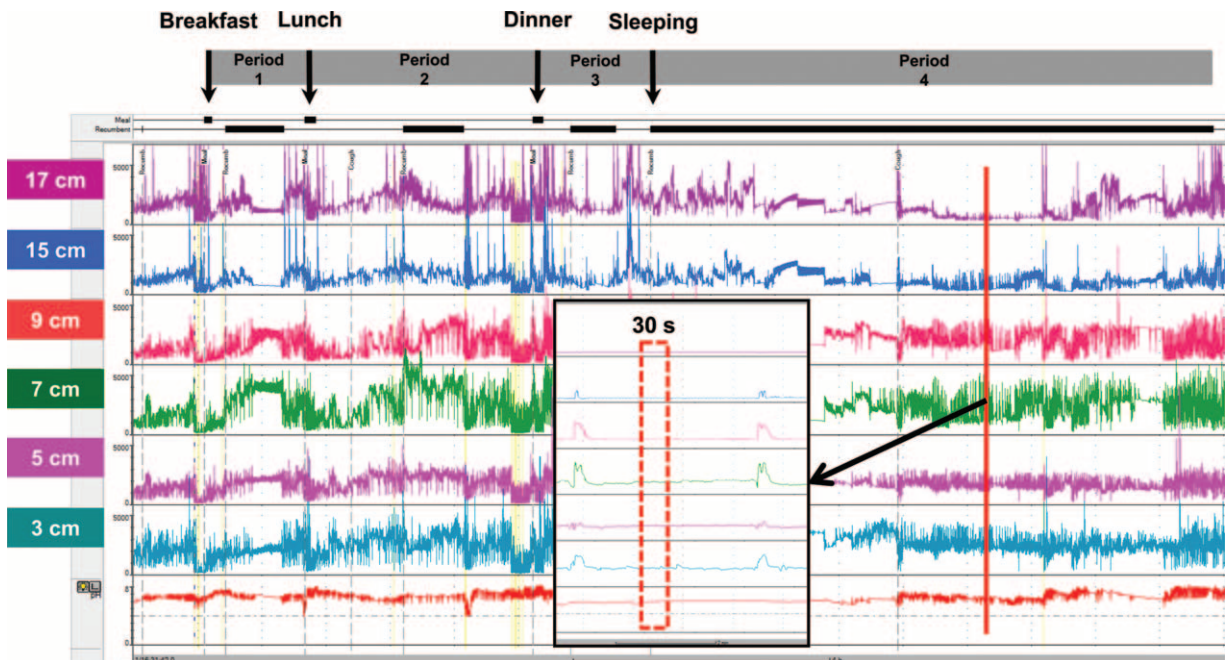


FIGURE 1. BI measurement protocol. At each time period, 3 different measures of 1-minute duration with constantly stable impedance level were selected for impedance measurement. Impedance of each period was calculated by averaging these 3 impedance levels. Then, BI was calculated by averaging the 4 period impedance levels. Proximal and distal esophageal BI was measured at 17 and 3 cm above the LES, respectively. BI = baseline impedance, GERD = gastroesophageal reflux disease, LES = lower esophageal sphincter.

range (IQR) or number of patients (%). There were no missing data. Continuous variables were compared nonparametrically using the Mann–Whitney *U*-test and Kruskal–Wallis test. Categorical variables were compared using the χ^2 test or Fisher exact test as appropriate. A *P* value of <0.05 was considered statistically significant. All of the analyses were performed using SPSS Statistics 20 (IBM, Chicago, IL) and GraphPad Prism 6 (GraphPad Software, San Diego, CA).

RESULTS

Demographics and Clinical Characteristics

A total of 77 patients with NCCP were included in the present study. Among them, 16 patients (20.8%) were classified into the GERD-related NCCP group and 61 (79.2%) into the non-GERD-related NCCP group. As shown in Table 1, there were no significant differences between the GERD-related NCCP and non-GERD-related NCCP groups regarding age, sex, HRM metrics including distal contractile integral, integrated relaxation pressure, and distal latency, complete bolus transit, IBT rate, presence of peristaltic disorders, and previous history of PPI treatment. However, the GERD-related NCCP group showed longer acid (5.2%, IQR 1.325–8.425 vs 0.3%, IQR 0.0–1.1, *P* < 0.001) and bolus (1.95%, IQR 0.9–3.125 vs 0.8%, IQR 0.3–0.8, *P* = 0.003) exposure time and more frequent PAE (62.5% vs 0%, *P* < 0.001), PBE (62.5% vs 24.6%, *P* = 0.004), and RE (56.3% vs 0%, *P* < 0.001) than the non-GERD-related NCCP group.

Baseline Impedance

BI at the distal esophagus was compared between the GERD-related NCCP, non-GERD-related NCCP, and control groups (Fig. 2A). BI did not significantly differ between the

non-GERD-related NCCP and control groups (2507 Ω , IQR 2156–3217 vs 3203 Ω , IQR 2366–3774, *P* = 0.245). However, the GERD-related NCCP group (2024 Ω , IQR 1619–2308) showed lower BI than the non-GERD-related NCCP and control groups (*P* = 0.002 and *P* = 0.007, respectively).

As shown in Figure 2B, BI of the non-GERD-related NCCP group was lower than the control group at the proximal esophagus (2507 Ω , IQR 2156–3217 vs 3855 Ω , IQR 3238–4182, *P* = 0.001) but was similar to the GERD-related NCCP group (2272 Ω , IQR 1896–2908, *P* = 0.629). The GERD-related NCCP group also showed lower BI than the control group at the proximal esophagus (*P* = 0.003).

Effect of Age on BI

In the 77 patients with NCCP, median age was 58 years. Thus, BI was compared between the 2 age groups (age <60 vs \geq 60 years). However, BI did not differ by age at both distal and proximal esophagus (Fig. 3).

DISCUSSION

Despite a significant medicosocial burden of NCCP,^{26–28} its pathophysiological mechanisms behind symptom generation remain to be elucidated. Esophageal visceral hypersensitivity has been demonstrated in most of the patients with non-GERD-related NCCP regardless of the presence of esophageal motility disorder.¹ Over the last decade, the impairment of esophageal mucosal integrity has become apparent to explain the symptom generation in the macroscopically normal mucosa in NERD.^{17,19,29} However, the role of esophageal mucosal integrity in NCCP has not been investigated. Thus, we conducted the first study to test our hypothesis that impaired esophageal mucosal integrity may also play a causative role in the non-GERD-related NCCP.

TABLE 1. Comparison of Baseline Characteristics between the GERD-related NCCP and non-GERD-related NCCP Groups

Variables	GERD (n = 16)	Non-GERD (n = 61)	<i>P</i>
Demographics			
Age, y	60 (53.25–66)	58 (52–63)	0.255
Sex, male	5 (31.3)	23 (37.7)	0.633
HRM metrics			
Distal contractile integral, mm Hg-s-cm	1254 (965–2036.75)	1453 (768–2218.5)	1.000
Integrated relaxation pressure, mm Hg	10 (7.25–12.5)	12.0 (9.0–15.0)	0.075
Distal latency, s	5.85 (4.525–6.475)	5.6 (4.65–6.5)	0.763
Complete bolus transit, liquid, %	40 (32.5–65)	20 (10–73.5)	0.419
Impaired bolus transit	13 (81.3)	47 (77.0)	0.053
Peristaltic disorders in the CC version 3.0			
Major disorders	1 (6.3)	5 (8.2)	0.451
Minor disorders	2 (12.5)	9 (14.8)	0.230
24-hr MII-pH			
Acid exposure time, pH <4.0, %	5.2 (1.325–8.425)	0.3 (0.0–1.1)	<0.001
PAE	10 (62.5)	0 (0)	<0.001
Bolus exposure time, %	1.95 (0.9–3.125)	0.8 (0.3–0.8)	0.003
PBE	10 (62.5)	15 (24.6)	0.004
RE	9 (56.3)	0 (0)	<0.001
History of PPI treatment	8 (50.0)	20 (32.8)	0.089

Data are shown as the median (IQR) or number (%) of patients. 24-hr MII-pH = 24-hour multichannel intraluminal impedance-pH monitoring, CC = Chicago classification, GERD = gastroesophageal reflux disease, HRM = high-resolution manometry, IBT = impaired bolus transit, IQR = interquartile range, NCCP = noncardiac chest pain, PAE = pathologic acid exposure, PBE = pathologic bolus exposure, PPI = proton pump inhibitor, RE = reflux esophagitis.

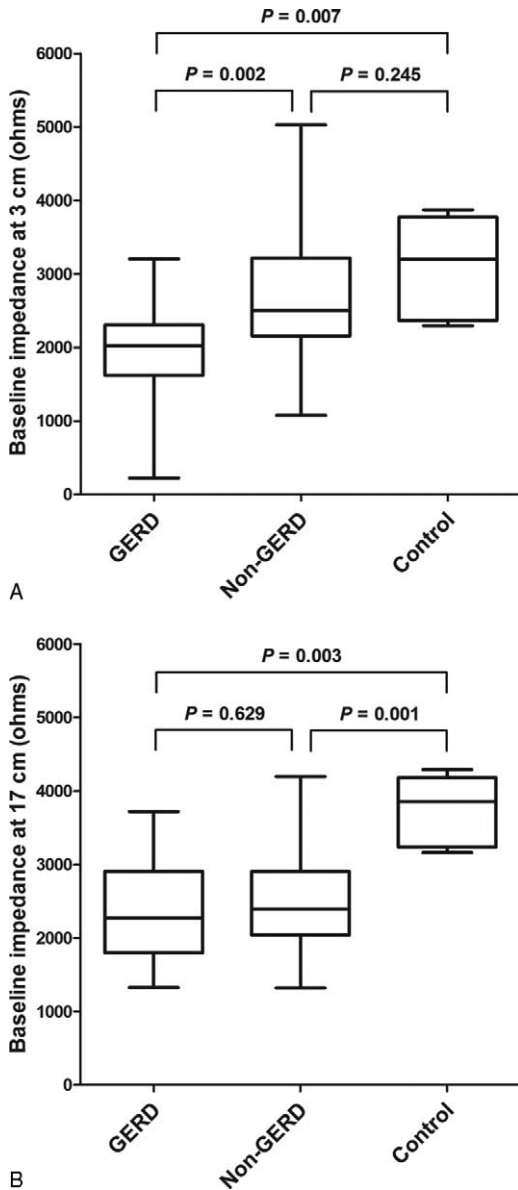


FIGURE 2. BI between groups at the distal and proximal esophageal mucosa. Note that BI of the non-GERD-related NCCP group was lower than the control group at the proximal esophagus but not at the distal esophagus. The GERD-related NCCP group showed lower BI than the control group at both distal and proximal esophagus. Whisker extends to the minimum and maximum values. BI = baseline impedance, GERD = gastroesophageal reflux disease, NCCP = noncardiac chest pain.

The GERD-related NCCP group showed lower BI than the control group at both distal and proximal esophagus. This observation is consistent with those of previous studies.^{30,31} Kessing et al³¹ demonstrated that BI is related to esophageal acid exposure, where BI at both distal and proximal esophagus in GERD patients with pathologic acid reflux was lower than in controls. In a study by Kandulski et al,³⁰ BI was compared between patients with functional heartburn (FH) and GERD. At the distal esophagus, BI was significantly lower in patients with erosive reflux disease (ERD) or NERD than those with FH. However, reduced BI levels were found only in patients with

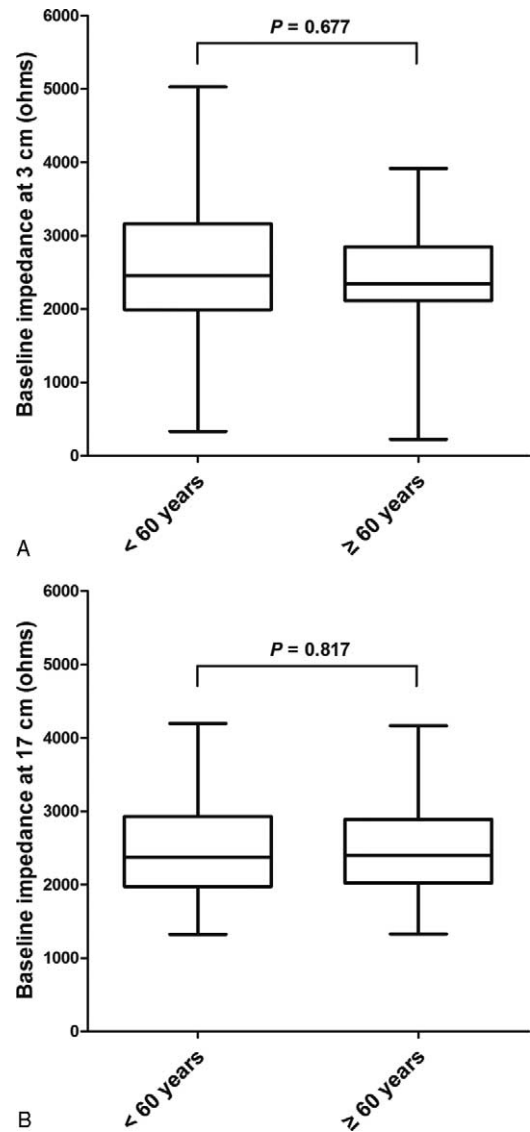


FIGURE 3. Comparison of BI according to age in patients with NCCP. Among 77 patients with NCCP, BI did not differ by age (age <60 vs ≥60 years) at both distal and proximal esophageal mucosa. Whisker extends to the minimum and maximum values. BI = baseline impedance, NCCP = noncardiac chest pain.

ERD at the proximal esophagus. As the patients with GERD-related NCCP were defined by the presence of PAE and/or RE in the present study, they seem to show lower BI at both distal and proximal esophagus than controls, indicating an impaired mucosal integrity along the whole esophagus.

Of interest, BI of the non-GERD-related NCCP group was significantly lower than the control group at the proximal esophagus. However, BI of the non-GERD-related NCCP group was higher than the GERD-related NCCP group and was similar to the control group at the distal esophagus. As the mucosa is more permeable to ionic flow due to dilated intercellular spaces, BI will be lowered when the esophageal mucosa integrity is impaired. Thus, our results indicate that the esophageal mucosa integrity may be impaired at the proximal esophagus in patients with non-GERD-related NCCP. The impaired mucosal integrity

renders the mucosa more vulnerable to symptomatic perception.^{32–34} Indeed, in a recent study including patients with NERD or FH, those with lower BI were more likely to painfully perceive the acid perfusion.³³ Once mucosal injury occurs, several inflammatory mediators are released in response to a variety of noxious stimuli. These mediators have the common effect of reducing the transduction threshold of a variety of cation channels on primary afferent myelinated or unmyelinated neurons.³⁵ In real life, it is possible that we are highly exposed to intake capable of disruption of the esophageal mucosal integrity by chemical, thermal, or mechanical injury, which could include many things besides refluxate such as hot tea and coffee, carbonated drinks, alcohols, spicy and salty foods, and drugs.^{36,37} Even acute stress could cause the impairment of esophageal mucosal integrity with a subsequent visceral hypersensitivity.³⁸ In a recent experimental study by Zhang et al,³⁹ mast cell activation impaired the esophageal mucosal integrity, which subsequently increased esophageal vagal nociceptive C fiber activation. Taken together, the impaired esophageal mucosal integrity at the proximal esophagus may play a causative role in the non-GERD-related NCCP. Plausible scenario is that patients with non-GERD-related NCCP received certain injuries that could be repetitive and subsequently develop impaired esophageal mucosal integrity, resulting in frequent symptom perception from various stimuli. To confirm our results, further studies to evaluate the effect of restoring the proximal esophageal mucosal integrity on the symptom relief in patients with non-GERD-related NCCP are warranted.

The present study had some limitations. First, the control group was rather small and consisted of younger patients than the NCCP groups. However, BI of the control group was similar to that of the previous study.³¹ In addition, BI of the non-GERD-related NCCP group was similar to that of GERD-related NCCP group at the proximal esophagus, whereas BI of the non-GERD-related NCCP group was higher than that of GERD-related NCCP group at the distal esophagus. These observations indicate that the mucosal integrity is impaired relatively at the proximal esophagus in patients with non-GERD-related NCCP. It is also unlikely that age has a substantial effect on BI because BI did not differ by the age groups (age <60 vs ≥60 years). Second, BI was measured by 1 investigator, resulting in a possible bias. Instead, the investigator was blinded to the patients group. In addition, each BI was calculated from the 12 impedance measurements, which might minimize the possibility of erroneous BI calculation. Furthermore, our findings came from the comparisons of BI between the groups. Thus, the interobserver agreement was not measured. Third, we did not confirm histologically dilated intercellular spaces in the NCCP groups, although BI measurement is a good surrogate tool for the assessment of esophageal mucosal integrity.¹⁷ Nevertheless, the present study has strength as the first study to evaluate BI in patients with NCCP to assess the role of impaired mucosal integrity in the genesis of NCCP symptom. In conclusion, our data suggested that the mucosa integrity is impaired at the proximal esophagus in patients with non-GERD-related NCCP, which might be a pathogenic mechanism of NCCP. Further studies to evaluate the functional and morphologic integrity of the esophageal mucosa in patients with non-GERD-related NCCP are warranted to confirm our findings.

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