Unexplained Chest Pain:

September 01, 2003 | Depression [1], Sleep Disorders [2]
By John C. Fang, MD [3]

ABSTRACT: Once you have excluded a cardiac origin of chest pain, focus the evaluation on esophageal, psychiatric, musculoskeletal, and pulmonary causes. Gastroesophageal reflux disease (GERD) and esophageal motility disorders are the most common causes of unexplained chest pain (UCP). If you suspect an esophageal disorder, empiric antisecretory therapy is the most cost-effective initial approach. If the patient remains symptomatic, order a 24-hour esophageal pH study with symptom analysis while the patient receives maximal acid suppression. Once GERD is excluded, the patient may be treated for visceral hyperalgesia with low-dose tricyclic antidepressants or standard doses of selective serotonin reuptake inhibitors. Panic disorder—the most common psychiatric disorder in patients with UCP—is often associated with atypical symptoms, such as palpitations and paresthesias, and other psychiatric disorders. If you suspect panic disorder, one approach is to give the patient a short-term, nonrefillable prescription for a benzodiazepine and refer him or her for psychiatric evaluation.

Noncardiac chest pain, or unexplained chest pain (UCP), can be defined as recurrent angina-like or substernal chest pain that after reasonable cardiac evaluation is found to be unrelated to the heart. Because microvascular angina may cause chest pain in patients who have normal coronary angiographic findings, UCP may be a more appropriate term than noncardiac chest pain. The estimated magnitude of UCP is remarkable. Up to 30% of the coronary angiograms performed in the United States show normal findings or insignificant obstruction. With more than 1 to 1.5 million angiograms done annually, up to 450,000 new cases of UCP could result each year. The estimated health care costs for the evaluation and treatment of patients with UCP are staggering: as high as $1.8 billion each year. The long-term mortality of UCP is low (less than 1% at 10 years). However, morbidity is high, which accounts for the substantial health care costs. These patients' activity is severely limited, their use of health care resources is extremely high, and half of them are unemployed; paradoxically, many persist in believing their pain is cardiac in origin even after cardiac causes have been ruled out clinically. As many as 75% of them continue to have chest pain. How best to identify treatable causes of chest pain—without ordering a battery of expensive diagnostic tests? Here I offer a cost-effective approach.

PATHOPHYSIOLOGY
The specific pathophysiologic mechanisms for esophageal-induced chest pain are not well understood. Two studies have noted the role of abnormal pain perception and afferent signaling (visceral hyperalgesia) in patients with UCP. In addition, panic disorder correlates highly with UCP as well as other functional GI tract diseases and may share a common pathophysiology. Many of these factors may overlap in subsets of patients. The abnormal nociception present in patients with psychiatric conditions, such as anxiety disorders, depression, and somatization, may overlap with esophageal and cardiac hypersensitivity in UCP patients. The pathophysiologic mechanism responsible for this overlap may be visceral hyperalgesia (Figure).
Gastroesophageal reflux disease (GERD) has a powerful role in the pathophysiology of UCP, as evidenced by the effectiveness of acid suppression therapy in UCP patients with GERD. Acid perfusion tests and ambulatory esophageal pH monitoring have demonstrated that acid reflux may induce chest pain. However, data from patients with esophagitis suggest that only about 20% of reflux events produce symptoms. UCP patients who have GERD may have a hypersensitivity to even physiologic amounts of acid reflux. Patients with GERD and psychiatric distress are more likely to perceive and report GERD symptoms and seek health care for those symptoms. The increased prevalence of esophageal motility disorders (EMDs) in patients who have UCP has led to the theory that chest pain results from stimulation of mechanoreceptors in the esophageal wall.
Although there is an increased incidence of EMDs in patients who have UCP, there is poor temporal correlation between EMDs found on baseline and episodes of chest pain tracked by ambulatory manometry.\textsuperscript{10}

It has been shown that patients with UCP have esophageal and, perhaps, more generalized visceral hyperalgesia. Visceral hyperalgesia is a mechanism by which the conscious perception of visceral sensation is heightened independent of the intensity of the peripheral stimulus. Studies using esophageal balloon distention and barostats have shown that patients with UCP have decreased thresholds for sensation and pain compared with control groups.\textsuperscript{11} Since this finding is similar to that in patients with irritable bowel syndrome, who have decreased thresholds for rectal balloon distention, the term "irritable esophagus" is used.\textsuperscript{11}

If afferent sensory neurons have been sensitized through previous noxious or repetitive stimulation, physiologic stimulation of any esophageal sensory receptor may activate additional nociceptive pathways and result in acute pain.\textsuperscript{12} The demonstration that esophageal acid infusion induces enhanced sensitivity to balloon distention in UCP patients and healthy controls provides evidence for the mutual sensitization of mechanosensitive nociceptors by stimulation of acid-sensitive chemoreceptors. Thus, symptoms resulting from the stimulation of any esophageal nociceptor (eg, by acid or stretching) may be perceived singly and centrally as chest pain.

UCP patients may perceive pain abnormally in response to various physiologic and/or pathophysiologic stimuli in the esophagus. Evidence of more generalized visceral hyperalgesia in patients with UCP has been demonstrated; in patients with syndrome X (microvascular angina), there is a high frequency of abnormal responses to esophageal balloon distention, positive Tensilon tests, and abnormal esophageal motility.\textsuperscript{13}

The incidence of psychiatric disorders—including anxiety, somatization, depression, and panic disorder—are high among patients with irritable bowel syndrome and those with UCP; this finding suggests that these conditions have a common pathophysiology. The most common psychiatric disorder in patients with UCP is panic disorder, which is found in 25% to 57% of affected patients.\textsuperscript{14}

In patients with UCP, there is a high frequency of abnormal responses to esophageal balloon distention, positive Tensilon tests, and abnormal esophageal motility.\textsuperscript{13}

DIFFERENTIAL DIAGNOSIS

Esophageal disorders. These are among the most common causes of UCP; they account for 50% to 60% of the identifiable diagnoses.\textsuperscript{16} Esophageal causes include GERD, EMDs, and the hypersensitive or irritable esophagus. These etiologic categories are not mutually exclusive, and one or all may contribute to a patient’s chest pain. In patients simultaneously monitored for dysmotility and acid reflux, both may be found to be associated with chest pain.\textsuperscript{17}

Many investigators have demonstrated that GERD is the most common esophageal abnormality in patients with UCP and is present in 22% to 66% of such patients. In 100 consecutive patients with UCP who underwent 24-hour esophageal pH testing, 50% of patients had either an abnormal amount of reflux plus a positive symptom index or a positive symptom index alone that associated chest pain with reflux events.\textsuperscript{18} Patients with UCP who have normal amounts of acid exposure with a positive symptom index may have visceral hyperalgesia or irritable esophagus. Because both coronary artery disease (CAD) and GERD are common disorders, GERD may cause chest pain in patients with proven obstructive coronary disease.

EMDs are found in a minority of patients with UCP. The largest study found that only 28% of UCP patients had an EMD on baseline testing.\textsuperscript{19} The most frequent abnormality was nutcracker esophagus, followed by (in decreasing order of frequency) a nonspecific EMD, diffuse esophageal spasm, a hypertensive lower esophageal sphincter, and achalasia.

However, the manometric response to therapy often is poor, and symptoms of chest pain may improve without a change in manometric findings and vice versa.\textsuperscript{20} This has led many investigators to believe that EMDs are epiphenomena rather than primary pathophysiologic events. Additional esophageal causes of chest pain may be found in UCP patients who have an EMD. One study showed that 35% of patients with nutcracker esophagus had pathologic GERD.\textsuperscript{21}

Cardiac disorders. Although cardiac causes of UCP are thought to be excluded by traditional cardiac testing, the heart may still be the source of pain. CAD may be the cause of UCP in patients who are believed to have noncardiac chest pain but who have not had angiography. A high percentage of patients with UCP have microvascular angina or syndrome X despite normal coronary angiographic findings. In addition, patients with syndrome X have been shown to have abnormalities in coronary flow reserve despite normal epicardial arteries.\textsuperscript{22} Patients with pericarditis and mitral valve prolapse may present with chest pain and normal coronary
arteries. Combined, prolonged Holter and pH monitoring has demonstrated that a small but significant percentage of patients referred by cardiologists for evaluation of UCP have chest pain episodes that are associated with ischemic ECG changes.\textsuperscript{23}

\textbf{Psychiatric disorders.} Panic disorder is often not suspected during the evaluation.\textsuperscript{24} Compared with patients who have a cardiac cause of chest pain, patients who have panic disorder and UCP are likely to be women, to be younger than 60 years, to present with atypical symptoms, and to have at least one other psychiatric disorder.\textsuperscript{25}

\textbf{Other disorders.} Keep in mind that other conditions that cannot be identified by physical examination alone sometimes can result in UCP. Evaluation for GI conditions, such as biliary colic and peptic ulcer disease, can be done by upper GI endoscopy and abdominal ultrasonography. Chest pain accompanied by acute dyspnea and perhaps hemoptysis suggests pulmonary embolism. If chest pain is associated with a "stitch" in the patient's side, fever, and dry cough, consider pleurisy in the differential. Cough and chest pain suggest pneumonia. Musculoskeletal disorders, such as costochondritis and myofascial syndromes, occasionally may present as UCP. Other miscellaneous causes of UCP are mediastinitis and aortic aneurysms. Chest wall syndromes, including costochondritis (Tietze syndrome), xiphoiditis, and fibromyalgia, are found in 13\% to 20\% of patients with UCP.\textsuperscript{26} Although chest wall tenderness may be found in up to 72\% of patients with UCP, tenderness should be considered diagnostic of a musculoskeletal chest wall syndrome only if pain is reproduced by palpation. Patients with exacerbations of asthma or chronic obstructive pulmonary disease often complain of chest pain and/or tightness.

\textbf{Chest wall syndromes, including costochondritis and myofascial syndromes, occasionally may present as UCP. Other miscellaneous causes of UCP are mediastinitis and aortic aneurysms. Chest wall syndromes, including costochondritis (Tietze syndrome), xiphoiditis, and fibromyalgia, are found in 13\% to 20\% of patients with UCP. Although chest wall tenderness may be found in up to 72\% of patients with UCP, tenderness should be considered diagnostic of a musculoskeletal chest wall syndrome only if pain is reproduced by palpation. Patients with exacerbations of asthma or chronic obstructive pulmonary disease often complain of chest pain and/or tightness.}

\textbf{CLINICAL PRESENTATION}

Often, the clinical history does not help distinguish an esophageal or psychiatric cause from a cardiac cause for the patient's symptoms. All may produce a pressure-like squeezing or burning substernal chest pain, which may radiate to the jaw, neck, arms, or back. Somatic, not cognitive, symptoms make up 10 of the 13 diagnostic criteria for panic attack, including chest pain, palpitations, nausea, and diaphoresis (Box).\textsuperscript{27} Pain may improve with the use of nitrates or calcium channel blockers, either as a result of the relaxation of smooth muscle in EMD or as a placebo effect in other noncardiac causes of chest pain. GERD that results in chest pain may be triggered by exercise, including treadmill testing. Features that suggest an esophageal origin include: Pain that continues for hours. Retrosternal pain without radiation. Pain that is relieved with antacids. Pain that disturbs sleep. The presence of more typical esophageal symptoms, such as dysphagia, odynophagia, regurgitation, and heartburn, suggests an esophageal cause and is found in up to 83\% of patients with UCP caused by an esophageal disorder. However, the presence of esophageal symptoms has a very poor predictive value in distinguishing between an esophageal and a cardiac source of chest pain.\textsuperscript{28} In one study, 11\% of patients with UCP in whom GERD had been determined to be the cause of their chest pain had no esophageal symptoms.\textsuperscript{18}

\textbf{A COST-EFFECTIVE APPROACH}

Despite very low overall mortality, UCP is associated with high health care costs and debility. However, patients with noncardiac chest pain have better functional status and make less use of health care resources than those with cardiac chest pain.\textsuperscript{29} Given the excellent survival rate, the multitude of available diagnostic tests, and the cost-conscious medical environment, a cost-effective approach to UCP is warranted (Algorithm). A thorough history and physical examination, initial laboratory tests, and chest radiography may suggest pulmonary, GI tract (biliary colic, peptic ulcer disease), musculoskeletal, and other causes of UCP. However, the initial evaluation will be unremarkable in most patients with UCP resulting from esophageal, psychiatric, or cardiac causes.

\textbf{Ruling out cardiac causes.} Always exclude significant CAD before proceeding with further diagnostic evaluation. Although there are a number of noninvasive tests for the evaluation of CAD, angiography is the gold standard. A negative finding on an angiogram indicates a very favorable prognosis even if it does not absolutely rule out the heart as the source of a patient's symptoms. At this point, offer reassurance. Many patients with UCP continue to believe that they have cardiac disease even after it has been ruled out.\textsuperscript{30}

\textbf{Evaluation and treatment of esophageal causes.} The diagnostic tests available for evaluating an esophageal cause of UCP include 24-hour pH monitoring, upper GI endoscopy, and esophageal manometry with provocative testing to attempt to reproduce symptoms. The best purely diagnostic
test in the evaluation of UCP is 24-hour pH monitoring combined with symptom analysis; it is the most sensitive and specific test for GERD.\cite{18}

Fifty percent to 60% of patients with UCP have either increased acid reflux and a positive symptom index or a positive symptom index alone (suggesting an acid-sensitive or irritable esophagus). Upper GI endoscopy in the absence of dysphagia has not been shown to be useful in the initial evaluation of UCP because only 10% to 25% of patients with UCP will have endoscopic evidence of esophagitis.\cite{31}

Reserve upper GI endoscopy for patients in whom complications of GERD-such as Barrett esophagus, esophageal stricture or ulcer, or esophageal cancer—are suspected.

Esophageal manometry combined with provocative testing will identify 25% to 30% of cases of UCP caused by an EMD, but this is controversial.\cite{18} The most extensively studied provocative tests include the Bernstein test and the Tensilon test. The Bernstein test attempts to reproduce symptoms by infusing acid into the distal esophagus. The Tensilon test attempts to reproduce symptoms by inducing forceful contractions in the esophagus by intravenous edrophonium infusion.

Test results may be abnormal in up to 25% of UCP patients who had unremarkable results from 24-hour ambulatory pH tests and stationary manometry. A positive test result in a patient with UCP identifies the esophagus as the likely source of the symptoms, whether caused by EMD, esophageal hyperalgesia, or GERD.

A much more cost-effective approach than the battery of diagnostic tests outlined above is initial empiric antisecretory therapy.\cite{7,8} A number of investigators have shown excellent results in treating patients who have UCP and GERD with acid-suppression agents.

Fass and associates\cite{7} studied initial empiric high-dose acid-suppression therapy in 37 patients with UCP using a double-blind crossover design. One week of high-dose omeprazole (40 mg every morning, 20 mg every evening) produced a greater than 50% improvement in symptoms in 54% of the patients overall and in 78% of patients with GERD. The sensitivity and specificity for this empiric trial for diagnosing GERD as the cause of UCP were an impressive 78% and 86%, respectively. Because these studies were performed in selected populations, the results cannot be generalized to other populations. However, an economic analysis comparing empiric omeprazole therapy with a conventional diagnostic strategy demonstrated significant cost savings and reductions in numbers of tests performed.\cite{7}

My approach is to prescribe a proton pump inhibitor twice daily for at least 1 month, although the appropriate duration remains controversial. If the patient remains symptomatic, I order a 24-hour pH study with symptom analysis while the patient receives maximal acid suppression. If the results show adequate acid suppression and a negative symptom correlation, GERD is essentially ruled out.

**Empiric therapy for visceral hyperalgesia.** Once GERD is excluded, the patient may be treated for visceral hyperalgesia; however, there are no data to recommend (or not recommend) initial empiric therapy for hyperalgesia over initial empiric therapy for GERD. This can be in the form of low-dose tricyclic antidepressants (TCAs) or standard doses of selective serotonin reuptake inhibitors (SSRIs).

Similar to treatment of functional bowel disorders, treatment of visceral hyperalgesia with antidepressants has been shown to be effective in patients with UCP. Probably because of their neuromodulatory and visceral analgesic properties, TCAs are effective at lower doses than those commonly used to treat depression.

Cannon and Epstein\cite{22} evaluated patients with UCP for cardiac, esophageal, and psychiatric abnormalities. Patients were then treated with low-dose imipramine, clonidine, or placebo. A high percentage of the patients had cardiac, esophageal, and/or psychiatric abnormalities, and only low-dose imipramine was effective in treating their chest pain. Perhaps most interesting, the effectiveness of imipramine was similar irrespective of the underlying cause of pain.

In a double-blind, placebo-controlled study, Clouse and colleagues\cite{20} treated symptomatic persons who had EMDs with low-dose trazodone (100 to 150 mg/d). The investigators found significant improvement in global symptoms and decreased distress in the patients who received trazodone. More recently, a randomized, double-blind, placebo-controlled trial of sertraline in patients with UCP showed that those who received the SSRI demonstrated a significant reduction in pain scores regardless of any concomitant improvement in psychological scores.\cite{32}

**Evaluation and treatment of psychiatric causes.** Because of the high incidence of psychiatric disorders in patients with visceral hyperalgesia and UCP, consider formal psychiatric evaluation and treatment early when there is sufficient clinical suspicion or later when the patient's chest pain is refractory to medical management. Query patients specifically about symptoms of panic disorder (see Box).

Both psychotropic medications (including TCAs, SSRIs, and benzodiazepines) and cognitive behavior
interventions are effective in 70% to 90% of cases of panic disorder; however, with the exception of benzodiazepines, these interventions may take 6 to 8 weeks to bring relief. Beitman and coworkers reported a significantly decreased frequency of panic attacks and chest pain episodes in persons treated with open-label alprazolam.

Although benzodiazepines provide almost immediate relief for patients with panic disorder, the potential for abuse and dependency make them problematic for long-term therapy. If panic disorder is suspected, the patient may be given a short-term, nonrefillable prescription for a benzodiazepine and may be referred to a mental health professional for further evaluation and pharmacologic and/or psychological treatments.

Cognitive behavior therapy is based on the theory that preoccupation with and misinterpretation of physical symptoms plays a central role in patients with UCP. In the largest study of cognitive behavior therapy in patients with noncardiac chest pain, 48% of patients randomized to this therapy were pain-free at 12 months compared with 13% of those in the control group.

If the patient remains symptomatic and/or an EMD is suspected, esophageal manometry may be performed with provocative testing (usually Bernstein and Tensilon tests) to establish the esophagus as the cause of the symptoms, even though test results may not necessarily direct therapy. However, simply the identification of an esophageal source of symptoms has been shown to reduce symptoms, medical visits, and lifestyle limitations.

There have been conflicting results regarding therapy with calcium channel blockers in symptomatic patients with spastic EMDs, usually caused by nutcracker esophagus. Given the tenuous evidence that UCP is due to EMDs and the marginal effectiveness of smooth muscle relaxants, it appears that calcium channel blockers or nitrates have a very limited role in the treatment of UCP.

**Evaluation and treatment of musculoskeletal disorders.** If a musculoskeletal chest wall syndrome is suggested by reproducible symptoms on palpation, initiate therapy with anti-inflammatory medications and local treatments.

**References:**

15. Cannon RO 3rd, Quyyumi AA, Mincemoyer R, et al. Imipramine in patients with chest pain despite...