

Evaluation of Noncardiac Chest Pain: Toward a Positive Diagnosis

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Introduction

Chest pain is a worrisome symptom for both patients and physicians. The prevalence of chest pain is quite common for patients in primary care practices, with studies reporting a prevalence of this symptom in 7% to 11% of patients.^{1,2,3} Up to 25% of the general population experiences some form of chest pain in their lifetime.⁴

However, not all chest pain is cardiac chest pain. An estimated 400,000 patients annually experience noncardiac chest pain for the first time,⁵ and a cardiac etiology is present in only 11% to 34% of the ambulatory population.⁶ Although adults are often the focus of chest pain analysis, adolescent patients also experience chest pain, with an estimated 650,000 physician visits annually by adolescent patients with the complaint of chest pain.⁷ Attention to patients with noncardiac chest pain is important because these patients are highly debilitated; even with negative angiograms, approximately 50% of these patients cannot exert themselves and are disabled by their pain.⁸

Noncardiac chest pain may present with various symptoms. For example, pain may be localized in or directly around the anterior chest wall, or the patient may feel that the pain emanates from deeper within the chest cavity; pain may radiate in patterns similar to cardiac chest pain; and pain may last only minutes or may extend to hours.⁹ As indicated in this case study, a vast array of etiologies may be responsible for noncardiac chest pain. However, psychogenic causes and gastrointestinal disorders are the focus of the primary care provider after coronary artery disease (CAD) is excluded.

Gastrointestinal etiologies. Gastrointestinal etiologies are important to consider, as demonstrated in this case study. One report estimates that at least 100,000 patients in the United States experience some form of chest pain from esophageal causes alone.¹⁰ However, assessment of patients with suspected noncardiac chest pain using esophageal studies alone is controversial because chest

pain and abnormal esophageal function may not be related. This lack of a relationship may potentially explain the limited effects of medical therapy directed against chest pain with a suspected esophageal etiology; thus, routine tests may not be cost effective.¹¹ In cases of suspected esophageal etiology, it has been postulated that the chest pain may instead be related to esophageal dysfunction that arises via food impaction, diffuse esophageal spasm, and achalasia.¹² However, these latter etiologies are diagnosed through the associated symptoms of dysphagia and regurgitation rather than esophageal studies.

Empiric treatment using omeprazole may be more effective than esophageal studies in diagnosing and treating gastrointestinal-related noncardiac chest pain. In a trial that compared administration of omeprazole before invasive testing with strategies that utilized invasive testing at the outset, the omeprazole strategy resulted in better outcomes. Eighty-four percent of patients in the omeprazole arm were symptom free after 1 year compared with 73% to 74% of patients who underwent invasive strategies. Further, the omeprazole strategy resulted in an 11% improvement in diagnostic accuracy and a 43% reduction in invasive testing, yielding an average cost savings of \$454 per patient compared with invasive strategies alone.¹³ Further study in this area is important because of the relative frequency of the symptoms and the significant cost savings that may be associated with empiric treatment.

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Psychogenic etiologies. Psychogenic etiologies are also an important causative concern of noncardiac chest pain. Noncardiac chest pain has a significant psychosocial component; 6% to 8% of patients are recognized by primary care providers as having a psychosocial component,^{14,15} which may be undiagnosed in up to 83% of patients.² Further, chest pain with associated panic disorder or infrequent panic is correlated with presentation to emergency departments (EDs),¹⁶ primary care physicians,¹⁷ and psychiatrists.¹⁸ However, the number of patients with noncardiac chest pain and psychogenic etiologies is currently unknown; small studies have reported that 22% to 62% of patients with psychogenic etiologies have some initial presentation of chest pain.^{19,20} This dearth of research is exacerbated by reports that, although panic states are common, panic states are rarely recognized in patients with chest pain in primary care practices, which leads to increased testing, increased use of medications, and increased risk of iatrogenic harm to these patients.⁶ These results reflect the difficulties in primary care provider recognition of psychiatric disorders.^{21,22} Clearly, this is an area that requires focus as primary care providers are given additional responsibilities for care and as costs continue to be the focus in the health care system. However, more importantly, cognitive therapy for patients with noncardiac pain appears to result in significantly better results, with both frequency and intensity of pain significantly reduced.²³

Summary. Overall, physicians must rule out cardiac disease in patients who present with chest pain. If the chest pain is deemed noncardiac in origin, empiric treatment for gastrointestinal causes and appropriate assessment for psychogenic etiologies are essential to address the patient's symptomatology. In particular, primary care physicians should consider panic disorders and states and should institute appropriate cognitive therapy to most effectively alleviate the patient's symptoms and conserve the ever-shrinking health care dollar.

CASE PRESENTATION

Initial Presentation

A 52-year-old man presents to the ED with squeezing substernal chest pain that woke him from sleep 2 hours earlier. The pain is steady, does not radiate to the neck or arms, and is not associated with light-headedness, palpitations, nausea, or vomiting.

History

The patient's father died of a heart attack at age 62 years. The patient reports that within the past year he was diagnosed with mild hypertension and hyper-

lipidemia. He is currently being treated with medications for both conditions. He has a 30 pack-year history of smoking. The patient is married, has three children, and works approximately 55 hours per week; he is also renovating a second home himself. He reports that he recently experienced several episodes of pain that were qualitatively similar to this presenting episode but not as severe. He does not associate the pain with activity, meals, or recumbency.

Physical Examination

Physical examination reveals a mildly obese man who appears anxious and is mildly diaphoretic. His blood pressure is 150/98 mm Hg, and his pulse is 104 bpm. The remainder of his physical examination is unremarkable. An electrocardiogram reveals sinus tachycardia and nonspecific ST-T wave changes. A chest radiograph is normal.

QUESTION

- **What are initial steps in the evaluation of patients with chest pain?**

DISCUSSION

Initial Evaluation of Recurrent Chest Pain

CAD is the leading cause of death in the United States, and approximately 25% of all deaths in the United States are caused by symptomatic CAD. The evaluation of patients with recurring chest pain always begins with the exclusion of significant cardiac disease. However, differentiating cardiac and noncardiac etiologies of chest pain is not always possible on clinical grounds alone. Additionally, CAD and many of the etiologies of noncardiac chest pain commonly coexist. For example, Davies et al²⁴ reported that certain clinical features were helpful in distinguishing esophageal etiologies of angina-like chest pain, but they also noted that as many as 50% of patients with anginal pain were found to have one or more symptoms of esophageal pain.²⁴ Thus, suspicion for symptomatic CAD must always be high, and its presence must be firmly established or excluded.

The extent of the cardiac evaluation is chiefly determined by the patient's age, family history, and other risk factors for cardiac disease (eg, hypertension, hyperlipidemia, diabetes mellitus, smoking). Various modalities are used to evaluate for myocardial ischemia, including resting electrocardiograms, exercise electrocardiography and echocardiography, various forms of stress scintigraphy, and coronary angiograms. Selection of appropriate diagnostic modalities largely depends on pretest suspicion for symptomatic CAD, the

patient's ability to participate in the studies, availability of diagnostic tests, and the physician's experience and preference.

Because of interest in providing more accurate diagnoses and more cost-efficient allocation of diagnostic resources, attention is focused on increasing the accuracy of risk stratification for patients presenting to acute care services.²⁵ These strategies frequently include 6- or 8-hour observation periods during which cardiac enzymes and resting electrocardiograms are monitored, as well as noninvasive testing for myocardial ischemia in patients at low risk for CAD. Although outcomes studies evaluating these methods are not yet available, their use in clinical settings is increasingly common.

RESULTS OF CARDIAC EVALUATION

In the ED, the patient undergoes a 6-hour rule-out protocol for myocardial infarction and demonstrates symptom resolution, normal cardiac enzymes, and a stable electrocardiographic pattern. Following this protocol, he undergoes a graded exercise tolerance test that discloses no abnormalities suggestive of myocardial ischemia. The patient is told that his chest pain is unrelated to CAD and is discharged.

Throughout the next 2 months, he continues to have episodes of chest pain, both with exertion and while at rest, resulting in two additional visits to the ED. During the second visit, the patient is admitted and undergoes cardiac catheterization. The procedure discloses normal coronary arteries, and the patient is again reassured that his chest pain is noncardiac and is discharged. One week later, he presents to his primary care physician complaining of persistent chest discomfort, asking again for an explanation of his symptoms as well as relief from the episodic pain.

QUESTION

- **What is the natural history of noncardiac chest pain?**

DISCUSSION

Follow-up of Noncardiac Chest Pain

Several studies show that patients with noncardiac chest pain have an excellent prognosis with respect to mortality but continue to experience considerable morbidity.²⁶⁻²⁸ In an important study by Ockene et al,²⁹ 57 patients with chest pain and normal coronary angiograms were informed that their pain was noncardiac in nature and that their activity need not be limited because of the pain. Although there was no mortality after an average follow-up of 16 ± 7.7 months, 47% of study subjects still described their activity as limited by the pain (compared with 74% prior to catheteriza-

tion). Additionally, 51% of subjects were still unable to work because of the pain (compared with 63% prior to catheterization), and 44% of subjects still believed that they had heart disease (compared with 79% prior to catheterization). Use of medical facilities was significantly reduced after catheterization. During follow-up, physicians were more likely than patients to believe that the symptoms had improved.

Although a normal coronary angiogram is reassuring to physicians, this result clearly leaves something to be desired from the patient's point of view. Establishing a positive diagnosis is critical for improving the quality of life and reducing the consumption of health care resources by patients with noncardiac chest pain. Ward et al²⁶ have shown that patients whose noncardiac chest pain was found to have an esophageal etiology were less likely to feel disabled by their pain and less likely to require continued physician evaluation than patients whose chest pain was not specifically diagnosed. Interestingly, although establishing an esophageal etiology for these subjects' chest pain did not result in a significant decrease in symptoms, it did significantly reduce the number of subjects who felt that their pain was cardiac in nature, felt disabled by their symptoms, and sought continued evaluation for the ongoing chest pain.

QUESTION

- **What are common causes of noncardiac chest pain?**

DISCUSSION

Noncardiac Causes of Chest Pain

After exclusion of epicardial CAD and other more obvious noncardiac etiologies, the differential diagnosis of chronic, unexplained noncardiac chest pain includes microvascular angina, esophageal disorders, psychiatric disorders, and musculoskeletal causes (Table 1). Importantly, these conditions frequently overlap and may be fundamentally linked. For example, approximately 33% of patients with documented microvascular angina have esophageal motility disorders, and 25% to 33% fulfill diagnostic criteria for panic attacks.^{30,31} At least 50% of noncardiac chest pain syndromes are attributable to gastroesophageal reflux disease (GERD) or panic or depressive disorders.

Microvascular angina. Although the existence of microvascular angina as a specific syndrome remains controversial and its pathophysiology remains elusive, microvascular angina may be a cause of myocardial ischemia in patients with normal epicardial coronary arteries. Cannon et al³² demonstrated that a subset of patients with exertional chest pain and normal coronary

arteries appeared to have abnormalities of coronary vasodilator reserve. These patients developed pain as a result of exercise, and many patients had evidence of cardiac wall motion abnormalities and reduced left ventricular ejection fraction. Despite the ominous findings, these patients usually enjoy a benign course, with no significant increase in cardiovascular mortality.^{33,34}

Esophageal disorders. Noncardiac causes of chest pain that are esophageal disorders include esophageal motility disorders, GERD, and abnormal visceral nociception.

Esophageal motility disorders. Although esophageal dysmotility is historically an important touchstone for diagnosing noncardiac chest pain,^{35,36} more recent evidence suggests that it is a much less common etiology of chest pain.³⁷ Initial observations suggested that esophageal dysmotility and spasm caused pain as a result of high amplitude contractions and possible concomitant esophageal ischemia.³⁵ As shown in **Table 2**, nonspecific esophageal motility disorders, such as the nutcracker esophagus and hypertensive lower esophageal sphincter, occur with similar frequencies across a variety of patient subsets. Achalasia, arguably the one motility disorder with a definable pathophysiology, is found with increased frequency only in patients with dysphagia. These observations suggest that, in the absence of other esophageal symptoms, particularly dysphagia, esophageal motility disorders are uncommon etiologies for noncardiac chest pain.^{38,39}

Gastroesophageal reflux disease. A large body of evidence supports the role of GERD in noncardiac chest pain. Pooled analysis of studies using simultaneous ambulatory monitoring of both esophageal pH and motor function have identified dysmotility in only 12% of patients studied, whereas abnormal esophageal acid exposure was documented in 29% of patients (**Table 3**).³⁹ These data are consistent with additional reports that have documented abnormal degrees of esophageal acid exposure in patients with noncardiac chest pain, with a prevalence of 25% to 60%.^{40–44}

Abnormal visceral nociception. Patients with chest pain of undetermined origin may have a lowered threshold to visceral sensation, or abnormal visceral nociception. In this condition, pain may not arise in a particular end organ, but rather in the nociceptive afferent nerves and the modulatory, perceptual, and localizing pain pathways of the central nervous system.^{45,46} In this condition, chest pain could be caused by a noxious stimulus involving the thoracic viscera, decreased threshold of visceral nociceptors, or an intrinsic disorder of nociceptive pathways.

Psychiatric disorders. Psychiatric disorders are also quite common in patients with noncardiac chest pain. In evaluating 229 patients presenting to the ED of a

Table 1. Common Etiologies of Chest Pain

Cardiovascular
Aortic aneurysm
Coronary artery disease
Microvascular angina
Mitral valve prolapse
Digestive
Abnormal visceral nociception
Cholelithiasis
Esophageal dysmotility (achalasia, diffuse esophageal spasm)
Gastroesophageal reflux disease
Nonpeptic esophagitis (pill or infectious)
Peptic ulcer disease
Psychiatric
Depression
Panic and anxiety disorders
Somatization
Pulmonary
Asthma
Pleural effusion
Pneumothorax
Pulmonary embolism or infarction
Pulmonary hypertension
Rheumatologic/musculoskeletal
Cervical and thoracic radiculopathy
Chest wall trauma
Costochondritis
Fibromyalgia
Varicella-zoster virus reactivation

large urban hospital, Yingling et al⁴⁷ identified panic disorder in 17.5% of patients and depression in 23.1% of patients. Similar prevalence rates for these disorders have also been reported by other researchers.^{48,49} Importantly, patients found to have panic or depressive disorders are much more likely to make multiple visits to acute care facilities, and their use of these costly resources exceeds that of patients with symptomatic CAD.⁴⁷ Identifying psychiatric disorders associated with noncardiac chest pain is clearly important both for resolving patient symptoms and for ensuring that resources are used efficiently.

Rheumatologic disorders. Rheumatologic disorders may also present as noncardiac chest pain. Chest wall syndromes, including costochondritis, are reported in

Table 2. Manometric Abnormalities in Patients with Chest Pain or Dysphagia

Study Population	Patients, n	Achalasia, %	DES, %	Nutcracker Esophagus, %	Total Nonspecific Disorders, %
CAD and suspected esophageal disease	251	0.0	4.3	13.5	26.6
Dysphagia	251	19.0	7.0	5.0	27.0
Noncardiac chest pain	1372	4.3	2.4	12.6	24.0
Unselected manometry	2811	5.8	3.6	16.4	32.4

CAD = coronary artery disease; DES = diffuse esophageal spasm.

Adapted with permission from Kahrilas PJ, Clouse RE, Hogan WJ: American Gastroenterological Association technical review on the clinical use of esophageal manometry. *Gastroenterology* 1994;107:1865–1884.

Table 3. Results of Six Studies of Ambulatory pH and Pressure Monitoring in Patients with Presumed Esophageal Chest Pain

Study	Total Patients, n	Number of Patients with Chest Pain Related to:		
		Motility	Reflux	Neither
1	22	3	5	9
2	21	4	12	2
3	15	0	6	5
4	45	6	11	24
5	25	2	2	17
6	8	1	4	2
Total (%)	136	16 (12)	40 (29)	59 (43)

Adapted with permission from Smout AM, Lam HG, Breumelhof R: Ambulatory esophageal monitoring in noncardiac chest pain. *Am J Med* 1992;92:74S–80S.

approximately 15% of patients, although the pain found on palpation does not always reproduce the presenting chest pain.⁵⁰ Additionally, fibromyalgia or fibrositis has been reported in up to 30% of patients with noncardiac chest pain.⁵¹

QUESTION

- **What is the approach to the patient with noncardiac chest pain?**

DISCUSSION

Evaluating Noncardiac Chest Pain

Determining whether the chest pain is truly noncardiac in etiology is the critical first step in the evaluation of noncardiac chest pain (Figure 1). Symptomatic CAD and other cardiac abnormalities must be excluded to the satisfaction of both the physician and patient. After

the exclusion of cardiac and other thoracic conditions, patients should be evaluated for panic disorder.

Screening for psychiatric disorders. The practice of the authors of this case study is to screen patients with noncardiac chest pain for panic disorder using a self-administered checklist (Figure 2) derived from the Prime-MD Patient Problem Questionnaire⁵² and based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV).⁵³ (Similar questionnaires to evaluate for depressive and somatoform disorders in primary care settings are also available.^{54,55}) Individuals with a positive screen for panic disorder should be promptly treated or referred for specialist evaluation and care. Because the presence of panic or depressive disorders strongly affects acute care resource use, prompt diagnosis and initiation of effective therapy are critical in achieving satisfying clinical and economic outcomes.⁴⁷

Screening and evaluation for esophageal disorders. Patients with noncardiac chest pain also need to be screened for esophageal disorders. Although a valid questionnaire for GERD exists, it is principally a research study tool and is somewhat cumbersome for use in a busy private practice or acute care setting.⁵⁶ At the very least, physicians evaluating patients with noncardiac chest pain should determine whether heartburn, regurgitation, dysphagia, odynophagia, and epigastric pain are present. Although these symptoms are frequently present in patients with an esophageal etiology for chest pain, approximately 11% of patients with an esophageal cause of chest pain have no other esophageal symptoms.⁴¹ Therefore, the absence of other esophageal symptoms should not necessarily preclude further evaluation.

Upper gastrointestinal endoscopy. Strategies for evaluating suspected esophageal chest pain continue to evolve. Patients with chest pain syndromes and dysphagia or other “alarm symptoms” (eg, weight loss, gross or occult bleeding, anemia) warrant prompt anatomic

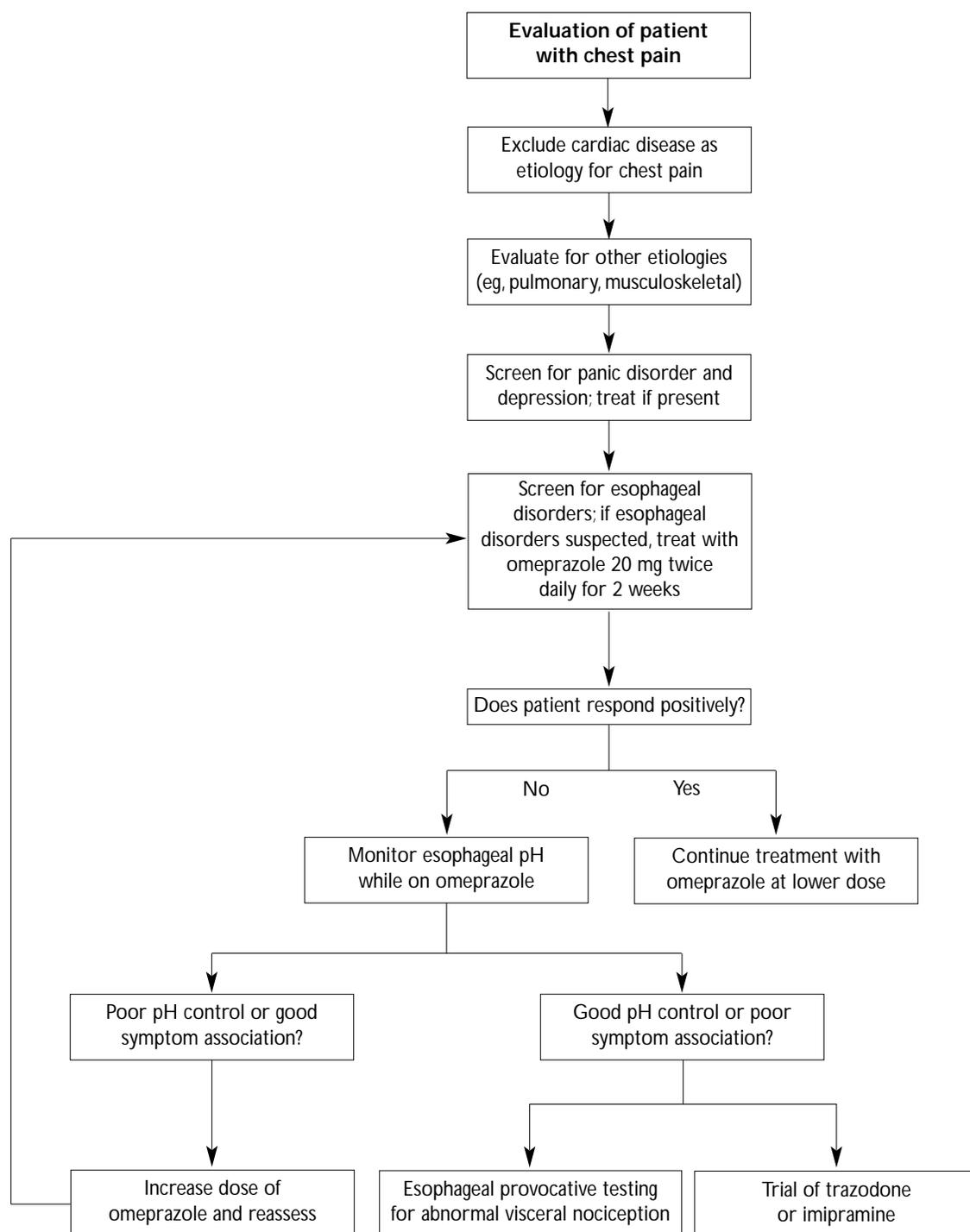


Figure 1. Algorithm of the suggested approach to the patient with noncardiac chest pain. After the exclusion of cardiac and other thoracic conditions, patients should be evaluated for panic disorder and treated accordingly. The presence of panic disorder does not preclude evaluation for concomitant disorders. In the absence of other esophageal symptoms, empiric therapy for gastroesophageal reflux disease is reasonable, with subsequent evaluation based on clinical experience.

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Directions: Read each question, and check either "Yes" or "No" in the right column.

- | | | |
|---|------------------------------|-----------------------------|
| 1) In the last 4 weeks, have you had an anxiety attack (a sudden feeling of fear or panic)? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 2) Has this experience ever happened before? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 3) Do some of these attacks come suddenly and "out of the blue" (in situations in which you don't expect to feel nervous or uncomfortable)? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 4) Do these attacks bother you a lot? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 5) Are you worried about having another attack? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 6) Think about your last bad anxiety attack, and answer the following questions: | | |
| A) Were you short of breath? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| B) Did your heart race, pound, or skip? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| C) Did you have chest pain or pressure? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| D) Did you sweat? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| E) Did you feel as if you were choking? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| F) Did you have hot flashes or chills? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| G) Did you have nausea, an upset stomach, or feel as if you were going to have diarrhea? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| H) Did you feel dizzy, unsteady, or faint? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| I) Did you have tingling or numbness in parts of your body? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| J) Did you tremble or shake? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| K) Were you afraid of dying? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |

Figure 2. Panic syndrome checklist. A screen is considered positive for panic disorder if the patient answers items 1 through 5 affirmatively and responds "Yes" to four or more questions in item 6. Data from Spitzer RL, Williams JB, Kroenke K, et al: Utility of a new procedure for diagnosing mental disorders in primary care: the PRIME-MD 1000 Study. *JAMA* 1994;272:1749–1756 and American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Association, 1994.

evaluation with upper gastrointestinal (UGI) endoscopy and other studies as clinically indicated. The utility of UGI endoscopy and radiography as first-line investigative modalities in patients with noncardiac chest pain is quite limited because both tests are insensitive for diagnosing GERD and most patients with GERD-induced chest pain do not have esophagitis.⁵⁷

Esophageal pH monitoring. Ambulatory esophageal pH monitoring has become the gold standard for evaluating esophageal acid exposure and diagnosing GERD.⁵⁸ In addition to documenting overall esophageal acid exposure (which is the most reliable test parameter for establishing a diagnosis of GERD), esophageal pH monitoring also allows for direct correlation of chest pain episodes with acid reflux episodes. This correlation is important because individuals with overall esophageal acid exposure within normal limits may still experience symptoms associated with isolated reflux events.^{41,59}

The procedure is performed by transnasally placing a 2-mm pH probe 5 cm above the lower esophageal sphincter and connecting it to a small recording device that the patient wears on his or her belt. While the test is being performed, patients are able to eat a normal diet, exercise, and perform activities generally without

restriction. The procedure is generally well tolerated. Meal periods and symptoms are recorded in a diary and may later be correlated with esophageal acid exposure levels.

Despite the quantitatively useful aspects of ambulatory esophageal pH monitoring, it is not a perfect diagnostic modality. Its overall sensitivity and specificity for diagnosing GERD is approximately 81% to 85% and 85% to 100%, respectively.^{60,61} Additionally, when patients without esophagitis are compared with asymptomatic controls, the test's sensitivity is reduced to 60% to 70%.⁵⁸ These factors significantly limit the utility of the procedure because the predictive value of the test is weakest in the clinical subset in which it is most needed.

Proton pump inhibitors as diagnostic modality. The limited sensitivity of pH monitoring has led some investigators to suggest use of a therapeutic trial of proton pump inhibitors, with pH monitoring reserved for patients who have partial or no response to treatment.⁵⁸ Several recent studies have demonstrated the efficacy of an empiric trial of high-dose proton pump inhibitors in patients with noncardiac chest pain.^{40,62–64} In these studies, investigators used omeprazole in

doses ranging from 40 to 60 mg/day, administered as a single or split dose for 1 to 8 weeks.

In perhaps the best designed of these trials, Fass et al⁴⁰ administered omeprazole (40 mg every morning and 20 mg nightly) for 1 week to 37 subjects with noncardiac chest pain. All subjects underwent endoscopy and pH monitoring before treatment, which was conducted in a double-blind, placebo-controlled, crossover design. Patients were considered GERD-positive if they had either a positive esophageal pH study or an endoscopy demonstrating esophagitis. Of 23 GERD-positive patients, 18 responded to omeprazole; only two of the 14 GERD-negative patients responded positively to omeprazole. Sensitivity for the "omeprazole test" was 78.3%, and the specificity was 85.7%. An economic decision analysis was performed for a 1-year period comparing the omeprazole test with conventional evaluation for suspected GERD. Empiric omeprazole was shown to save \$573 per average patient and resulted in a 59% reduction in the number of diagnostic procedures.

Although further study regarding this approach is needed, proton pump inhibitors, given in high doses for a brief period of time, appear to represent a useful tool in the evaluation and treatment of noncardiac chest pain. The authors of this case study presently employ proton pump inhibitors, given twice daily for a 2-week period. Patients returning with persistent or incompletely relieved symptoms then undergo esophageal pH monitoring while on medication. This approach allows for assessment of therapeutic efficacy as well as correlation of symptoms with esophageal pH levels. And, although the omeprazole test requires further evaluation, the data clearly show that it has a sensitivity and specificity comparable to pH monitoring for patients with noncardiac chest pain, without the hassle or expense; in fact, this diagnostic strategy may actually be cost-saving if the patient is completely responsive to the omeprazole.

Esophageal acid perfusion test. Because GERD is the most common esophageal etiology of noncardiac chest pain,³⁸⁻⁴² initial investigative efforts should address this consideration. The esophageal acid perfusion test, introduced by Bernstein and Baker in 1958, was long used to identify esophageal acid exposure as a mechanism of pain in subjects with noncardiac chest pain. However, this test has largely been replaced by esophageal pH monitoring and empiric trials of acid suppressive therapy. Although this test has good diagnostic specificity, it lacks sensitivity when compared with ambulatory esophageal pH monitoring. In a study of 75 patients with noncardiac chest pain who underwent both esophageal acid perfusion and pH monitor-

ing, "Bernstein's test" was found to have a specificity of 90% but a sensitivity of only 36%.⁶⁵

Esophageal manometry. Esophageal motility disorders are uncommon causes of chest pain in the absence of dysphagia or other esophageal symptoms;^{37,38} therefore, esophageal manometry has little use as a first-line diagnostic modality in the evaluation of noncardiac chest pain in these cases. However, esophageal manometry can be used in cases of noncardiac chest pain to localize the lower esophageal sphincter to facilitate accurate pH probe placement in the further evaluation of GERD.

INITIAL TREATMENT AND FURTHER EVALUATION

After a negative screen for panic disorder, the patient is placed on oral omeprazole (20 mg twice daily). He returns for follow-up in 2 weeks and reports a 30% reduction in his symptoms.

While still taking the omeprazole, the patient is referred for esophageal manometry and pH monitoring. Manometry fails to disclose significant esophageal dysmotility; pH monitoring demonstrates that esophageal acid exposure is within normal limits. The patient has a single episode of chest pain during the study, which is not associated with an acid reflux event.

QUESTION

- **What are appropriate next steps in establishing a diagnosis in this patient?**

DISCUSSION

Establishing a Diagnosis

Some individuals with no evidence of psychiatric disorders, GERD, or esophageal dysmotility have persistent chest pain with no obvious etiology. At this stage of investigation, many physicians empirically administer psychoactive medication because of the high prevalence of psychiatric disorders in patients with noncardiac chest pain, the recognized psychophysiologic effects of depression and anxiety on esophageal motor function, and the potential benefits of these medications for managing chronic pain syndromes.⁶⁶ Trazodone and imipramine have both been shown to be effective in this setting, with an approximately 50% improvement in self-reported symptom scores versus placebo^{67,68} (Figure 3).

Esophageal provocative testing. Alternatively, patients at this stage may be referred for esophageal provocative testing to determine whether they have abnormal visceral nociception that may respond favorably to agents used to treat chronic pain syndromes. Additionally, patients who reach this level of evaluation are likely experiencing frequent symptoms and are

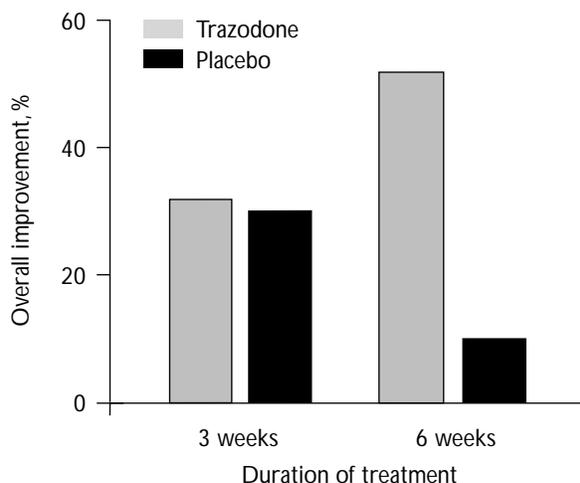


Figure 3. Effect of trazodone (100 to 150 mg/day) on symptom rating at 3 and 6 weeks of treatment. Subjects rated symptoms on a scale that ranged from “100% worse” to “100% better.” Adapted with permission from Clouse RE, Lustman PJ, Eckert TC, et al: Low-dose trazodone for symptomatic patients with esophageal contraction abnormalities: a double-blind, placebo controlled trial. *Gastroenterology* 1987;92:1027–1036.

often highly motivated to determine the cause of their problem. These provocative studies offer an opportunity for a positive diagnosis, which is the most critical determinant of a successful clinical outcome.

The fundamental principle of these provocative tests is that an esophageal stimulus, which is generally not perceived as adverse by asymptomatic individuals, is adverse to patients with abnormal visceral nociception. Similar observations have been made at angiography in patients with chest pain and normal coronary arteries. Right-heart catheter manipulation, pacing, and intracoronary injection of contrast medium were more likely to evoke chest discomfort in these individuals than in patients with valvular heart disease or cardiomyopathy.⁶⁹ Recognition of this entity allows initiation of useful therapies (ie, imipramine or trazodone) in the management of chronic pain syndromes.^{67,68}

Edrophonium infusion (called the *Tensilon test*) and graded esophageal balloon distension are most commonly used. In the practice of the authors of this case study, these studies are performed in addition to pH monitoring after the patient has failed a trial of omeprazole. Administration of the cholinesterase inhibitor edrophonium chloride increases the amplitude and duration of esophageal contractions in all patients and reproduces pain in 18% to 55% of patients with noncardiac chest pain, but not in symp-

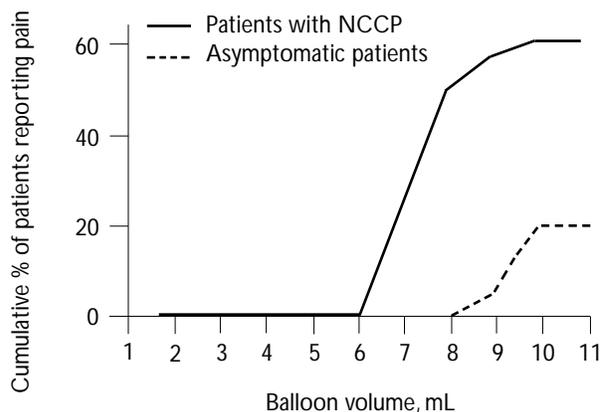


Figure 4. Response to intraesophageal balloon distension of the esophagus. NCCP = noncardiac chest pain. Adapted with permission from Richter JE, Barish CF, Castell DO: Abnormal sensory perception in patients with esophageal chest pain. *Gastroenterology* 1986;91:845–852.

tomatic control patients.^{70–73} Graded intraesophageal balloon distension also identifies individuals with noncardiac chest pain who develop pain in response to distension at volumes not perceived as adverse by asymptomatic controls (**Figure 4**).⁷⁴

Further study in this area is needed, most importantly to determine whether response to provocative esophageal testing predicts a response to neuromodulatory agents. Clearly, it would be advantageous to further identify subsets of patients with noncardiac chest pain who would respond to specific therapeutic agents. At present, the greatest value of provocative testing is providing the patient with a positive diagnosis.

FURTHER TESTING AND CLINICAL COURSE

The patient undergoes provocative esophageal testing with both edrophonium and balloon distension. He develops typical chest pain after infusion of edrophonium, but not after a saline placebo; typical chest pain also develops at 7 mL of balloon distension. The patient is happy that “somebody finally found something” and is relieved that “it’s not all in [his] head.” Because of the demonstrated benefits of trazodone in reducing noncardiac chest pain symptoms, the patient is started on oral trazodone 150 mg 4 times daily.

At a follow-up visit 6 weeks later, the patient reports that his pain still occurs but with less frequency and severity. He has not missed work and has resumed recreational activities. He has not sought medical care in the interim. Overall, the patient feels that his quality of life has significantly improved.

SUMMARY

Noncardiac chest pain is a common and costly problem. After exclusion of cardiac disease, a careful interview and evaluation should be performed to determine the presence of disorders of other thoracic viscera. In the absence of positive findings, patients should be evaluated and treated for panic or depressive disorders. Additionally, the high prevalence of esophageal disorders, particularly GERD, also warrants evaluation. In the absence of other esophageal symptoms, the omeprazole test is a reasonable and possibly cost-saving strategy. Individuals who fail a trial of proton pump inhibitors should be referred for esophageal pH monitoring while on medication to determine esophageal acid exposure and association of symptoms with acid reflux events. In the absence of reflux as an obvious cause, esophageal manometry, either stationary or ambulatory, should be performed to exclude motility disorders. Ideally, provocative testing should be performed simultaneously because it helps the physician make a positive diagnosis and identify patients with abnormal visceral nociception. Patients whose chest pain does not have an obvious etiology, and perhaps those with positive provocative studies in particular, should receive a trial of trazodone or imipramine.

There is a need for formal outcomes evaluation in this area. Favorable outcomes (ie, decreased resource consumption and improved patient functioning) have been shown to occur not only by excluding mortal conditions such as CAD but also by rendering a positive diagnosis.^{26,29} This case study offers a concise, practical diagnostic strategy that does not depend heavily on inpatient services or endoscopy.

The approach outlined in this case study emphasizes the detection and treatment of common and treatable causes of noncardiac chest pain, including panic disorder and abnormal visceral nociception. The former condition has been shown to be a major determinant of acute care resource utilization, and the latter is a treatable entity not commonly considered. The authors of this case study are presently conducting outcomes studies to determine the predictive value of provocative testing with regard to response to imipramine, to develop an esophageal screening questionnaire for use in the ED, and to determine the predictive value and efficacy of the omeprazole test.

HP

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