

# Is Noncardiac Chest Pain Truly Noncardiac?

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**ABSTRACT:** Many causes of noncardiac chest pain (NCCP) have been studied and gastroesophageal reflux disease is considered to be the major cause. However, studies have reported that treatment with a proton pump inhibitor does not effectively provide relief for NCCP-related symptoms, and these symptoms frequently recur. These findings suggest that patients with cardiac disease may be excluded completely from the NCCP group. Several examinations can be conducted to verify the presence of cardiac disease. Such examinations include the assessment of biochemical markers, rest and exercise electrocardiogram, echocardiography, cardiac computed tomography, stress myocardial perfusion imaging, cardiac magnetic resonance imaging, and coronary angiography (CAG). However, the presence of functional coronary artery diseases (CADs), such as vasospastic angina and/or microvascular angina, cannot be detected using these modalities. These functional CADs can be diagnosed by CAG with spasm-provocation testing and/or physiological coronary measurement. Thus, when a patient who is suspected of having NCCP takes a proton pump inhibitor and does not respond well, further examination—including assessment for possible functional CADs—may be needed.

**KEYWORDS:** Noncardiac chest pain, cardiac chest pain, gastroesophageal reflux disease, vasospastic angina, microvascular angina

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## Introduction

Noncardiac chest pain (NCCP) is defined as chest pain that is similar to that which occurs in angina pectoris, but without obvious cardiac-related causes.<sup>1,2</sup> Of the numerous causes of NCCP, gastroesophageal reflux disease (GERD)-related NCCP is considered the most prevalent.<sup>3–8</sup> Therefore, antireflux drugs—including proton pump inhibitors—have been proven to be effective in the treatment of NCCP.<sup>2,5,9–11</sup> Nonetheless, it has been accepted that NCCP patients have higher rates of recurrence of chest symptoms.<sup>2,12–15</sup>

The first half of this article summarizes the general concepts of NCCP. In the second half, we mention the possibility that functional coronary artery diseases (CADs), such as vasospastic angina (VSA) and/or microvascular angina (MVA), overlap with NCCP and that caution be taken in the presence of functional CAD among NCCP patients.

## Noncardiac Chest Pain

### *Frequency and diagnosis of NCCP*

Patients with NCCP occasionally present in the clinical setting. There are reports that give the worldwide prevalence of NCCP as approximately 14% to 33%.<sup>1,2,16–19</sup> It has also been reported that patients with NCCP who visit the emergency department (ED) account for 2% to 5% of all emergency presentations and comprise more than 50% of all patients with chest pain presenting at the ED.<sup>1,19,20</sup> Such patients undergo several examinations for cardiovascular diseases on visiting the ED or outpatient clinic. These examinations include the assessment of myocardial enzymes, D-dimer, brain natriuretic peptide, electrocardiogram (ECG), echocardiography, cardiac computed tomography (CT), myocardial perfusion imaging, cardiac magnetic resonance imaging, and coronary angiography (CAG). The physician in

charge decides which examinations to conduct, and if the examinations are negative for cardiovascular diseases, a diagnosis of NCCP is made.<sup>5</sup> Noncardiac chest pain has reportedly been observed more frequently in women than in men.<sup>21</sup>

### *Possible causes of NCCP*

Many causes of NCCP have been considered, including esophageal, musculoskeletal, gastrointestinal, respiratory, and psychological causes.<sup>1,2,18,19,22</sup> Gastroesophageal reflux disease (GERD), esophageal motility disorders, and functional dyspepsia—which is not frequent in the clinical setting—are known esophageal causes of NCCP.<sup>1,2,8,20</sup> Gastroesophageal reflux disease (GERD)-related NCCP is the most prevalent of these causes.<sup>3–8</sup> The impedance-pH study by Karlaftis et al<sup>5</sup> showed that 58% of all patients with NCCP presented with GERD-related NCCP. In addition, it also showed that GERD-related NCCP was characterized by the frequent presence of chest symptoms in the postprandial period and by good responses to antireflux drugs.<sup>5</sup> Interestingly, there are reports that some patients with abnormal findings or previous myocardial infarction who were experiencing chest pain were determined to have GERD based on CAG findings.<sup>23,24</sup>

### *Treatment and prognosis of NCCP*

The optimal treatment for NCCP has not been determined because of the multifactorial nature of this disease. However, proton pump inhibitors are worth considering. Indeed, taking antireflux drugs, including a proton pump inhibitor, has been proven to be effective in patients with GERD-related NCCP.<sup>2,5,9–11</sup> However, no effective treatments have been identified for patients with NCCP who do not respond to antireflux



drugs or those with non-GERD-related NCCP. Because of the psychological comorbidities—including anxiety and depression<sup>2,25</sup>—that are considered to be involved in the pathogenesis of NCCP, treatment that includes a combination of antidepressant and antireflux drugs may be effective in these patients.<sup>25</sup>

NCCP has been proven to have a good prognosis;<sup>2,12</sup> however, some studies have shown a relatively high risk of cardiac events in patients with NCCP in comparison with those with CAD.<sup>13,14</sup> Eslick and Talley<sup>14</sup> showed that cardiac mortality during a 4-year follow-up was 5.5% and 11% in patients with NCCP and cardiac chest pain (CCP), respectively. In this study, the subjected patients with NCCP were those who visited the ED<sup>14</sup> who may have contributed to the results. Recently, Mol et al<sup>19</sup> reported that patients with NCCP (5.1%) had fewer major adverse cardiac events (MACEs) at 1-year follow-up than patients with CCP (8.3%). Although the figure is lower, the 5.1% MACE rate in patients with NCCP is noteworthy. Even in this study, all patients who were studied visited the ED. These results suggest that cardiac events in NCCP patients occur at a frequency that cannot be ignored. More importantly, the common finding of all studies was the higher rate of recurrence of chest symptoms.<sup>2,12-15</sup> Potts and Bass<sup>15</sup> showed that 74% of patients with NCCP reported chest symptoms, and of these patients, 34% reported having had chest symptoms weekly for 11 years. Furthermore, Ruigomez et al<sup>26</sup> reported that 49% of patients with NCCP visited the ED again and 42% of these patients underwent repeated cardiac workup during their follow-up. These findings may also suggest that significant attention be paid to the methods used to exclude CCP.

### Modalities for Excluding Heart Diseases

In general, there are many modalities that can be used to exclude the presence of heart diseases. Table 1 shows the modalities, which are biochemical markers (including troponins, brain natriuretic peptide, and D-dimer), rest and exercise ECG, echocardiography, cardiac CT, rest and stress myocardial perfusion imaging, cardiac magnetic resonance imaging, and CAG. Selecting the ideal modalities for patients with chest pain may depend on the judgment of the physician in charge, who should consider time, cost-effectiveness, and patient-dependent factors such as renal function. However, it is difficult to exclude functional CAD, such as VSA or MVA, despite using these modalities.<sup>27,28</sup> To our knowledge, there have been few discussions describing the exclusion of VSA and MVA in most studies that investigate NCCP.

### Possible Functional CAD in NCCP Patients

#### *Vasospastic angina (VSA)*

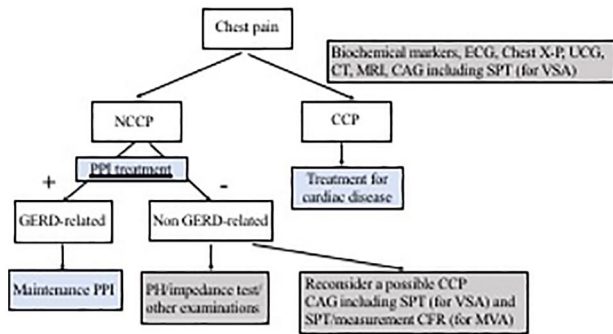
VSA is a type of functional CAD that is characterized by transient vasoconstriction of the epicardial coronary arteries, leading to myocardial ischemia.<sup>29,30</sup> VSA is relatively frequent in female patients.<sup>31,32</sup> Chest symptoms related to VSA can sometimes continue in the long term,<sup>27</sup> but there is not always

**Table 1.** Modalities for differentiating CCP.

MODALITIES	EXCLUSION CARDIOVASCULAR DIAGNOSIS
Biochemical markers	
Troponins	ACS
Brain natriuretic peptide	Heart failure
D-dimer	PTE
Electrocardiogram	
Rest	ACS
Exercise	Obstructive coronary stenosis
Echocardiography	ACS, heart failure, PTE, aortic dissection, cardiomyopathy
Computed tomography	
Contrast enhanced	PTE, aortic dissection
Cardiac	Obstructive coronary stenosis
Myocardial perfusion imaging	
Stress	Obstructive coronary stenosis
Cardiac MRI	ACS, cardiomyopathy
CAG	Obstructive coronary stenosis
Spasm-provocation test	VSA
Physiological measurement	Obstructive coronary stenosis, MVA

Abbreviations: ACS, acute coronary syndrome; CCP, cardiac chest pain; MRI, magnetic resonance imaging; MVA, microvascular angina; PTE, pulmonary thromboembolism; VSA, vasospastic angina.

an accompanying increase in cardiac enzymes in patients who experience chest symptoms for a longer duration. Thus, VSA may be considered in patients with chest pain who present to the ED but do not show significant ST-T changes on ECG or an increase in cardiac enzymes. Although VSA has been the cause of fetal arrhythmia and sudden cardiac death,<sup>33-35</sup> the prognosis of VSA has generally been proven to be relatively good compared with that of obstructive CAD.<sup>36,37</sup> The characteristics of patients with VSA seem to be somewhat similar to those of patients with NCCP, taking the following findings into consideration: relatively high frequencies in women, onset at rest, and a relatively good prognosis. The diagnosis of VSA has generally been made on the basis of typical chest pain that lasts from midnight to early morning and is accompanied by transient ST-T changes on ECG.<sup>27</sup> It is not very difficult to diagnose VSA in patients with typical findings. However, chest symptoms do not always occur at night, but can occur throughout the day. Atypical chest symptoms can sometimes occur in VSA patients.<sup>38</sup> Furthermore, Sato et al<sup>38</sup> have reported that only 23% to 46% of VSA patients documented ST-T changes during spontaneous attacks and that documenting transient ST-T changes during spontaneous attacks in the clinical



**Figure 1.** Management algorithm of patients with CCP or NCCP. CCP indicates cardiac chest pain, CFR: coronary flow reserve, CT: computed tomography, GERD: gastroesophageal reflux disease, MRI: magnetic resonance imaging, MVA: microvascular angina, NCCP: noncardiac chest pain, PPI: proton pump inhibitor, SPT: spasm-provocation test, ECG: echocardiogram, VSA: vasospastic angina.

setting are sometimes difficult. As such, we sometimes do not achieve the diagnosis of VSA in the clinical setting if we only assess chest symptoms and ST-T changes on ECG, as stated in the guideline.<sup>27</sup> It has been recommended to perform a pharmacological spasm-provocation test (SPT) to test for VSA in patients who are not diagnosed with VSA, but who had chest symptoms and no significant ST-T changes on ECG.<sup>27,39</sup> Although there have only been a few studies investigating the effectiveness of cardiac CT for VSA, coronary CT is generally recommended to rule out the presence of obstructive coronary stenosis, as this examination has a reduced ability to detect VSA.<sup>27,40,41</sup>

We have recently shown that GERD was significantly more prevalent in patients with VSA (21%) than in those with obstructive coronary stenosis (3%) or with normal coronary arteries (7%).<sup>42</sup> These findings for VSA were marked in female patients compared to the findings in their male counterparts.<sup>42</sup> These results must be noted with caution, however, as the study had many biases. These biases include that the diagnosis of GERD was made on the basis of the medical history, as well as the fact that all studied patients underwent CAG. Nonetheless, it is possible that—especially in female patients—VSA may have been misdiagnosed as GERD, particularly nonerosive gastroesophageal reflux. As shown earlier, patients with non-GERD-related NCCP had recurrent chest symptoms at their follow-up.<sup>2,12–15</sup> Thus, when physicians first make the diagnosis of NCCP or when clinicians in outpatient clinics meet patients with NCCP who do not respond well to antireflux drugs, they should consider VSA as a possibility and should also consider performing a pharmacological SPT (Figure 1). Sublingual nitroglycerin may be helpful in distinguishing VSA from NCCP as it has been proven to be effective in relieving chest symptoms in VSA.

### Microvascular angina (MVA)

MVA is also one of the functional CADs and is characterized by vasoconstriction of the coronary artery at the microvasculature

level, leading to myocardial ischemia.<sup>43</sup> This disease has more frequently been observed in women and has a good prognosis, although frequent recurrence of chest symptoms may be experienced.<sup>27,43</sup> The diagnosis of this disease can be made on the basis of a negative pharmacological SPT and reduced microvascular function, as well as the presence of usual chest pain and transient ST-T changes on ECG, the absence of epicardial coronary spasm during SPT, and the presence of a reduced coronary flow reserve.<sup>43</sup> In contrast to VSA, therapies for MVA are less effective. However, there are some treatments to reduce chest symptoms in patients with MVA.<sup>44</sup> To date, there are few reports that show a clear relationship between NCCP and MVA; however, the presence of MVA may be a possible cause of NCCP. Thus, when clinicians in outpatient clinics meet patients with NCCP who do not respond well to antireflux drugs, or patients with non-GERD-related NCCP, they should consider MVA as a possible cause, perform a pharmacological SPT, and measure the microvascular function.

### NCCP versus VSA or MVA

There have been several trials involving the use of vasodilators in patients with NCCP.<sup>45–53</sup> Not all trials were effective in preventing chest symptoms in NCCP. Although several factors may contribute to the results (eg, doses per day, duration of vasodilator use, and the presence of adverse effects), NCCP is a multifactorial disease, and a single pharmacological therapy may not always be successful in preventing the associated chest symptoms. Therefore, pharmacological SPT and microvascular function measurement should be used to determine the presence of VSA or MVA in patients with NCCP, and the most appropriate therapy should be provided to the targeted patients.

It is possible for patients to have both functional CAD and GERD. In such cases, physicians should control the content and dose of coronary vasodilators to consider whether patients' chest symptoms are derived mainly from either functional CAD or GERD. It is well known that the use of calcium channel blockers (CCBs) worsens GERD-related symptoms because of the dilation of the smooth muscles of the esophagus.<sup>24,54</sup> Much attention should be paid to the possibility of actualization of GERD-related symptoms secondary to CCB use as a treatment for VSA. With the exception of patients with both functional CADs and GERD, in general, taking a CCB may be used as a rough diagnostic test.<sup>27</sup> If chest symptoms improve after taking a CCB, then the cause of chest symptoms may be cardiac in etiology; however, if chest symptoms worsen after CCB use, then the cause of them may be esophageal.

### Conclusions

NCCP has multifactorial causes and its diagnosis is made on the exclusion of CCP. This diagnosis must be made with caution because functional CADs, such as VSA and/or MVA, may occur along with NCCP. When making a diagnosis of




NCCP or managing patients with NCCP who do not respond to antireflux drugs, or patients with non-GERD-related NCCP, the possibility of functional CAD should be considered.

### Author Contributions

All authors contributed equally to the conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

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