REVIEW ARTICLE

비심인성 흉통: 진단 및 치료의 최신지견

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Noncardiac Chest Pain: Update on the Diagnosis and Management

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Noncardiac chest pain (NCCP) is defined as recurring, angina-like, retrosternal chest pain of noncardiac origin. Although patients with NCCP have excellent long-term prognosis, most suffer persistently from their symptoms. Several pathophysiological mechanisms have been suggested, including gastroesophageal reflux disease (GERD), esophageal motility disorder, esophageal hypersensitivity, and psychological comorbidity. Among them, GERD is the most common cause of NCCP. Therefore, GERD should first be considered as the underlying cause of symptoms in patients with NCCP. Empirical proton pump inhibitor (PPI) treatment with a preferably double dose for more than 2 months could be cost-effective. PPI test can also be used for diagnosis of GERD-related NCCP, but it should be considered for patients with NCCP occurring at least weekly and its duration should be at least 2 weeks. However, upper endoscopy and esophageal pH monitoring are necessary when the diagnosis of GERD is uncertain. Esophageal impedance-pH monitoring could further improve the diagnostic yield. Patients with GERD-related NCCP should preferably be treated with a double dose PPI until symptoms remit (may require more than 2 months of therapy for optimal symptom control), followed by dose tapering to determine the lowest PPI dose that can control symptoms. However, treatment of patients with non-GERD－related NCCP is challenging. An empirical treatment of antidepressants could be considered. If there are specific esophageal motility disorders, smooth muscle relaxants or endoscopic treatment may be considered in selected cases. If none of these traditional treatments is effective, a psychology consultation for cognitive behavioral therapy should be considered. (**Korean J Gastroenterol 2015;65:76-84**)

Key Words: Diagnosis; Gastroesophageal reflux disease; Noncardiac chest pain (NCCP); Therapy

INTRODUCTION

Noncardiac chest pain (NCCP) is defined as recurring, angina-like, retrosternal chest pain of noncardiac origin.[1] In the diagnostic evaluation of chest pain, exclusion of coronary artery disease (CAD) is of great importance.[2] However, as a patient's history and characteristics do not reliably distinguish between cardiac and noncardiac causes of chest pain,[3] a reasonable cardiac evaluation is required.[4] Decisions regarding which tests to pursue should be made by the treating cardiologist.[1] According to data from a chest pain clinic in the United Kingdom, nearly half of patients with NCCP nevertheless are not convinced by their negative cardiac diagnosis and experience ongoing chest pain.[5]

Epidemiologic data of NCCP are limited. In a recent meta-analysis including 16 studies from 14 separate populations, pooled prevalence of NCCP was 13% (95% CI, 9-16%).[6] However, significant heterogeneity was present

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among reported studies. In a Korean population study (n=1,417),[7] the prevalence of chest pain was 7.9%. Patients with NCCP report poor quality of life,[8,9] while increased mortality is unusual.[10-13] Cohort studies show that many patients with NCCP (67-74%) continue to experience symptoms,[11-13] resulting in high healthcare cost.[14]

Despite this significant burden, the pathophysiological mechanisms behind symptom generation remain to be elucidated. However, advances in understanding NCCP have been made in the past decade. This review describes the recent evidence regarding diagnosis and treatment in patients with NCCP; only esophageal-related causes for NCCP are covered here.

DIAGNOSIS

Because the morbidity and mortality of CAD far exceeds that of esophageal-related causes of NCCP, further esophageal workup is warranted only after cardiac disease has been ruled out.[15]

1. GERD is the most common cause of NCCP (GERD-related NCCP)

In a prospective, double-blind, randomized clinical trial (RCT) of patients with NCCP and GERD documented by 24-hour pH monitoring, patients on omeprazole achieved greater overall symptom improvement when compared with placebo (81% vs. 6%, p=0.001).[16] A recent systematic review including 6 RCTs also reported similar results.[17] The therapeutic gain of >50% improvement with proton pump inhibitors (PPIs) relative to placebo was 56-85% in NCCP patients with objective evidence of GERD and 0-17% in those without objective evidence of GERD.

Epidemiologic study data support the association between NCCP and GERD. Markedly higher prevalence of NCCP was observed for subjects who also reported GERD (OR, 4.71; 95% CI, 3.32-6.70) and increased according to frequency of GERD symptoms.[6] Similar results were also reported in a Korean study.[7] GERD was reported in 61.6% of subjects with chest pain. According to presence of GERD the prevalence of chest pain was markedly different: 3.6% in subjects with no GERD symptoms, 28.8% in those with occasional GERD symptoms, and 44.0% in those with frequent GERD symptoms.

Therefore GERD should be considered first as the underlying cause of symptoms in patients with NCCP.

2. Upper endoscopic evaluation is necessary in patients with NCCP

In the absence of a gold standard for the diagnosis of GERD, upper endoscopy provides objective evidence of GERD. The presence of reflux esophagitis on endoscopy could confirm the diagnosis of GERD-related NCCP. In addition, in Korea, with a high prevalence of peptic ulcer disease and gastric cancer, the coexistence of GERD-related NCCP with other gastric diseases should also be considered.[18] In addition, endoscopy in patients with alarm symptoms results in a significant yield of cancer and serious benign diseases such as peptic ulcer, stricture, and severe esophagitis.[19] Thus upper endoscopy should precede other testing in the evaluation of NCCP.

However, the prevalence of esophageal mucosal abnormalities consistent with GERD is lower in patients with NCCP compared with that observed in patients with GERD.[1] A United States' study using a national endoscopic database compared upper endoscopic findings between patients with NCCP only and patients with GERD symptoms only.[20] Hiatal hernia, erosive esophagitis, and Barrett's esophagus were less common in NCCP patients than in GERD patients (28.6%, 19.4%, and 4.4%, respectively, vs. 44.8%, 27.8%, and 9.1%, respectively). Hiatal hernia or Barrett's esophagus does not necessarily mean that patient's symptoms are caused by reflux. Thus negative upper endoscopy is quite common in patients with NCCP and further reflux testing is necessary.

3. Twenty-four hour esophageal pH monitoring is a good diagnostic tool for GERD in patients with NCCP

Increased acid reflux is another objective evidence of GERD. Abnormal acid reflux on esophageal pH monitoring suggests association between GERD and NCCP. Unlike erosive esophagitis, abnormal acid reflux is common in patients with NCCP, ranging between 28% and 62%.[21-25] In a recent study including 348 suspected NCCP patients, abnormal acid reflux was found in 28% patients without erosive esophagitis on endoscopy.[21] Thus authors suggest pH monitoring for patients with NCCP who do not have erosive esophagitis, particularly those in whom objective evidence of GERD is required (off PPI therapy).

4. Impedance–pH monitoring is better than pH monitoring alone in the evaluation of NCCP

Although the yield of a combination of upper endoscopy and pH monitoring is high,[17] even more cases of GERD could be detected in patients with NCCP. Nonacid reflux may cause chest pain.[26,27] In a study performing 24-hour impedance-pH monitoring twice on and off PPI in patients with PPI-refractory GERD,[27] the number of heartburn episodes related to reflux decreased on PPI compared with off PPI, while the numbers of chest pain episodes and regurgitation were not different. In another study with PPI-refractory GERD patients,[28] the number of weakly acidic refluxes was abnormal in all patients, whereas the number of acid and weakly alkaline refluxes was normal in the vast majority of patients. Thus, both acid and nonacid refluxes may be involved in the pathogenesis of NCCP. We also showed that evaluation of esophageal bolus exposure by 24-hour impedance-pH monitoring improved detection of GERD in patients with NCCP.[29] Thus impedance-pH monitoring is better than pH monitoring alone in the evaluation of NCCP. In patients with PPI-refractory NCCP impedance-pH monitoring could be performed on PPI therapy, while in patients requiring objective evidence of GERD it should be performed off PPI therapy. However, impedance-pH monitoring off PPI seems to offer the best chance to assess a relationship between symptoms and reflux episodes.[27]

5. PPI test can be used to confirm the diagnosis of GERD–related NCCP

Given the high prevalence of GERD in patients with NCCP and excellent efficacy of PPI in them,[6,17] empirical PPI treatment for 2-3 months could be cost-effective in management of NCCP. In addition, NCCP patients with typical reflux symptoms are more likely to have GERD-related NCCP than those without typical reflux symptoms.[30] Accordingly, empirical PPI treatment is a cost-effective diagnostic strategy in NCCP patients with typical reflux symptoms.

In contrast to empirical PPI treatment, a short course (1-2 weeks) of high-dose PPI trial (PPI test) could confirm the diagnosis of GERD in patients with NCCP.[23] Several trials using different PPIs (omeprazole, lansoprazole, and rabeprazole) and occasionally different design have demonstrated the acceptable diagnostic performance of PPI test.[24,31-33] The sensitivity, specificity, positive predictive value, and negative predictive value of PPI test ranged from 75% to 92%, 67% to 90%, 58% to 90%, and 71% to 94%, respectively. PPI test is also noninvasive and readily available. Thus, PPI test could be used by primary care physicians as an initial diagnostic tool for GERD in patients with NCCP.[34] In addition, it offers significant cost savings when compared to other diagnostic tests for GERD.[23,35]

However, there are limitations to wide use of PPI test in patients with NCCP. Optimal dosage and duration of PPI and definition of a positive test have not been established. The steady maximum mean percentage time of gastric pH > 4 is noted after taking PPI for 7 days.[36] Thus 7 days are probably sufficient to see the effects of PPI in patients with frequent symptoms. However, it may be too short to reach a diagnosis in patients with less frequent symptoms. In a Korean study including 42 patients with at least weekly NCCP,[25] no significant difference for a positive PPI test was observed between the GERD-related NCCP group (50%) and the non-GERD－related NCCP group (23%) during the first week of PPI testing but during the second week, GERD-related NCCP patients had a higher positive PPI test (81%) than non-GERD－related NCCP patients (27%). These data suggest that PPI test can be used as an effective diagnostic tool for patients with NCCP occurring at least weekly, and its duration should be at least 2 weeks.

6. Esophageal manometry could be helpful in the evaluation of NCCP

Esophageal manometry is the best tool for detection of abnormal esophageal motor function.[37] In patients with NCCP, 30% have abnormal esophageal motility on manometry.[38,39] However, the relationship between these abnormal motilities and chest pain remains unclear and specific esophageal motility disorders such as achalasia and nutcracker esophagus, and diffuse esophageal spasm are found in only a minority of patients.[30,38,39] Likewise, the American Gastroenterological Association guidelines on esophageal manometry state that manometry is not indicated as the initial test for chest pain because of the low specificity of the findings and the low likelihood of detecting a clinically significant motility disorder.[37]

However, manometry could detect achalasia, jackhammer esophagus or nutcracker esophagus, and distal esophageal spasm that could explain the patient's chest pain.[40-45] Thus, when dysphagia is accompanied by chest pain manometry

should be employed because the above-mentioned primary motility disorders likely to have dysphagia. In addition, we suggest that esophageal manometry should be performed to investigate causes of non-GERD－related NCCP. Although the percentage of patients with motility disorders associated with chest pain is small, manometry plays a role in making a diagnosis of functional chest pain.[46] In addition, manometry is commonly used to determine correct positioning for pH electrode placement. In such circumstances, patients could complete esophageal manometry with additional efforts of drinking even small sips of water. Thus, to modify concisely a diagnostic algorithm esophageal manometry could be performed together with pH monitoring as a primary workup, especially in NCCP patients without typical reflux symptoms who are likely to have non-GERD－related NCCP.

TREATMENT

Because it is a heterogeneous disorder treatment of NCCP has been very challenging. Several pathophysiological mechanisms have been suggested, including GERD, esophageal motility disorder, esophageal hypersensitivity, and psychological comorbidity.[1,47] Thus, treatment of patients with NCCP should target the specific underlying mechanism responsible for patient's symptoms.

1. GERD－related NCCP

GERD is the most common cause of NCCP, and PPIs are the most effective, antisecretory medications that are currently available.[17,23] In a meta-analysis including 7 RCTs (a total of 232 patients) for efficacy of PPI therapy in reducing NCCP symptoms,[48] the pooled RR of continued chest pain after PPI treatment was 0.54 (95% CI, 0.41-0.71) using the individual studies' definition of response giving a number needed for treatment of three (95% CI, 2-4). Five RTCs provided data on symptom improvement of >50% with a pooled RR for continued chest pain of 0.60 (95% CI, 0.44-0.81). If any improvement in chest pain was used to define the response to PPI, the pooled RR was 0.51 (95% CI, 0.33-0.79). In a recent systematic review including 6 RCTs,[17] chest pain response ranged from 75% to 92% and the therapeutic gain of >50% improvement with PPIs relative to placebo was 62% (range, 56-85%) in GERD-related NCCP patients. In a meta- analysis including five RCTs that were sufficiently similar to be suitable for analysis, the pooled RR for >50% improvement in chest pain with PPI therapy compared with placebo was 4.3 (95% CI, 2.6-6.7) in GERD-related NCCP patients.

However, dose and duration of PPI treatment in 6 published RCTs included in the two meta-analyses are inconsistent. Four trials were short course (1 week to 2 weeks), twice-daily PPI trials,[23,24,31,33] one 4 weeks, standard dose PPI trial,[32] and one 8 weeks, twice-daily PPI trial.[16] All trials except one[32] used twice-daily PPI regimens, resulting in doses that were higher than those approved for treatment of GERD. However, responses of twice-daily PPI trials were similar to that of standard dose PPI trial. Thus, the opinion that NCCP treatment requires a high-dose PPI may or may not be correct, which is not based on clinical trial evidence demonstrating a dose-response relationship.

In conclusion, patients with GERD-related NCCP should preferably be treated with a double dose PPI until symptoms remit, followed by dose tapering to determine the lowest PPI dose that can control symptoms.[4] As with other extra-esophageal manifestations of GERD, NCCP patients may require more than 2 months of therapy for optimal symptom control.[4,49]

2. Non－GERD－related NCCP

Treatment of patients with non-GERD－related NCCP has focused on esophageal (hypercontractile or spastic) motility disorders and esophageal visceral hypersensitivity.

1) Esophageal (hypercontractile or spastic) motility disorders

High amplitude contraction or spasm of esophageal smooth muscle may cause chest pain. Thus several trials using calcium channel blockers, nitrates, anticholinergics, or botulinum toxin injection and recent trials with endoscopic myotomy have been conducted to show the efficacy in patients with chest pain and esophageal motility disorder.

Nifedipine was tried in 3 RCTs. In the two RCTs involving patients with nutcracker esophagus[50] and esophageal spasm,[51] nifedipine failed to demonstrate its superior efficacy compared to placebo. In contrast, patients with various esophageal motor disorders, including hypertensive lower esophageal sphincter (LES), nutcracker esophagus, diffuse esophageal spasm, and achalasia who received nifedipine (10 mg by mouth, three times a day) for 4 weeks showed significant improvement compared to those who received placebo.[52] Diltiazem (60 to 90 mg by mouth, four times a day)

for 8 weeks significantly improved chest pain in patients with nutcracker esophagus when compared with placebo.[53,54] However, in a study involving 8 patients with diffuse esophageal spasm, the effect of diltiazem was not significant.[55] In the treatment of NCCP, calcium channel blockers are limited by a transient esophageal motor effect and side effects such as hypotension, bradycardia, and edema.[4,56]

Although several open-label studies have reported that nitrates improve symptoms and esophageal motility patterns in patients with chest pain and esophageal dysmotility, they have been limited by a small number of patients and inconsistent results in regard to drug efficacy.[57-61] Sildenafil, a potent selective inhibitor of cyclic guanosine monophosphate -specific phosphodiesterase type 5, has been shown to improve esophageal motility in patients with nutcracker esophagus or hypertensive LES.[62,63] However, thus far, no studies specifically addressing NCCP patients have been reported. Improvements of esophageal contraction have been reported in patients with nutcracker who were treated with the anticholinergic agents, cimetropium bromide (10 mg intravenously)[64] and atropine (10 μg/kg intravenously).[65] However, clinical data regarding the efficacy of anticholinergic agents (especially of an oral formulation) on symptom improvement in NCCP patients have yet to be reported.

Botulinum toxin injection at the gastroesophageal junction leads to 50% reduction of chest pain episodes in 72% of patients with spastic esophageal motility disorders whose major complaint is chest pain for a mean duration of 7.3 months.[66] Several recent studies have reported successful treatment of patients with spastic esophageal disorder by peroral endoscopic myotomy (POEM).[42,67-69] POEM is a promising treatment option for spastic esophageal motility disorders because it allows myotomy not only of the LES but also of the esophageal body, where the hypertensive contractions occur. However, a causal relationship between chest pain and abnormal contraction of esophageal smooth muscle should be confirmed before treatment. Because chest pain is an intermittent event and not generally elicited during a manometry, clinical significance of abnormal esophageal contraction is unclear. Moreover, abnormal esophageal contraction may occur as a result of esophageal hypersensitivity or acid reflux.[70,71] Ambulatory esophageal manometry or provocative maneuvers could confirm the relation between chest pain and esophageal contractions, although those methods are difficult to perform in practice. Taken together, although these endoscopic treatments have shown good results, clinical data regarding the safety and efficacy are still lacking and greater caution should be used in selection of patients.

2) Esophageal visceral hypersensitivity

Visceral hypersensitivity is a key underlying mechanism of patients with non-GERD－related NCCP, regardless of whether esophageal motility disorder is present. Patients with chest pain and nutcracker esophagus were more likely to experience pain (9/10) than the control (2/12) by stepwise esophageal balloon distensions.[70] When esophageal balloon distension test was performed after excluding GERD and achalasia from 332 NCCP patients, hypersensitivity was found in 71% (128/181) of the remaining patients.[21] When esophageal motility disorders other than achalasia were also excluded, hypersensitivity was found in 78% (108/139) of the remaining patients. Peripheral and central mechanisms have been proposed to be responsible for visceral hypersensitivity in patients with NCCP.[72,73] Consequently, drugs that can alter esophageal pain perception have become the mainstay of therapy in patients with non-GERD－related NCCP.

In a recent systematic review of published trials regarding effects of antidepressants on non-GERD－related NCCP,[74] 6 RCTs involving 251 patients were evaluated and drugs included were selective serotonin reuptake inhibitors (paroxetine [n=2][75,76] and sertraline [n=1][77]), tricyclic antidepressant (impramine [n=1][78]), serotonin-norepinephrine reuptake inhibitor (venlafaxine [n=1][79]), and a triazolopyridine (trazodone [n=1][80]). They found that the percentage reduction in chest pain, when compared to placebo, was significant with venlafaxine (50% *vs.* 10%, p<0.001), sertraline (63% *vs.* 15%, p=0.02), and imipramine (52% *vs.* 1%, p=0.03). The improvement in chest pain symptoms was independent of improvement in depression scores. Clinical global improvement was also noted in patients on venlafaxine, sertraline, paroxetine, and trazodone. In a recent study,[81] combination of pain coping skill training plus sertraline showed the highest response, compared to either alone or placebo, in patients with NCCP. However, adverse effects were more common in the antidepressants treatment group (33-75%) than in the placebo (12-65%).[75,77-80] Adverse effects were also reason for discontinuation of trials in 53% of the treatment groups compared with 29% of the placebo group.[74] In addition, clinical data regarding the efficacy of antidepressants

for NCCP are limited to a few studies of modest size.

After an open-label pilot trial,[82] an RCT showed that theophylline (200 mg by mouth, twice a day), an adenosine receptor antagonist, for 4 weeks improved pain in patients with chest pain and esophageal hypersensitivity by relaxing the esophageal wall and decreasing hypersensitivity.[83] However, the study was small (n=19) and no further studies supporting the results have been reported.

3) Psychosomatic treatment

Treatment of patients with NCCP refractory to pharmacotherapy is challenging. Psychological comorbidity including panic disorder, anxiety, major depression, and more has been shown to be common in patients with NCCP and affects up to 75%,[1] suggesting that treatment of the underlying psychological factors may result in better patient outcomes.

Because cognitive behavioral therapy (CBT) has been reported to be useful for treatment of panic disorders, it has been proposed that it may be useful in NCCP.[2] The purpose of CBT is to educate patients in order to correct the misattributions regarding chest pain as being harmful. Several studies have demonstrated good efficacy of CBT in patients with chest pain.[2,4,84,85] In an RCT, patients who received CBT for 4-12 weeks had significantly better chest pain control (48%) than those in the control group (12%) at a 12-month follow-up.[86] In another study involving patients with persisting NCCP after negative cardiac evaluation, 12 sessions of CBT significantly decreased the pain severity and the number

of pain-free days as compared to control, at 3 and 6 months.[87] However, in another RCT including patients with NCCP and benign palpitation, chest pain was not improved with three sessions of CBT.[88] Hypnotherapy showed greater improvements in chest pain, pain intensity, and overall well-being, but not in pain frequency reduction in an RCT with 28 NCCP patients.[89]

In conclusion, treatment of patients with NCCP refractory to pharmacologic therapy could be considered for CBT at the experienced center.

CONCLUSION

GERD appears to be the most common cause of NCCP. Therefore GERD should first be considered as the underlying cause of symptoms in patients with NCCP. Empirical PPI treatment with a preferably double dose for more than 2 months could be cost-effective in patients with concomitant typical reflux symptoms. PPI test can be used for diagnosis of GERD-related NCCP but it should be considered for patients with NCCP occurring at least weekly and its duration should be at least 2 weeks. Upper endoscopy and esophageal pH monitoring provide objective evidence of GERD, and thus are necessary when the diagnosis of GERD is uncertain. Esophageal impedance-pH monitoring could further improve the diagnostic yield, particularly in patients with PPI-refractory NCCP.
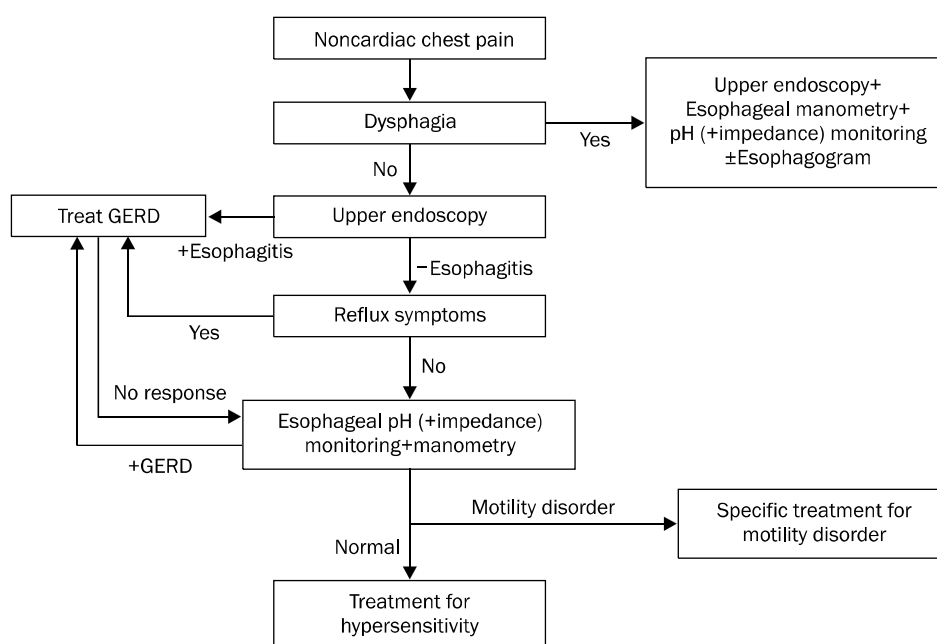
Fig. 1. Proposed approach to patients with noncardiac chest pain in Korea. GERD, gastroesophageal reflux disease.

Treatment of patients with NCCP should target the specific underlying mechanism responsible for patient's symptoms. Patients with GERD-related NCCP should preferably be treated with a double dose PPI until symptoms remit (may require more than 2 months of therapy for optimal symptom control), followed by dose tapering to determine the lowest PPI dose that can control symptoms. In patients with non-GERD—related NCCP, an empirical treatment of antidepressants (preferably venlafaxine, sertraline, and imipramine) should be considered. If specific esophageal motility disorders such as jackhammer esophagus or nutcracker esophagus and distal esophageal spasm are detected, smooth muscle relaxants or endoscopic treatment may be considered in selected cases. If none of these treatments is helpful, a psychology consultation is necessary for psychosomatic treatment such as CBT. Our suggested algorithm for management of patients with NCCP is shown in Fig. 1.

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