Noncardiac chest pain (NCCP) is not only a difficult disorder to define but is also complex in characterization and treatment.\textsuperscript{1–3} It represents a symptom of chest pain not of cardiac etiology characterized as burning or squeezing in nature with or without radiation. A cardiac cause must be ruled out in every patient in whom a work-up of potential NCCP is being considered. Approximately 20\% to 30\% of patients with chest pain have normal cardiac catheterization and may be classified as NCCP, representing more than 200,000 new cases annually in the United States.\textsuperscript{4} Patients with NCCP are a challenge to primary care and subspecialty services such as cardiology and gastroenterology. These patients are likely to have a high level of health care use and undergo many tests and empiric therapies, and they are usually poorly satisfied with the care provided.\textsuperscript{5} NCCP is often a heterogeneous disorder with many potential causes including gastroenterologic diagnoses (Box 1).

Gastroesophageal reflux disease (GERD) represents 1 of the most common gastroenterologic causes of NCCP.\textsuperscript{1–3} Nearly 25\% to 60\% of patients with NCCP have abnormal prolonged ambulatory pH findings.\textsuperscript{6} In this group of patients, the presence of baseline heartburn may be helpful but not definitive for the association of GERD with patients’ chest pain episodes. The current dilemma in this disorder is identifying when GERD may be responsible for the patient’s presentation and what to do if empiric therapy fails to resolve the patient’s symptoms. This article presents the current evidence for GERD as a cause of NCCP and highlights the best currently available tests for this group of patients.
**CLINICAL PRESENTATION**

GERD-related NCCP may resemble angina. The pain may be described as squeezing or burning in the substernal location with possible radiation to the neck, arms or back. It may be worse postprandially and in the supine position and occasionally post exercise or during emotional stress. Heavy exercise may induce the typical symptoms of GERD, such as heartburn and regurgitation, and may cause NCCP. The pain may last minutes or hours and may be intermittent for days. Symptoms usually resolve with antacids, proton pump inhibitors (PPIs), or rest. The presence of typical GERD symptoms such as heartburn and regurgitation are independently associated with NCCP although they do not predict response to PPI therapy. In a population study by Eslick, 53% and 58% of patients with NCCP had concomitant heartburn and regurgitation. Therefore, both conditions may coexist but the causal link may be more difficult to establish. In a recent study the presence of classic reflux symptoms and response to antacid therapy were important in establishing GERD-related NCCP.

**PATHOPHYSIOLOGY**

An esophageal origin for recurring NCCP was considered likely by William Osler in 1892 who first suggested that esophageal spasm might play a role in patients’ symptoms. However, later studies using ambulatory pH monitoring tests and pressure monitoring suggested that reflux of gastric content, mainly acid, may be the most common cause of patients’ symptoms of chest pain. Chemostimulation and mechanostimulation are the 2 broad concepts put forward as the main pathogenesis of reflux-induced symptoms. Esophageal pain may be a manifestation of nociceptor activation by chemoreceptors responding to chemical or thermal stimulation or mechanostimulation responding to esophageal wall stretch. Once activated, the receptors transmit their signal through small unmyelinated C-fibers; the pain is usually perceived as dull, burning, gradual, and poorly localized. In contrast, when the signals are transmitted with myelinated fibers, the perception is of sharp, sudden, and well-localized pain. The activated esophageal wall nociceptors transmit their signal peripherally and centrally. The latter is required for pain perception. It is suggested that, because the esophagus and heart share a common innervation, esophageal nociceptor activation may influence coronary circulation. In this study, the investigators found a significant reduction in coronary blood flow with esophageal acid perfusion.

<table>
<thead>
<tr>
<th>Box 1 Potential gastroenterologic causes of NCCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Gastroesophageal reflux disease (GERD)</td>
</tr>
<tr>
<td>• Esophageal motility disorder</td>
</tr>
<tr>
<td>• Esophageal hypersensitivity</td>
</tr>
<tr>
<td>• Biliary colic</td>
</tr>
<tr>
<td>• Pancreatitis</td>
</tr>
<tr>
<td>• Hepatitis</td>
</tr>
<tr>
<td>• Pneumoperitoneum</td>
</tr>
<tr>
<td>• Peptic ulcer disease</td>
</tr>
<tr>
<td>• Splenomegaly</td>
</tr>
</tbody>
</table>

Oranu & Vaezi 234
which was also associated with typical angina pain. This finding was attributed to an esophagocardiac inhibitory reflex. Similar reduction in coronary blood flow was identified by Rosztoczy and colleagues in 45% of patients with NCCP.

GERD may also cause a hypersensitivity response manifested as NCCP. Peripheral sensitization of esophageal sensory afferents may lead to heightened response to even normal physiologic acid reflux. Infusion of 0.1 N hydrochloric acid in normal subjects was found to reduce the perception threshold for pain. The reduction in the pain threshold is most likely caused by increased central excitability by activation of the nociceptive C-fibers. Some also suggest autonomic dysfunction in patients with NCCP. In a study of NCCP and healthy volunteers, Tougas and colleagues showed that patients with acid sensitivity had a higher baseline heart rate and lower baseline vagal activity than acid-insensitive patients. Acid perfusion cardiac outflow increased in patients with acid sensitivity and not in those with insensitive esophagus.

Distention of the esophagus may also play a role in spatial summation, as a result of input from multiple neuronal cells that are more in the upper striated muscle part of the esophagus. Esophageal distention with or without priming of esophageal mucosa by exposure to gastric content has some effect on the mechanostimulator pathway of GERD. The biomechanical and sensory characteristics of the upper, middle, and distal esophagus of 11 healthy volunteers were evaluated by Patel and Rao. This group reported a lower threshold of pain sensation in the proximal esophagus compared with the other esophageal segments and postulated that the proximal esophagus might have a larger number of mechanoreceptors than the distal esophagus with distention in the proximal esophagus contributing to the generation of symptoms during a reflux. The priming of the esophagus after exposure to gastric content was evaluated by Fass and colleagues and DeVault who unlike Mehta and colleagues and Peghini and colleagues found no accentuation of mechanical stimulation after acid exposure. Sarkar and colleagues demonstrated induction of hypersensitivity in the proximal esophagus after exposure of distal esophagus to hydrochloric acid suggesting that the latency of esophageal evoked potential is reduced thus leading to visceral hypersensitivity. Sustained contraction of the esophageal longitudinal muscle is also suggested as a potential causative factor in patients with NCCP. In this study, the investigators suggested that heartburn was associated with short duration of contraction and chest pain was associated with longer contraction duration.

In addition to reflux of acid, nonacid causes may be important in NCCP. Siddiqui and colleagues assessed the causative role of bile acids in esophageal symptoms with a modified Bernstein acid-infusion test and esophageal barostat balloon distensions, in healthy individuals and patients with nonerosive disease. 0.1 M hydrochloric acid; 2 mM and 5 mM chenodeoxycholic acid and ursodeoxycholic acid infusions were used at least 7 days apart. Significantly higher pain thresholds (with regard to volume and time) were found for ursodeoxycholic acid than for chenodeoxycholic acid, than for acid infusion, suggesting a possible role for bile acids in the generation of esophageal symptoms and pain.

**DIAGNOSTIC TESTING**

Given the lack of sensitivity of the current diagnostic testing in NCCP, no test can be considered as the gold standard. The most commonly used tests include barium swallow, upper endoscopy, ambulatory pH (with or without impedance monitoring), and PPI trial. Barium esophagram has a low sensitivity (20%–30%) in diagnosing GERD, and should be considered when there is an associated complication such as dysphagia in patients with GERD or NCCP. In addition, reflux of barium during
an esophagram is of questionable significance and can seen in up to 20% of healthy people.\textsuperscript{27} Upper endoscopy is valuable for diagnosing esophageal mucosal injury related to GERD such as erosive esophagitis, ulceration, peptic stricture, and Barrett esophagus. However, patients with NCCP have lower incidence of esophageal findings at endoscopy. Thus, the clinical yield of this test is low in this group of patients.\textsuperscript{28}

Ambulatory 24-hour pH monitoring is regarded as an important physiologic test in diagnosing GERD. It has a sensitivity ranging from 79% to 96% and specificity from 85% to 100%.\textsuperscript{29–31} Normal pH findings on 24-hour esophageal pH monitoring are present in up to 25% of patients with erosive esophagitis and 50% of patients with nonerosive reflux disease.\textsuperscript{32–34} This is most commonly caused by diet and lifestyle modification during the study period as a result of the nasopharyngeal location of the traditional pH catheter. The introduction of a wireless ambulatory pH capsule and longer duration (48 hours) of recording has somewhat improved the sensitivity of pH testing.\textsuperscript{35} In patients with NCCP, pH monitoring is abnormal in 50% to 60% of patients. Hewson and colleagues\textsuperscript{36} reported prevalence of abnormal pH in 48% of 100 patients with NCCP; 60% had a positive symptom index (SI). The overzealous conclusion from this study was that pH monitoring and SI measurement is the single best test in patients with NCCP. However, a subsequent study did not confirm these conclusions\textsuperscript{37} reporting that SI positivity was not a common occurrence in NCCP. Multichannel intraluminal impedance with a pH sensor allows the detection of acidic and weakly acidic reflux.\textsuperscript{38} This recent technique dramatically improved the detection of reflux, regardless of its pH. Well-controlled studies in NCCP patients using impedance monitoring are needed to assess the role of weakly or nonacid reflux.

The PPI trial is currently the most attractive alternative to the modalities discussed earlier because it combines knowledge of symptomatic response with a therapeutic trial of acid suppression. The test uses a short course of high dose PPI to diagnose GERD in those with NCCP. The main requirement of the PPI trial is to achieve a significant symptomatic improvement from as many patients as possible within a short time period. Diagnostic accuracy of a PPI trial is summarized in Table 1.\textsuperscript{32,39–44} In most studies the test was considered to be positive if symptom assessment scores improved by 50% to 75% compared with baseline. Overall these trials suggest a sensitivity ranging from 69% to 92% and a specificity ranging from 67% to 86% for a PPI trial in NCCP. A recent meta-analysis\textsuperscript{45} of randomized controlled studies in NCCP suggested that PPI therapy reduces symptoms in NCCP and may be useful as a diagnostic test in identifying abnormal esophageal acid reflux. The study reported a pooled risk ratio for continued chest pain after PPI therapy of 0.54 (95% confidence interval [CI] 0.41–0.71). The overall number to treat to achieve benefit was 3 (95% CI 2–4). The pooled sensitivity, specificity, and diagnostic odds ratio for the PPI test versus pH monitoring and esophagastroduodenoscopy (EGD) were 80%, 73%, and 14% (95% CI 5.5–34.9). However, the studies were heterogeneous and small in sample size with evidence of publication bias. In a different meta-analysis,\textsuperscript{46} the investigators used 6 of the published controlled trials and found that the use of a PPI trial as a diagnostic test for GERD in NCCP has an acceptable sensitivity and specificity and may be used as an initial test. The investigators reported an overall sensitivity and specificity of 80% and 74%. The PPI trial showed significant higher discriminative power with a summary diagnostic odds ratio of 19.4 (95% CI 8.5–43.8) compared with 0.61 (95% CI 0.2–1.9) in the placebo group. Thus, there seems to be adequate evidence in support of a PPI trial as the initial test of choice in patients with NCCP to assess if symptoms may be from GERD and this may be cost effective.\textsuperscript{32,47} The PPI test saved US$575 per patient with NCCP and the test was associated with 79% and 81% reduction in the use of pH monitoring and EGD, respectively.
Provocative tests such as the edrophonium test (Tensilon test) or the Bernstein test are no longer recommended or commonly used in the evaluation of patients with NCCP. Edrophonium, a short-acting acetylcholinesterase inhibitor, increases esophageal motility by increasing the amplitude and duration of esophageal contractions. This test initially showed clinical presentation of chest pain in 50% of patients; however, a response to this test does not indicate a motility disorder as the cause of the patients’ symptoms. The Bernstein test requires perfusion of 0.1 N hydrochloric acid into the esophagus in an attempt to reproduce the patients’ symptoms of NCCP if GERD related. It has low sensitivity and with the emergence of PPIs it has become less valuable in NCCP.

**MANAGEMENT**

In patients with NCCP in whom a PPI trial is successful in improving symptoms, tapering of the dose of PPI to once daily and subsequently to the minimal dose of acid suppression is recommended. The role of lifestyle modification in GERD and even in NCCP is questionable. The recent American Gastroenterological Association guidelines for treating GERD question the role of lifestyle changes such as raising the head of the bed, avoiding fat, chocolate, alcohol, caffeine, mints, or garlic. There is no concrete evidence for their effectiveness. However, weight loss in those who may be overweight or obese is recommended and may result in improvement of GERD and subsequently NCCP. Similarly, given the lower efficacy of H2-receptor antagonists

<table>
<thead>
<tr>
<th>References</th>
<th>Dosing</th>
<th>No. of Patients</th>
<th>Symptom Improvement (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young et al[^39]</td>
<td>Omeprazole 80 mg/d 1 day</td>
<td>30</td>
<td>75</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>Squillace et al[^40]</td>
<td>Omeprazole 80 mg/d 1 day</td>
<td>17</td>
<td>50</td>
<td>69</td>
<td>75</td>
</tr>
<tr>
<td>Xia et al[^41]</td>
<td>Lansoprazole 30 mg/d 4 weeks</td>
<td>68</td>
<td>50</td>
<td>92</td>
<td>67</td>
</tr>
<tr>
<td>Pandak et al[^42]</td>
<td>Omeprazole 40 mg twice a day 2 weeks</td>
<td>37</td>
<td>50</td>
<td>90</td>
<td>67</td>
</tr>
<tr>
<td>Fass et al[^32]</td>
<td>Omeprazole 40 mg every morning and 20 mg every evening 7 days</td>
<td>37</td>
<td>50</td>
<td>78</td>
<td>86</td>
</tr>
<tr>
<td>Fass et al[^43]</td>
<td>Lansoprazole 60 mg every morning and 30 mg every evening 7 days</td>
<td>40</td>
<td>50</td>
<td>78</td>
<td>82</td>
</tr>
<tr>
<td>Fass et al[^44]</td>
<td>Rabaprazole 20 mg every morning and 20 mg every evening 7 days</td>
<td>20</td>
<td>50</td>
<td>83</td>
<td>75</td>
</tr>
</tbody>
</table>
(H2RAs) in suppressing acid, it is intuitive that they may not result in as great a benefit in symptom relief as PPIs if GERD is the cause of patients’ presenting NCCP. H2RAs have shown a limited response in this group of patients. In a small uncontrolled study by Stahl and colleagues, 49 13 patient with NCCP were treated with ranitidine 150 mg orally four times a day. Seven of the 13 patients did not respond but increasing the dose resulted in a clinical response in all patients. This study highlights the need for aggressive acid suppression initially in this group of patients. In addition to less aggressive acid suppression by H2RAs, tolerance usually develops with these agents after 2–3 weeks of repeated use resulting in decline in efficacy. Therefore, the initial use of PPIs in NCCP is the preferred initial approach.

The role of pH and/or impedance monitoring in those unresponsive to aggressive acid suppression is to often document normality rather than abnormal results. One important clinical question in the management of patients unresponsive to a PPI trial is if pH monitoring should be performed on or off PPI therapy. The answer to this question is currently controversial but the most recent study using impedance monitoring on therapy and wireless pH monitoring off therapy suggests that a combined approach may be necessary. 50 Pritchett and colleagues 50 studied 39 patients with refractory extraesophageal symptoms with impedance/pH monitoring on twice daily PPIs, and then the same patients were evaluated with wireless pH monitoring off acid suppressive therapy. The study showed that on-therapy impedance testing was normal in 64% of patients, whereas off PPI therapy resulted in normal pH findings in only 28% of patients (Fig. 1). Thus, in most patients with persistent throat symptoms, on-therapy testing is more likely to exclude GERD as the cause than off-therapy pH testing. If impedance/pH testing is negative in these patients, diagnosis other than reflux should be considered.

An algorithm for the treatment of patients with NCCP is presented in Fig. 2. Given the beneficial response and more aggressive acid suppression with PPIs and that PPIs are also used as a diagnostic test to determine the cause of NCCP, an initial trial of 1 to 2 months of PPI therapy is a reasonable approach (see Fig. 2). In patients who respond to PPI therapy, tapering the dose to minimal acid suppression should be attempted. If patients do not improve after 2 months of therapy with PPIs, diagnostic testing such as pH monitoring or impedance pH monitoring may be useful in assessing if the patient’s acid or nonacid reflux is controlled while on therapy. Impedance/pH monitoring (if available) or pH monitoring should be used while patients are on therapy to assess for continued reflux. If this test is normal then a search for causes other than

![Fig. 1. The likelihood of abnormal pH off therapy if abnormal impedance on therapy was present. Efficacy of esophageal impedance/pH monitoring in patients with refractory GERD, on and off therapy.](image)
GERD should be initiated. pH testing off PPI therapy will only assess the presence of acid reflux at baseline but does not suggest a causal link between GERD and NCCP. Surgical fundoplication cannot be recommended if patients do not respond to PPI therapy. In a selected population of patients (those responsive to PPI therapy) surgical success is to be expected similar to typical GERD.51

**SUMMARY**

In patients with NCCP the most important clinical consideration is to rule out a cardiac cause given its life-threatening nature. Because many patients with NCCP may not present with the classic symptom of GERD, an empiric trial with PPI therapy can be used as a diagnostic test and as therapy. Twice daily PPI therapy is recommended for 1 to 2 months. Diagnostic testing such as EGD, pH, or impedance monitoring is predominately used for those unresponsive to PPI therapy. Response to PPI therapy can suggest a possible causal link between GERD and NCCP and lack of response should prompt a search for other causes of NCCP.

**REFERENCES**


43. Fass R, Pulliam G, Haden C. Patients with non cardiac chest pain receiving an empirical trial of high dose lansoprazole, demonstrate early symptom


