

Recent Advances in Noncardiac Chest Pain in Korea

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Gastroesophageal reflux disease (GERD) is the most common cause of noncardiac chest pain (NCCP) and is present in up to 60% of patients with NCCP in Western countries. In Korea, after a reasonable cardiac evaluation, GERD is reported to underlie 41% of NCCP cases. Typical reflux symptoms are frequent in Korean patients suffering from NCCP. Therefore, a careful history of the predominant symptoms, including heartburn and acid regurgitation, is relatively indicative of the GERD diagnosis in Korea. In Korea, in contrast to Western countries, patients aged 40 years and over who have been diagnosed with NCCP but who are without alarming features should undergo endoscopy to exclude gastric cancer or peptic ulcers because of the higher prevalence of peptic ulcer disease and gastric cancers in the region. In a primary care setting, in the absence of any alarming symptoms, a symptomatic response to a trial of a proton pump inhibitor (PPI) is sufficient for the presumptive diagnosis of GERD. In addition, the optimal duration of a PPI test may be at least 2 weeks, as GERD symptoms tend to be less frequent or atypical in Korean patients than in patients from Western countries. In patients diagnosed with GERD-related NCCP, long-term therapy (more than 2 months) with double the standard dose of a PPI is required to alleviate symptoms. Esophageal dysmotility is relatively uncommon, and pain modulators seem to offer significant improvement of chest pain control in non-GERD-related NCCP. Most traditionally available tricyclics or heterocyclics have many undesirable effects. Therefore, newer drugs with fewer side effects (for example, the serotonin - norepinephrine reuptake inhibitors) may be needed. (*Gut Liver* 2012;6:1-9)

Key Words: Noncardiac chest pain; Gastroesophageal reflux disease; Upper endoscopy; Proton pump inhibitor; Serotonin

- norepinephrine reuptake inhibitor

INTRODUCTION

Following a reasonable cardiac evaluation, noncardiac chest pain (NCCP) is defined as a recurring angina-like or substernal chest pain which is believed to be unrelated to the heart.¹⁻³ It affects approximately one-third of the population during lifetime.^{3,4} It is a benign condition with an estimated 10-year mortality of less than 1%.⁵ However, the associated morbidity is very high, mainly resulting from inability to work and from the use of health care services.⁶ Several pathophysiological mechanisms have been suggested, including gastroesophageal reflux disease (GERD), esophageal motility disorders, visceral hyperalgesia, psychiatric disturbances, abnormal cerebral processing of the visceral stimulation, and disrupted autonomic activity.^{7,8} The diagnosis and management of patients with NCCP is a frequent and perplexing problem for clinicians. Even after a reasonable cardiac evaluation, many patients continue to present a diagnostic and therapeutic challenge to their primary care physicians. These patients are frequently highly debilitated and tend to use a disproportionate level of health care resources, including recurrent doctor and emergency room visits, hospitalizations, and prescription medication, leading to indications of poor satisfaction with their medical care.^{9,10}

GERD is known to be the most common cause of NCCP.^{1,11,12} It is known to be present in up to 60% of patients with NCCP in the world.¹³ Similarly, in a prospective analysis conducted in Korea in 58 patients with NCCP, 41% were diagnosed with GERD based on upper endoscopy and 24-hour esophageal pH monitoring (Fig. 1).¹⁴ Concerning age factors, the population-based study by Eslick *et al.*³ showed that the prevalence of NCCP tended to decrease with increasing age. Moreover, young

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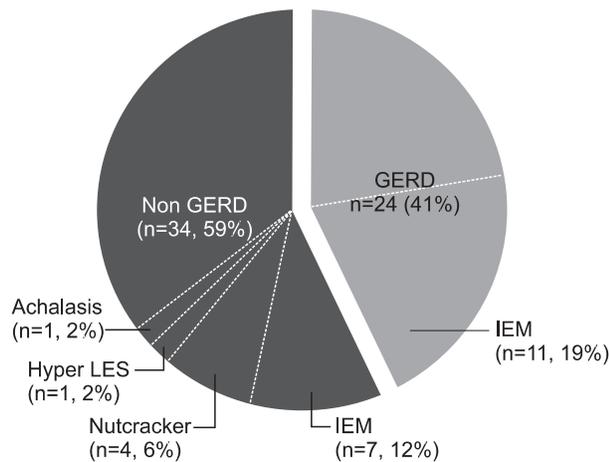


Fig. 1. Upper gastrointestinal evaluation. Gastroesophageal reflux disease (GERD)-related noncardiac chest pain (NCCP) is found in 24 (41%) of 58 subjects on upper endoscopy and/or ambulatory 24-hour esophageal pH monitoring. Esophageal motility disorder is found in 24 subjects (41%), including 18 with ineffective esophageal motility, 4 with nutcracker esophagus, one with hypertensive lower esophageal sphincter (LES), and one with achalasia. GERD-associated esophageal dysmotility is found in 11 (19%) patients, and non-GERD-associated esophageal dysmotility is found in only 13 subjects (22%). Non-GERD, non-GERD-related NCCP; Hyper LES, hypertensive LES; Nutcracker, nutcracker esophagus; IEM, ineffective esophageal motility.

age may be one of the potential risk factors for NCCP.¹⁵ Interestingly, in a recent report in Korea, the incidence of GERD was reported to be lower in young patients suffering from NCCP, compared with middle aged patients.¹⁶

DIAGNOSIS

The causes of NCCP are diverse. The esophagus has been determined to be the major source of NCCP, with GERD as the most common cause. After cardiac evaluation, the available diagnostic tests include upper endoscopy, conventional esophageal manometry, ambulatory 24-hour esophageal pH monitoring, and combinations of the above. A short-term clinical trial using a high-dose proton pump inhibitor (PPI) has been also used as a useful tool for diagnosing GERD-related NCCP.¹⁷ However, these diagnostic tests have some limitations, and none of these tests can measure all aspects of NCCP. Recently, the advent of combined esophageal impedance-pH metering and high-resolution manometry (HRM) has been introduced.

1. Typical reflux symptoms in Korea

NCCP entails a complex set of symptoms, which, in its broadest context, includes patients with heartburn, acid regurgitation, dysphagia, dyspepsia, pleurisy, and others. Among these, typical reflux symptoms (heartburn or acid regurgitation) are significantly and independently associated with the presence of NCCP. Heartburn and acid regurgitation, the principal symp-

toms of GERD, has been traditionally considered less common in Asia.^{1,12,18} In North American studies,¹³ most patients with GERD-related NCCP have typical reflux symptoms. In contrast, Chinese patients with GERD-related NCCP rarely present with typical reflux symptoms.¹² This may be related to the fact that there is no direct translation of the word 'heartburn' in most Asian languages. However, in our recent study, a thorough symptom assessment elicited the presence of "heartburn" and "acid regurgitation" in patients initially suspected to have "angina."¹⁴ Thus, 41% of the patients with NCCP presented with typical reflux symptoms. In this study, typical reflux symptoms made GERD-related NCCP more likely presenting high values of sensitivity and specificity. The ability of typical reflux symptoms to heighten the pretest probability of GERD-related NCCP is impressive in Korean population,¹⁴ although the sensitivity of these symptoms (67%) is lower than that of the PPI test (80%) that was reported by a recently published meta-analysis of controlled studies.¹⁹

Chest pain characteristics alone may not be useful in differentiating NCCP from cardiac chest pain,²⁰ therefore, these characteristics may not make the diagnosis of GERD-related NCCP,^{1,12} by themselves and their clinical value is limited, in the absence of other tests. Nevertheless, in patients suffering from NCCP, with or without typical reflux problems, a careful symptom assessment based on chest pain characteristics may be useful for general practitioners because it is easy to apply and may provide support for other diagnostic tests, assisting with the clinical judgement. However, some Korean patients may complain of epigastric soreness or chest discomfort when referring to heartburn. During patient interviews, first of all, interviewers should be cautious in the way in which they use and interpret the term "heartburn," because many patients do not understand the meaning of the term. A careful history of predominant symptoms including heartburn and acid regurgitation is relatively indicative of the diagnosis of GERD in Korea. When symptoms are less clear-cut, an empirical trial of PPIs would be extremely helpful.¹⁴

2. Upper endoscopic evaluation with or without alarm symptoms

Upper endoscopy is commonly used in clinical practice as the first diagnostic tool to evaluate subjects referred for NCCP. However, many authorities believe that the yield of upper endoscopy in NCCP patients is very low. This general perception is based on very few studies that are commonly limited to one center's experience and include a very small number of participants.^{12,17,21-24} Studies that assessed endoscopic findings in NCCP patients reported a wide range of esophageal mucosal findings. Wong *et al.*¹² reported a low incidence of erosive esophagitis (2.56%) among Chinese patients with NCCP who underwent upper endoscopy. However, other studies that assessed the performance of a PPI therapeutic trial in NCCP reported that esopha-

geal erosions were documented in 15-34% of the patients.^{17,25,26} Recently, a total number of 3,688 consecutive patients undergoing upper endoscopy for NCCP were analyzed. Of the NCCP patients, 44.1% had normal upper endoscopy, 28.6% showed a hiatal hernia, 19.4% erosive esophagitis, 4.4% Barrett's esophagus, and 3.6% stricture/stenosis. Most of the endoscopic findings in NCCP were GERD-related.²⁷

Presently, upper endoscopy of the NCCP patients without reported alarm symptoms (dysphagia, odynophagia, anorexia, and weight loss) is not recommended as a necessary diagnostic step in the workup of NCCP. Prompt endoscopy in patients with alarm symptoms results in a significant yield of cancer and of serious benign diseases such as peptic ulcer, stricture, and severe esophagitis (13%).²⁸ In the Asia-Pacific region, including Korea, patients with alarm features are likely to have gastric diseases rather than esophageal diseases due to the higher prevalence of peptic ulcer disease and gastric cancer in the region. Nevertheless, alarm features have a low predictive value and suggest advanced, rather than early, malignancy.²⁹ Therefore, every patient with NCCP had better undergo endoscopy. Diagnostic strategies in Korea must take into account the coexistence of GERD-related NCCP with other common conditions, such as gastric cancer and peptic ulcer. There is a need to perform endoscopy if upper gut symptoms, including NCCP, are persistent or relapse frequently.

Upper endoscopy only identifies a low level of upper gastrointestinal pathology, and the usefulness of upper endoscopy for the evaluation of NCCP has been questioned.^{12,30} However, patients with NCCP are still commonly referred for upper endoscopy; we believe it's a useful screening test, as it enables the

direct visualization of mucosal injury and facilitates guidance for treatment.

3. The PPI test and its optimal duration

An empirical trial with a PPI (the PPI test) was introduced as a non-invasive, readily available alternative diagnostic tool for NCCP.¹⁷ The test, which utilizes a short course of a high-dose PPI, was found to be highly sensitive and specific for diagnosing GERD-related NCCP (Table 1).^{19,31} Several observations have confirmed the usefulness of the PPI test for the diagnosis of NCCP.^{11,17,19} It is readily available for primary care physicians and increases their role in evaluating and treating patients suffering from GERD-spectrum disorders. It offers significant cost savings when compared to other diagnostic tests. As well, in Asia, it has been demonstrated that PPI test is a simple and clinically practical method for diagnosing GERD.³² However, the studies reporting on the empirical trials of PPI defined differently the "successful" reduction of GERD symptoms. In addition, there is little information on whether different doses of PPIs and the length of treatment with the PPIs made a difference in diagnosing GERD.³³ Because of the differences in results from previous studies, some believe that the symptomatic response to the PPI test does not confidently diagnose GERD. The optimal duration of the PPI test has not been determined fully. In several studies, the duration has been about 7 days.³⁴ Earlier pharmacological studies with therapeutic doses of PPI showed that this duration is long enough to reach a steady-state inhibition of acid secretion.²⁵ Therefore, 7 days are probably long enough to see the effects of the PPI and reach a diagnosis in patients with symptoms that occur frequently.^{21,35} However, it may be too

Table 1. PPI Test Performance Summaries in Noncardiac Chest Pain¹⁹

Study	No.	PPI, dose, duration	Study design	GERD, %	Responder	Reference standard(s)	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+	LR-
Fass (1998)	39	Omeprazole, 60 mg, 1 wk	RCT, crossover	62	> 50%	pH-metry, endoscopy	78	86	90	71	5.48	0.25
Bautista (2004)	40	Lansoprazole, 90 mg, 1 wk	RCT, crossover	45	> 50%	pH-metry, endoscopy	78	91	88	83	8.56	0.24
Fass (2002)	20	Rabeprazole, 40 mg, 1 wk	RCT, crossover	60	> 50%	pH-metry, endoscopy	83	75	83	75	3.33	0.22
Pandak (2002)	44	Omeprazole, 80 mg, 2 wk	RCT, crossover	53	> 50%	pH-metry, endoscopy	95	61	73	92	2.44	0.08
Squillace (1993)	17	Omeprazole, 80 mg, 1 day	RCT, crossover	76	> 50%	pH-metry	69	75	90	43	2.77	0.41
Xia (2003)	36	Lansoprazole, 30 mg, 4 wk	RCT, parallel group	33	> 50%	pH-metry	92	67	58	94	2.75	0.13
Chambers (1998)	31	Omeprazole, 40 mg, 6 wk	Open label	17	No a priori definition	pH-metry	0	68	0	76	0	1.46
Dickman (2005)	35	Rabeprazole, 40 mg, 1 wk	RCT, crossover	35	> 50%	pH-metry, endoscopy	75	90	83	75		

PPI, proton pump inhibitor; GERD, gastroesophageal reflux disease; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio; RCT, randomized controlled trial.

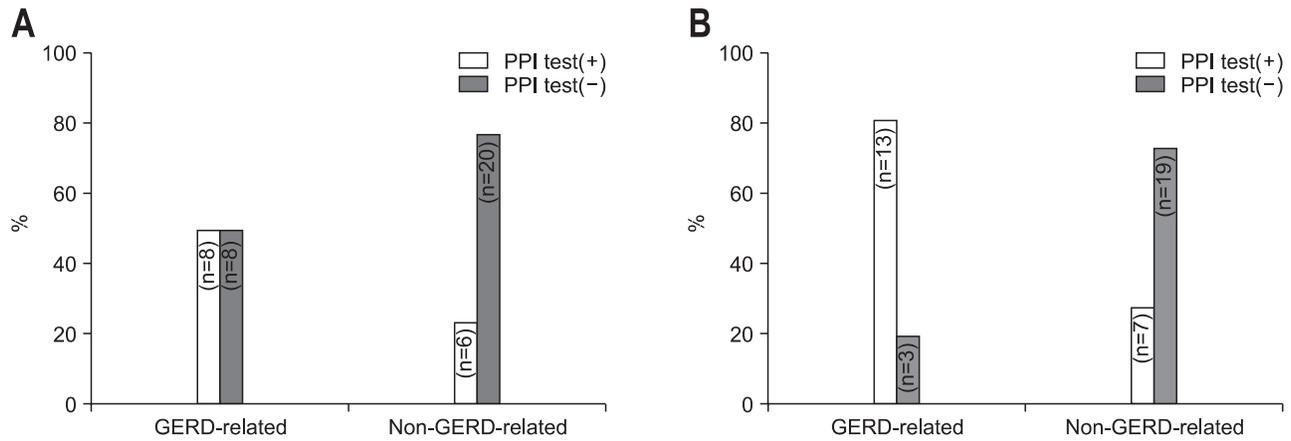


Fig. 2. A comparison of the proton pump inhibitor (PPI) test between gastroesophageal reflux disease (GERD)-related noncardiac chest pain (NCCP) and non-GERD-related NCCP groups. During the second week of the PPI trial (B), the fraction of positive PPI tests is significantly higher in the GERD-related NCCP group (81%) than in non-GERD-related NCCP group (27%) ($p=0.001$). However, during the first week of the PPI trial (A), there is no significant difference between the two groups (GERD vs non-GERD=50% vs 23%, $p=0.1$).

short of a time interval in patients with less frequent symptoms and in patients with atypical symptoms, such as GERD-related laryngeal or upper respiratory symptoms.^{22,36}

In the study by Fass *et al.*, the therapeutic trial of the PPI lasted only 7 days in the NCCP subjects who had at least 3 episodes per week.^{21,23,35,37} Consequently, the one week PPI test may be most useful for patients with frequent chest pain symptoms. However, in all patients who report chest pain irrespective of its frequency, the one week PPI trial may not be long enough to diagnose GERD-related NCCP. It is not suggesting that the NCCP patients should complete a full period of 8 weeks of PPI treatment before determining the beneficial effect of the medication. However, the time frame reported by Fass *et al.*¹⁷ may be too short.³⁰ Especially in Korea or in Asia in general, compared with Western countries, a larger number of patients may have infrequent chest pain^{2,24,25,38,39} and the above diagnostic guidelines would exclude many of these patients. Hence, we agree that the duration of the PPI test may highly depend on the frequency of the symptom.⁶ In our recent uncontrolled trial, the two-week rabeprazole trial resulted in symptom improvement in 81% of the GERD-related NCCP patients and this result was statistically significant compared with the non GERD-related NCCP patients.⁴⁰ However, for the one-week rabeprazole trial, only 50% of the GERD-related NCCP patients responded to the PPI treatment (Figs 2 and 3).⁴⁰ These data suggest that PPI test remains the best available diagnostic tool for patients with, at least weekly, NCCP suspected GERD, but that such a trial should extend for at least 2 weeks.

4. Are other tests useful?

1) Manometry

The relationship between NCCP symptoms and motility abnormalities is known to be even more problematic. These were reflected in the American Gastroenterological Association guidelines for esophageal manometry, which recommended that

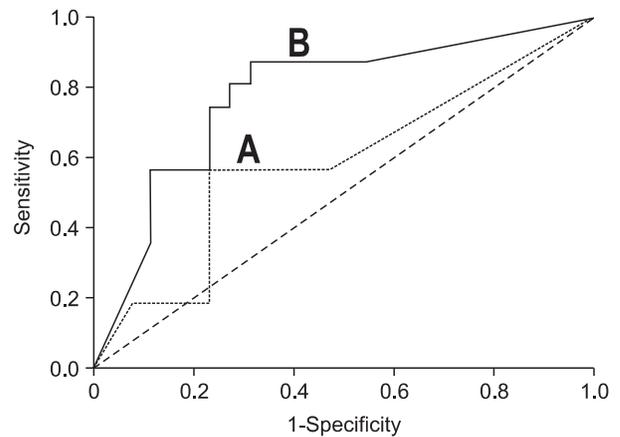


Fig. 3. The receiver operating characteristic (ROC) curve of the proton pump inhibitor (PPI) test for gastroesophageal reflux disease (GERD)-related noncardiac chest pain during the first week (A) and the second week (B). The reduction in chest pain corresponded to 0.78 in the area under ROC with an accuracy of 77.1% during the second week of the PPI test. Additionally, there is a significant difference between the areas under the ROC curves for the first and second weeks of the PPI test ($p<0.05$).

manometry should not be used as the initial test for the evaluation of the patients with NCCP.^{2,41} In our study, the specific esophageal motility disorders, such as achalasia, nutcracker esophagus, and hypertensive lower esophageal sphincter (LES) were found in only 10% of the investigated patients.¹⁴ Even though esophageal manometry may be used to ensure the accurate placement of the ambulatory monitoring probes and may be helpful prior to antireflux surgery, esophageal manometry is not generally used to diagnose GERD in a primary setting.

HRM allows for continuous measurements from a large number of closely spaced sensors connected to a software capable of analyzing large volumes of pressure data; it is easier to perform than a regular esophageal manometric investigation because a pull-through is not necessary. However, there is no current

available data to show an increased diagnostic yield of HRM when compared with standard manometry in the evaluation of patients with NCCP. On the other hand, if there is suspicion of achalasia, diffuse esophageal spasm, or nutcracker esophagus, HRM might supply more prognostic information than standard manometry.⁴²

2) Ambulatory 24-hour esophageal pH monitoring

Ambulatory 24-hour esophageal pH monitoring is generally thought to be the most accurate method for the identification of GERD in patients with NCCP.^{43,44} Unfortunately, this test is limited by a lack of physician and patient acceptance, a lack of standardization (i.e., variability in what is considered normal and abnormal), and an inability to determine the true sensitivity and specificity of the technique.^{1,45} A negative ambulatory pH study off therapy helps to exclude GERD if a PPI test fails.

3) Combined esophageal impedance-pH metering

Although conventional pH monitoring can quantify esophageal acid exposure and can be used to evaluate the association between symptoms and acid reflux, it cannot reliably detect non-acid reflux.⁴⁶ Recently, the advent of combined esophageal impedance-pH metering has allowed the detection of non-acid reflux, as well as acid reflux. The detection of reflux episodes by changes in intraluminal resistance to alternating current (i.e., impedance), combined multichannel intraluminal impedance (MII) and pH monitoring offers the opportunity to detect bolus exposure (both acid and non-acid reflux episodes) and to evaluate the relationship between symptoms and reflux.⁴⁶ Refluxate presence, distribution, and clearing are primarily detected by MII-pH, and can be simply characterized as acid or non-acid, based on the pH change, and as a liquid, gas, or a mix, based on the MII.⁴⁷ In our recent data, combined impedance-pH monitoring improved both the detection and characterization of the NCCP and suggested that pathological bolus exposure plays a major role in eliciting NCCP.⁴⁸

TREATMENT

The treatment of patients with an esophageal source of chest pain remains a challenging problem. The management of functional esophageal chest pain is largely empirical. Because GERD is the most common cause of esophageal chest pain, anti-reflux therapy plays an important role in the diagnosis and treatment of the patients with NCCP. In patients with non GERD-related NCCP, treatment should be targeted to esophageal motility disorders or visceral hyperalgesia, because esophageal motility disorders or visceral hyperalgesia are thought to play an important role in the genesis of the NCCP.^{49,50}

1. The treatment of GERD-related NCCP using PPIs

The treatment of GERD-related NCCP should involve life style

modification and pharmacological intervention. Elevating the head of the bed at night, reducing fat intake, stopping smoking, and avoiding foods that exacerbate reflux have been shown to decrease reflux symptoms.⁴⁹

The PPIs are the most efficacious medical intervention for GERD. Studies have shown repeatedly and consistently that PPIs are superior to histamine 2 receptor antagonists (H₂RAs) in healing the esophageal mucosa and relieving GERD-related symptoms in patients with GERD.⁵¹⁻⁵³ In a meta-analysis, the authors demonstrated that after 12 weeks of treatment, healing rates were 83.6% with PPIs, 51.9% with H₂RAs, 39.2% with sucralfate, and 28.2% with placebo.⁵⁴ In addition, the treatment with PPIs resulted in healing rates of esophageal inflammation and relief of heartburn symptoms that were two-fold higher than what was observed in patients receiving H₂RAs. Similarly, PPIs demonstrated superiority in relieving heartburn symptoms in patients with non erosive reflux disease (NERD), when compared to H₂RAs.⁵⁵⁻⁵⁷ Even when 'soft' clinical endpoints were used, such as average heartburn severity score or days without heartburn, the PPIs were significantly better than the H₂RAs. The superiority of the PPIs over the H₂RAs in the treatment of the erosive reflux disease was not limited to acute therapy, but has also been demonstrated in maintenance studies over a period of time as long as 11 years.⁵⁸ Similar comparative trials in NERD are not currently available.

Laparoscopic fundoplication relieves heartburn and acid regurgitation in most patients with GERD, but its effect on the chest pain is less clear. The published data report only short-term outcomes from a limited number of patients, usually suffering from a mild form of the disease. These therapies are considered experimental and should not be routinely performed.¹

Therefore, in patients with GERD-related NCCP, long term therapy (more than 2 months) with commonly double the standard dose of a PPI is preferentially required to relieve their symptoms.

2. The treatment of non GERD-related NCCP using a pain modulator

Anticholinergic drugs, such as atropine, L-hyoscyamine, and pirenzepine, induce a decrease in the amplitude of the esophageal peristalsis and in the LES pressure, as seen with manometry; although they may be useful for the treatment of hypercontractile esophageal disorders, there is not enough published data examining their value in the symptomatic management of the patients with NCCP. There are very few clinical trials investigating the use of smooth muscle relaxants in the treatment of the NCCP; when data exists, it mostly demonstrates a transient effect. Injection of the botulinum toxin, a potent local anticholinergic agent, was introduced for the treatment of patients suffering from NCCP without achalasia or reflux-related spastic esophageal disorders. Some studies showed favorable outcomes, however, placebo-controlled trials are needed to confirm re-

sults.⁴⁹

Psychological or psychiatric disorders may be either the cause or the effect of the NCCP in many patients. Nevertheless, reliable diagnosis procedures may not be easily applied in acute situations. Despite the presence of extensive evidence linking visceral hypersensitivity and non GERD-related NCCP, the mechanism underlying visceral hypersensitivity has not been fully elucidated. This problem makes the treatment of the non GERD-related NCCP quite difficult. Indeed, therapeutic gains with the PPI treatment were obtained in only 9-39% of the patients with non GERD-related NCCP.^{11,25,27} Hence, the principal treatment of the non GERD-related NCCP moved towards pain-modulating agents, such as psychotropic drugs or adenosine receptor antagonists, on the basis that the underlying mechanism was increased pain perception or visceral hyperalgesia.^{59,60} Antidepressants have been used as pain modulators to treat

patients with esophageal disorders causing chest pain. At low doses, antidepressants have beneficial effects in the treatment of the chronic pain syndromes of somatic and visceral origin. The majority of the traditionally available tricyclics or heterocyclics have many undesirable effects. Therefore, newer drugs with mitigated side effects are needed. Patients with NCCP are more likely to present with hypochondriasis, anxiety, and panic disorders. Hence, psychological treatment in the form of reassurance has been the mainstay of the management of the NCCP. Recently, in a randomized, double-blind, placebo-controlled, crossover trial, we evaluated the clinical efficacy of venlafaxine, a serotonin-norepinephrine reuptake inhibitor, for functional chest pain in young adult patients. We found that venlafaxine hydrochloride resulted in a significant decrease of the symptom score, with endurable side effects, compared with the efficacy of placebo (Fig. 4).⁶¹

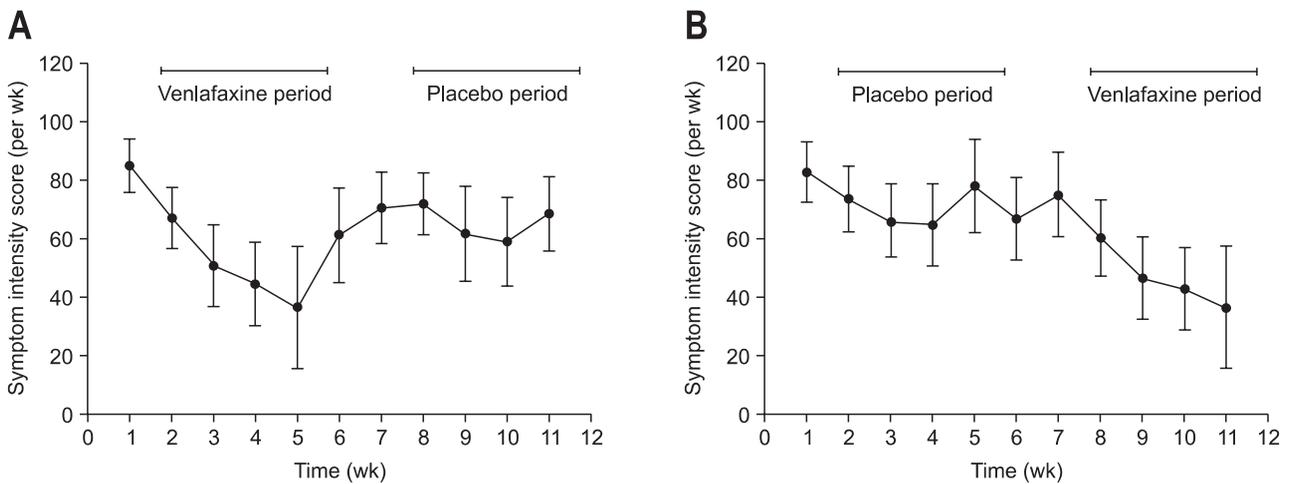


Fig. 4. Mean symptom intensity score per week for sequence A (venlafaxine first and placebo second) (A) and sequence B (placebo first and venlafaxine second) groups (B), respectively. The linear mixed model with a random subject effect is performed to determine the carryover effect, the period effect, and the treatment effect of the drug for the ranks of the symptom intensity score in the repeated measure cross-over design. Venlafaxine treatment resulted in a significantly lower symptom intensity score when compared with the placebo treatment ($p < 0.001$).

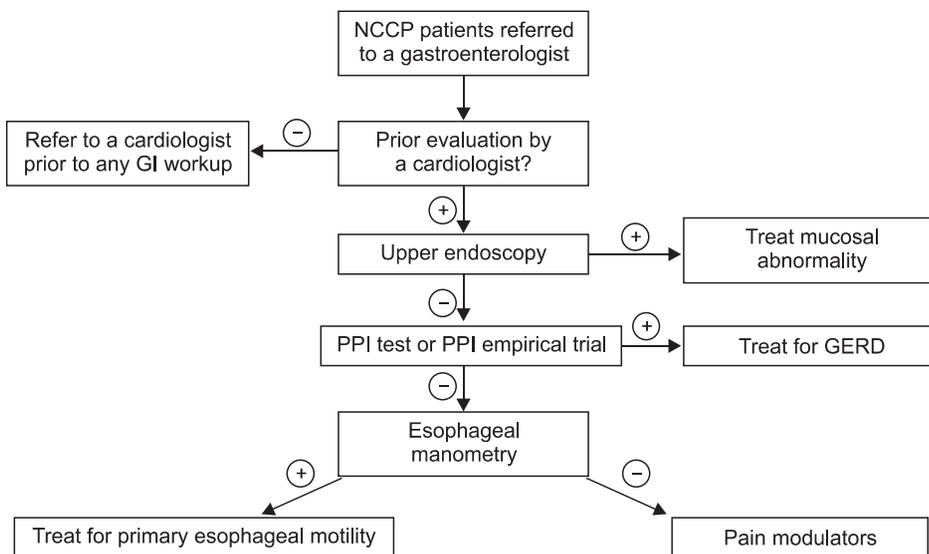


Fig. 5. Proposed diagnostic evaluation of patients with noncardiac chest pain (NCCP) in Korea. GI, gastrointestinal; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

SUMMARY

Evaluation for esophageal disorder in patients with NCCP should be undertaken after a cardiac cause has been excluded. The initial evaluation with endoscopy is warranted irrespective of alarm symptoms. Then, GERD should be excluded by using the PPI test. If the PPI test is negative or the patient did not respond to empirical therapy, esophageal manometry could be performed primarily to exclude esophageal motility disorders, such as achalasia; pH testing has a limited role in evaluating patients who failed intense PPI treatment.

Treatment of the NCCP remains a difficult problem due to the heterogeneous nature of the disorder. Gastroesophageal reflux is the best studied condition contributing to the NCCP. Pharmacological trials of acid inhibition show a robust response rate for patients with GERD-related NCCP. In patients with non GERD-related NCCP, treatment should be targeted to esophageal motility disorders or visceral hyperalgesia. However, there are not enough clinical trials to date. The role of the newly reported serotonin and adenosine receptor pathway opens another opportunity for further research to better understand the neurotransmitters involved in the genesis of the visceral chest pain (Fig. 5).

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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