

EDUCATION PRACTICE

Noncardiac Chest Pain

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Clinical Scenario

A 45-year-old man is referred to the outpatient gastrointestinal clinic by his primary care physician for the evaluation of a 4-year history of unexplained, intermittent, substernal chest pain. The patient describes the pain as squeezing, pressure-like, or heaviness, which does not radiate to the back, neck, arms, or jaws. The pain is continuous and unrelated to exertion, emotion, or exposure to cold, and might occur several times a week. Furthermore, the pain might last for hours and is not relieved by rest or nitroglycerin. The patient was admitted twice during the last year to the cardiac care unit but ruled out for myocardial infarction. Before referral to the gastrointestinal clinic, the patient underwent a cardiac workup that included a stress test and a cardiac catheterization; all were within normal limits. The patient's medical history was remarkable only for recently diagnosed hypertension, currently well controlled on an angiotensin-converting enzyme inhibitor. The patient denies dysphagia, odynophagia, anorexia, nausea, vomiting, weight loss, or history of hematemesis or anemia. His primary care physician found no specific cause for his recurrent chest pain and thus initially treated the patient with NSAIDs without symptom relief and subsequently with histamine blockers (ranitidine 300 mg twice a day for 2 months) followed recently by standard dose proton pump inhibitor (PPI, omeprazole 20 mg once a day) for 2 months without symptom relief. An upper endoscopy by another gastroenterologist showed a nondilated, normal-appearing esophagus, as well as normal gastric and duodenal mucosa.

How should the patient be further evaluated, and what therapeutic options are currently available for him?

The Problem

Noncardiac chest pain (NCCP) or unexplained chest pain is defined as recurring angina-like retrosternal chest pain of noncardiac origin. NCCP is very common in the general population, with mean annual prevalence of approximately 23%. NCCP is also the most common

atypical manifestation of gastroesophageal reflux disease (GERD). Clinical history does not reliably distinguish between cardiac and esophageal cause of chest pain. This is compounded by the fact that patients with history of coronary artery disease might also experience chest pain of noncardiac origin. Consequently, patients with chest pain should initially be evaluated by a cardiologist because the morbidity and mortality of coronary artery disease far exceed those of esophageal disorders.

Chest pain is one of the most common reasons for patient visits to the emergency department and for admissions to the coronary care unit. However, only 15%–34% of patients presenting with chest pain to ambulatory clinics are ultimately diagnosed with coronary artery disease. It should be noted that 30% of the patients thought to have chest pain caused by coronary artery disease have normal coronary angiogram. In addition, coronary artery disease was found in up to 25% of the patients defined as having an atypical chest pain. Therefore, all patients who present with chest pain, regardless of its character, should initially undergo a proper cardiac evaluation before being referred to a gastroenterologist. Once cardiac cause has been excluded, other noncardiac causes should be considered. Recently, several studies have shown that 50% of the cardiologists and 70% of the primary care physicians manage NCCP patients by themselves, suggesting that the majority of these patients are never referred to a gastroenterologist for further evaluation.

The pathophysiology of NCCP remains to be fully elucidated. Identified underlying mechanisms are diverse and not uncommonly overlap. Of the gastrointestinal causes, GERD is by far the most common cause of NCCP. Other gastrointestinal-related etiologic factors

Abbreviations used in this paper: GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter; NCCP, noncardiac chest pain; PPI, proton pump inhibitor.

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Table 1. Proposed Underlying Mechanisms for Noncardiac Chest Pain

Main mechanisms
Gastroesophageal reflux
Visceral hypersensitivity
Psychological comorbidity
Panic attack
Anxiety
Depression
Other mechanisms (unclear clinical significance)
Esophageal dysmotility
Abnormal mechanophysical properties
Hyperactive
↓ compliance
Sustained longitudinal muscle contractions
Altered central processing of visceral stimuli
Altered autonomic activity

that have been proposed include esophageal motility disorders, abnormal mechanophysical properties of the esophagus, sustained esophageal longitudinal muscle contractions, visceral hypersensitivity, altered central processing of intraesophageal stimuli, autonomic dysregulation, and psychological comorbidity (Table 1).

In our patient despite lack of improvement of chest pain on PPI once a day, GERD remains a possible underlying mechanism.

Gastroesophageal Reflux Disease

GERD has been reported to be the most common esophageal cause for NCCP. Between 25%–60% of the patients with NCCP have abnormal 24-hour esophageal pH monitoring and/or abnormal upper endoscopy. Reports of typical GERD symptoms (heartburn and acid regurgitation) might be present in up to 70% of the patients and are highly predictive of GERD-related NCCP. Erosive esophagitis has been documented in 10%–70% and abnormal esophageal acid exposure in 40%–60% of the GERD-related NCCP patients. Several studies have found that patients with GERD-related NCCP often report chest pain that is provoked by meals or recumbency and might be relieved by antacids. The presence of abnormal esophageal acid exposure or erosive esophagitis in patients with NCCP might suggest association only. However, review of therapeutic studies in NCCP revealed that up to 80% of the patients with either erosive esophagitis or abnormal pH testing responded to potent antireflux treatment. Consequently, the presence of esophageal mucosal injury and/or abnormal esophageal acid exposure is highly predictive that GERD is the likely underlying cause of patients' symptoms.

In a subgroup of patients with syndrome X, a reduction in coronary artery blood flow in response to acid

perfusion into the distal esophagus has been observed. Syndrome X is defined as typical chest pain and electrocardiographic changes suggestive of myocardial ischemia on stress test but patent coronary arteries on angiogram. The reduction in coronary blood flow was associated with typical anginal pain, suggesting the presence of esophagocardiac inhibitory reflex.

Esophageal Dysmotility

In NCCP patients who lack any evidence of GERD, esophageal dysmotility is commonly entertained as the underlying cause. However, the role of esophageal dysmotility in symptom generation of NCCP patients is highly controversial. Although often entertained as an etiologic factor of NCCP in the absence of GERD, the role of esophageal dysmotility in NCCP is likely very limited. More than 70% of the patients with non-GERD-related NCCP have normal esophageal motility. When esophageal dysmotility is documented by esophageal manometry, it is rarely associated with reports of chest pain. Studies have repeatedly shown that chest pain will often improve without any normalization of the esophageal motor disorder. Unlike GERD, for which PPIs are highly effective in alleviating symptoms, we are still devoid of pharmacologic agents that can effectively treat esophageal dysmotility. This compromises our ability to determine the relationship between chest pain and manometric findings.

The most commonly encountered esophageal dysmotility in patients with NCCP is hypotensive lower esophageal sphincter (LES), commonly associated with GERD. In patients with non-GERD-related NCCP, nutcracker esophagus is the most common esophageal motility disorder documented, followed by nonspecific esophageal motility disorder, diffuse esophageal spasm, hypertensive LES, and achalasia. Interestingly, in one study, it was found that most patients with chest pain associated with nutcracker esophagus responded symptomatically to antireflux treatment. In addition, normalization of the nutcracker motility phenomenon was documented only in the minority of the patients, suggesting that GERD was the likely cause of their symptoms rather than the high amplitude contractions in the distal esophagus.

As a result of the weak correlation between documented esophageal dysmotility during manometry and chest pain, some have postulated that motility disorders serve more as a marker for a presently poorly understood esophageal abnormality that contributes to the underlying etiology of NCCP. Consequently, one might argue that esophageal motor disorders, with the exception of achalasia, have no direct etiologic role in symptom gen-

eration of patients with NCCP and thus should not be pursued diagnostically or therapeutically.

Visceral Hypersensitivity

It has been hypothesized that peripheral sensitization of esophageal sensory afferents leads to subsequently heightened responses to physiologic or pathologic stimuli of the esophageal mucosa. In addition, central sensitization at the brain level or the dorsal horn of the spinal cord might modulate afferent neural function and thus enhance perception of intraluminal stimuli. What causes peripheral or central sensitization remains to be determined. Esophageal tissue injury, inflammation, spasm, or repetitive mechanical stimuli can all sensitize peripheral afferent nerves. Esophageal hypersensitivity can persist long after the original stimulus is no longer present and the esophageal mucosa has healed. However, it is unclear what factors determine the persistence of such esophageal hypersensitivity.

Patients with non-GERD-related NCCP have lower perception thresholds for pain at baseline or after esophageal stimulation with acid. Other studies demonstrated short-term sensitization of mechanosensitive afferent pathways by transient exposure to acid. Thus, in patients with NCCP, acid reflux might induce sensitization of the esophagus, and this might alter the way in which normal esophageal distentions are perceived. Furthermore, patients with NCCP exhibited concurrent visceral and somatic pain hypersensitivity, suggesting central sensitization as an important underlying cause.

Other Mechanisms

Studies have also demonstrated other sensorimotor, autonomic, or psychological abnormalities in patients with NCCP, including long duration of longitudinal muscle contractions and altered central processing of intraesophageal stimulation. A subset of patients with NCCP exhibits autonomic dysregulation (increased vagal cardiac outflow). In addition, between 17%–43% of the patients with NCCP have some type of psychological abnormality such as panic disorder, anxiety, or major depression.

The prognosis of patients with NCCP is favorable. In long-term follow-up studies, very few subjects developed cardiovascular-related disorders. Nevertheless, the natural history of NCCP in most patients is characterized by the persistence of symptoms, repeated clinic visits or hospital admissions, chronic use of cardiac medications despite lack of evidence for cardiac cause, repeated cardiac catheterizations, interruptions to daily activities, and impaired quality of life. Studies demonstrated that only a small fraction of patients with NCCP feel reas-

sured. Consequently, NCCP is a costly disorder, resulting in a significant economic burden on the health care system.

Management Strategies and Supporting Evidence

Once cardiac cause has been properly excluded, usually by a cardiologist, other non-esophageal-related abnormalities that include musculoskeletal disorders of the chest, pulmonary/pleuritic abnormalities, gastric or biliary diseases, as well as panic disorder should also be ruled out.

The currently available diagnostic tests in NCCP are primarily designed to evaluate patients for GERD, esophageal dysmotility, and visceral hypersensitivity as the potential underlying mechanism for symptoms. The role of the different diagnostic tests in NCCP has evolved over the years, primarily as a result of the introduction of the PPI therapeutic trial and the recognition of the limited sensitivity of the diagnostic tests.

Upper Endoscopy

Upper endoscopy is the gold standard for diagnosing erosive esophagitis, GERD complications like stricture and ulceration, and Barrett's esophagus. In the presence of alarm symptoms (weight loss, dysphagia, anorexia, upper gastrointestinal bleeding, anemia), upper endoscopy should be considered as the initial evaluative tool in patients with NCCP. It has been suggested that in patients who lack alarm symptoms, the test has a very low diagnostic yield. However, it appears that a subset of the GERD-related NCCP patients might harbor Barrett's esophagus, and thus the GERD screening guidelines should apply to these patients as well.

pH Testing

Because of the introduction of the PPI test or the PPI empirical therapy, the role of 24-hour esophageal pH testing in NCCP has evolved during the last decade. At present, the test is used primarily to assess NCCP patients who failed PPI therapy. The addition of symptom index does not increase the sensitivity of the test, because reports of chest pain symptoms are relatively uncommon during the pH test. The wireless pH system allows 48–72 hours of recording time, which improves, specifically in NCCP, the number of subjects recording symptoms during the pH test and increases the number of symptoms available for association with acid reflux events.

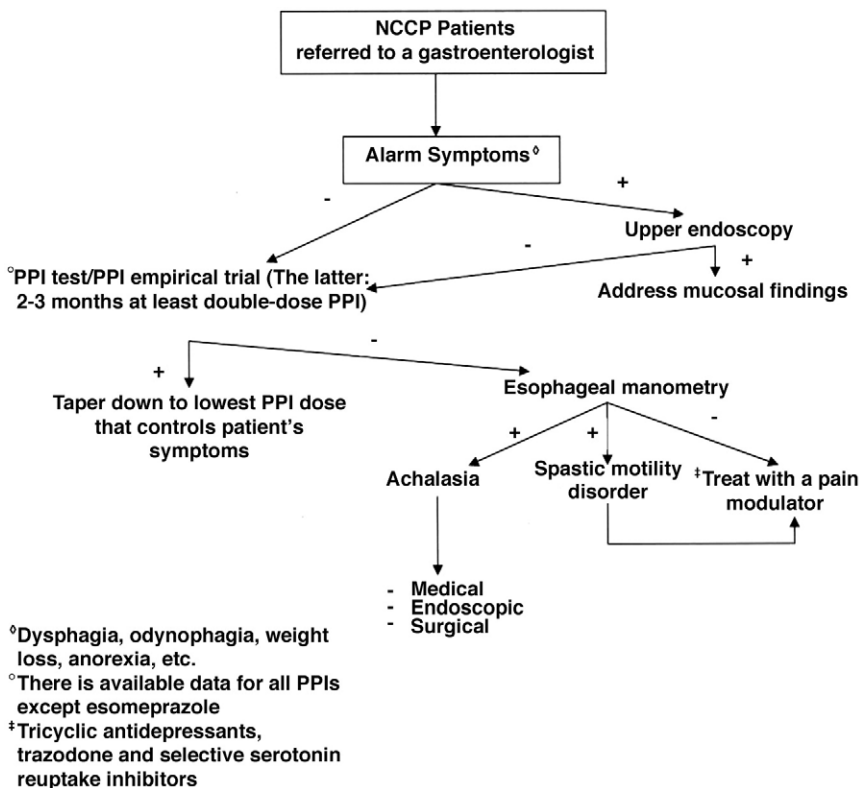


Figure 1. Diagnosis and treatment flow chart for noncardiac chest pain.

Proton Pump Inhibitor Test

The use of a short course of high-dose PPI to diagnose GERD-related NCCP has gained popularity because of its simplicity, availability, and cost-effectiveness. The sensitivity of the PPI test for GERD-related NCCP has ranged from 69%–95% and the specificity from 67%–86% in different studies. The dosages of PPIs used ranged from 60–80 mg daily for omeprazole, 30–90 mg daily for lansoprazole, and 40 mg daily for rabeprazole. The trial duration ranged from 1–28 days.

Esophageal Manometry

Presently, patients who did not respond to anti-reflux treatment (non-GERD-related NCCP) are likely to undergo esophageal manometry. NCCP patients with esophageal motility abnormalities (primarily spastic motor disorders), other than achalasia, respond better to pain modulators than to any of the smooth muscle relaxants. As a result, the usefulness of esophageal manometry in NCCP is likely limited to excluding achalasia as the underlying cause of patients' chest pain.

Other Tests

Provocative testing, like the edrophonium test (Tensilon test; Baxter Healthcare Corporation, Deerfield, IL), acid perfusion test, balloon distention test, ergonovine test, and bethanechol test have all fallen out of favor,

primarily because of their low sensitivity and some because of potential side effects.

Some of the patients with NCCP require evaluation by an expert psychologist or psychiatrist because of the high prevalence rate of psychological abnormalities. Deciding who should be referred is determined individually, but the likely candidates are those who appear to be refractory to therapeutic interventions or those who display clear features of a psychological disorder.

Treatment

Treatment in NCCP should be directed to the likely underlying mechanism of chest pain, hence, anti-reflux medications for gastroesophageal reflux and pain modulators for patients with non-GERD-related NCCP. Muscle relaxants have shown only a limited efficacy in patients with esophageal dysmotility. **Figure 1** provides a suggested treatment algorithm.

Patients with GERD-related NCCP should be treated with at least double-dose PPI until symptoms remit, followed by dose tapering to determine the lowest dose that can control the patient's symptoms. As with other extraesophageal manifestations of GERD, NCCP patients might require more than 2 months of therapy for optimal symptom control. Other antisecretory modalities, such as histamine 2 receptor antagonists or PPI once

daily, have no role in the acute and likely chronic treatment of NCCP patients.

Most patients with GERD-related NCCP will require long-term treatment with a PPI to maintain symptom control. In patients who failed empirical therapy (2–3 months) with double-dose PPI, pH testing on therapy is likely to be normal.

Very few studies have examined the value of laparoscopic Nissen fundoplication in patients with GERD-related NCCP. Although these surgical studies demonstrated a high success rate of antireflux surgery in GERD-related NCCP patients, it should be emphasized that the patients included were very carefully selected, and it is not clear whether the data are generalizable.

The treatment of esophageal dysmotility in patients with NCCP remains an area of intense controversy. Data supporting the use of nitrates are scarce and not uncommonly based on anecdotal experience. Sublingual nitroglycerin and long-acting nitrate preparations appear to have no effect on esophageal amplitude contractions of healthy subjects. Reports about the value of long-acting nitrates in patients with NCCP and esophageal dysmotility are conflicting.

Calcium channel blockers (diltiazem, nifedipine, verapamil) are the most studied smooth muscle relaxants in patients with NCCP and esophageal dysmotility. These drugs appear to be of limited value and might be complicated by side effects, such as hypotension, constipation, and pedal edema. In small clinical trials, diltiazem (60–90 mg 4 times daily) and nifedipine (10–30 mg three times daily) demonstrated a limited duration symptomatic response only after a significant lag between onset of therapy and symptom relief in patients with NCCP and nutcracker esophagus.

Data about the use of other therapeutic modalities in NCCP patients with esophageal dysmotility are even scarcer. The antispasmodic cimetropium bromide reduced amplitude of esophageal contractions in NCCP patients; hydalazine improved chest pain and dysphagia and decreased the amplitude and duration of esophageal contractions in patients with NCCP.

Botulinum toxin injection into the LES was used in a few uncontrolled trials that included patients with NCCP and documented esophageal spastic motility disorder. Injection of botulinum toxin into the LES in one study resulted in 50% reduction of chest pain in 72% of the subjects. A total of 100 units of botulinum toxin was injected circumferentially, with 5 injections of 20 units each at the gastroesophageal junction. Unfortunately, the mean chest pain-free duration was only 7 months, and

50% of the patients required a second injection to maintain remission.

Similarly, the role of pneumatic dilation or long esophageal myotomy (Heller's myotomy) with or without antireflux surgery in patients with NCCP and non-achalasic dysmotility remains controversial and is best avoided.

Pain modulators or visceral analgesics have been shown to significantly improve symptoms in NCCP patients as compared to placebo. Several classes of drugs have been evaluated, and they include the tricyclic antidepressants, trazodone, selective serotonin reuptake inhibitors, and theophylline. Antidepressants have been used as pain modulators for almost 2 decades to treat patients with chest pain of presumed esophageal origin.

The mechanism by which tricyclic antidepressants reduce visceral pain remains poorly understood. Some authors suggested a central effect, whereas others suggested a peripheral effect. Imipramine has been shown to increase esophageal perception thresholds for pain in normal subjects without affecting esophageal tone, suggesting a visceral analgesic effect. A similar effect that was independent of cardiac, esophageal, or psychiatric testing results at baseline was noted in NCCP patients. In addition, tricyclic antidepressants provide a long-term effect in NCCP patients, although dropout rate as a result of side effects might reach 30%. Treatment with tricyclic antidepressants should start at a low dose (10–25 mg) that is administered at bedtime and then increased by 10-mg to 25-mg increments per week to a non-mood-altering goal of 50–75 mg per day. Because of the varied effects of tricyclic antidepressants on their respective receptors (acetylcholine, histamine 1, and α -adrenergic), failure of one tricyclic to improve symptoms is not indicative of future failure of other tricyclic antidepressants.

The use of selective serotonin reuptake inhibitors in NCCP has scarcely been studied. As with tricyclic antidepressants, a neuromodulatory effect has been proposed to mediate their effect on visceral pain. In a randomized, double-blind, placebo-controlled trial, patients receiving sertraline (50–200 mg) reported reduction in chest pain score, regardless of whether improvement of the psychological score was documented. The study confirms the potential role of selective serotonin reuptake inhibitors in the treatment of patients with non-GERD-related NCCP.

Low-dose trazodone (100–150 mg/day), an antidepressant and anxiolytic, has been shown to improve symptoms of non-GERD-related NCCP patients with esophageal dysmotility, without affecting amplitude of esophageal contractions. Information about other compounds with visceral analgesic effect has been limited to isolated reports in the

literature. In an open-labeled trial, infusion of theophylline alleviated chest pain in patients with functional chest pain of presumed esophageal origin, possibly by blocking adenosine receptors. Octreotide given subcutaneously (100 μ g) increased esophageal perception thresholds for pain in normal subjects.

Reassurance about the benign nature of the disorder has been emphasized as an important early therapeutic intervention in patients with NCCP. However, patients' symptoms are seldom relieved by reassurance only, resulting in the need for additional treatment. In patients who have panic disorder, treatment with alprazolam and clonazepam has been demonstrated to reduce panic attack frequency, chest pain episodes, and anxiety scores. However, benzodiazepines should be used cautiously in NCCP patients, primarily because of their addictive effect. Behavioral therapy can be effective in patients with NCCP.

Areas of Uncertainty

The roles of nonacidic or weakly acidic reflux as well as bile reflux in patients with NCCP remain to be elucidated. The clinical value of brain imaging studies like positron emission tomography and functional magnetic resonance imaging in NCCP remains unknown.

Lifestyle modifications have been suggested to accompany any therapeutic intervention for GERD. Studies to support the popular implementation of lifestyle modifications such as elevating the head of the bed at night, reducing fat intake, smoking cessation, and avoiding foods that exacerbate gastroesophageal reflux remain scarce. It is also unclear whether lifestyle modifications help in patients with GERD-related NCCP.

The value of endoscopic techniques to treat gastroesophageal reflux in patients with GERD-related NCCP remains unclear. Except for a few preliminary studies in highly selected patients, there is very little support for any of the currently available endoscopic treatments in NCCP. The exact role of these techniques in clinical practice is being questioned, and the injection technique (Enteryx) was withdrawn from the market because of unacceptable side effects.

The clinical value of pro-motility drugs or serotonin-related compounds (such as tegaserod and alosetron) in NCCP is yet to be demonstrated.

Published Guidelines

Currently, there are no published guidelines that specifically address the management of NCCP. In the recent American Gastroenterological Association technical review on the clinical use of esophageal manometry, the authors recommended that manometry should not be routinely used

as the initial test for chest pain because of the low specificity of the findings and the low likelihood of detecting a clinically significant disorder.

Recommendations

The patient presented should be treated with a double-dose PPI (eg, omeprazole 20 mg twice a day) until symptoms remit, followed by dose tapering to determine the lowest dose that can control the patient's symptoms. Duration of treatment should be at least 2 months, although longer duration of treatment (3–6 months) might be required in a subset of patients.

If the patient does not respond to double-dose PPI during a longer duration, performing pH testing on therapy would be a low-yield procedure. Esophageal manometry should be considered only if achalasia is suspected. Otherwise, a trial of pain modulators is recommended. We prefer to start with low-dose tricyclic antidepressants (10–25 mg) administered at bedtime and increased by 10-mg to 25-mg increments per week to a maximal, non-mood-altering dose of 50–75 mg per day.

Finally, evaluating psychological comorbidity is important, especially in patients who appear to be refractory to current therapeutic management. Referral to a psychologist or psychiatrist who is an expert in the field of functional bowel disorders would be of benefit.

Suggested Reading

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