Noncardiac Chest Pain

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The clinical approach to the patient with unexplained chest pain is complex, as the history does not clearly separate cardiac from noncardiac etiologies. After a careful work-up has excluded coronary artery disease, a systematic search for an esophageal etiology is the next step. Gastroesophageal reflux disease (GERD) is most commonly associated with noncardiac chest pain and should be the first diagnosis pursued. A therapeutic trial of antisecretory therapy with proton-pump inhibitors is the most efficient initial approach to diagnosis and therapy of GERD-related chest pain and can easily be instituted by a cardiologist familiar with the optimal use of proton-pump inhibitors.

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The diagnostic and therapeutic approach to the patient with recurring unexplained chest pain in the substernal area has been a source of clinical uncertainty for more than a century. Close to 5 million people arrive at emergency rooms annually with complaints of chest pain, with about 2 million admissions at a cost of about $8 billion.[1,2] After evaluation, about 40% of patients admitted in order to rule out coronary disease are eventually found to be free of any coronary artery disease.[3-5] Two studies have shown that 81% to 86%

of all patients presenting to emergency rooms with chest pain did not have a final diagnosis of cardiac ischemia.[6,7] Evaluation and treatment of these patients is a major clinical challenge for all specialties, as the history does not comfortably differentiate coronary disease from other causes of chest pain, including esophageal disease. This is the case even when a cardiologist sees the patient and takes a detailed history.[8] The major esophageal cause of chest pain, gastroesophageal reflux disease (GERD), may be triggered by exercise,[9] may cause exertional chest pain that mimics angina pectoris even during exercise testing, and may lower anginal threshold.[7]

Although the presence of heartburn, dysphagia, and regurgitation suggests a noncardiac etiology, these features do not confirm it. The typical historical features used to differentiate cardiac from esophageal pain, such as relief by nitroglycerin or antacids, are insensitive and nonspecific. Other features that suggest a noncardiac origin for the pain include pain that lasts longer than 2 to 3 hours, pain that does not radiate laterally, meal-related pain, or pain that awakens the patient from sleep;[7] however, none of these are specific or sensitive enough to allow us to confidently rule out coronary artery disease without a cardiac evaluation. Coronary artery disease and GERD can coexist. In fact, studies have shown that many patients with coronary artery disease will have 1 or more symptoms of reflux disease, and up to 50% have concurrent GERD.[10] Further, in a recent study of 415 male patients with coronary artery disease, the patients had fewer chest-pain episodes, emergency department visits, and hospitalizations if they were taking proton-pump inhibitors (PPIs), implying that GERD may coexist in a large number of these patients.[11] Therefore, the cardiologist is often the focal point of management of such patients, even after cardiac disease has been ruled out, and can play an important role in their initial therapy. This review focuses on the approach to diagnosis and therapy of the patient with noncardiac chest pain, with a major focus on GERD as the cause.

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Differential Diagnosis and Therapeutic Approach

Whereas it is clear that patients with normal cardiac findings or with insignificant coronary artery narrowing have an excellent prognosis with regard to cardiac morbidity and mortality, and a negative angiogram finding provides strong evidence to reassure patients that their recurrent chest pains are not life-threatening, most patients will continue to have recurring chest pain and compromised lifestyle, and continue to believe they have heart disease even after it has been ruled out. This continued morbidity and the subsequent health care costs of recurring hospital visits, medication use, and office visits mandate a careful, thoughtful approach to managing these patients. A thorough systematic evaluation, focusing on GERD and other esophageal disease as the proximate cause, often will reveal a diagnosis, providing reassurance and a positive patient outcome.

The initial approach after the cardiac work-up should inquire about symptoms suggestive of biliary tract, pulmonary, and chest wall disease. If the history and physical examination do not point to these areas, no direct testing is needed. In particular, an ultrasound of the gallbladder rarely proves fruitful in these patients. Esophageal motility abnormalities are present in 25% to 30% , but rarely are associated with the spontaneous production of chest pain when testing is performed.[12] The presence of dysphagia should raise suspicion of a motility abnormality or structural lesion but may also be indicative of GERD. The cardiologist should not fall into the trap of making an empiric diagnosis of diffuse esophageal spasm. This is, in fact, a rare finding in these patients—seen in less than 5%.[13] Motility testing should therefore be reserved for the patient in whom GERD has been ruled out. The spectrum of GERD-related abnormalities in patients with noncardiac chest pain is quite wide. Typical reflux symptoms of heartburn or acid regurgitation are frequently seen in these patients. Chest pain was reported in 37% of those experiencing heartburn symptoms at least once a week and in 30.7% of patients with heartburn less than once a week in a population-based study.[14] Another population-based study, designed to assess the prevalence of noncardiac chest pain, found that in subjects identified as chest pain patients, 53% also experienced heartburn and 58% regurgitation.[15] Because GERD itself is so common in the general population, the presence of heartburn and regurgitation in a patient with noncardiac chest pain cannot be considered diagnostic.

The traditional diagnostic tests used to detect GERD-related noncardiac chest pain include a barium swallow,

upper gastrointestinal endoscopy, and prolonged ambulatory esophageal pH monitoring. In general, both the barium swallow and upper endoscopy have little value in the diagnosis of GERD if alarm symptoms such as dysphagia, weight loss, or gastrointestinal bleeding are absent. The barium study has a low sensitivity (20%) in diagnosing GERD and lacks the specificity to demonstrate erosive esophagitis.[16] Gastroenterologists have traditionally used endoscopy as the first test in their approach to patients with suspected esophageal disease, and indeed endoscopy is an extremely accurate test for diagnosing esophageal mucosal involvement in GERD. However, for patients with noncardiac chest pain, the presence of erosive esophagitis is rare, occurring in only 10% to 35% of these patients,[7,17] when systematically studied. GERD-related complications such as stricture, ulcer, and Barrett's esophagus are likewise infrequent. When such patients are systematically evaluated, Barrett's esophagus is seen rarely (0%-9%).[18-20] Endoscopic studies also have found only anecdotal evidence of peptic ulcer disease in patients with noncardiac chest pain, leaving us with the conclusion that endoscopy is of little use in the primary evaluation of these patients.

Prolonged ambulatory esophageal pH monitoring is the preferred technique to document abnormal esophageal acid exposure and demonstrate a correlation between reflux and symptoms. Numerous studies have suggested that approximately 50% of patients with noncardiac chest pain will have increased esophageal acid exposure, or a high symptom correlation of reflux episodes with chest pain, or exercise-induced reflux.[21-23] However, many patients will not have their typical chest pain during a prolonged monitoring period, which to some extent minimizes the value of this test. Other disadvantages of prolonged esophageal pH monitoring using the traditional transnasal catheter are cost, patient inconvenience, and lack of availability for many physicians. The reported sensitivity has varied from 60% to 96%, and specificity from 85% to 100%, potentially minimizing its value as an early diagnostic test.[24] The newly available wireless pH monitoring system (Bravo™; Medtronic, Shoreview, MN) allows prolonged monitoring with a radiotelemetry pH capsule attached to the mucosal wall of the esophagus.[25] This well-tolerated technique may afford a longer monitoring period and allow more sensitivity and specificity for this diagnostic test; however, as of this writing, it has not been systematically studied in large numbers of patients with noncardiac chest pain.

The ideal intervention for patients with noncardiac chest pain would combine a diagnostic test and treatment with a single modality. Thus, a trial of antisecretory therapy has become the favored mode of "diagnosing" GERD-related noncardiac chest pain while at the same time beginning treatment. This approach is simple, noninvasive, and potentially cost-effective, and can be used by any care provider with an understanding of the optimal use of antireflux pharmacotherapy. PPIs are the ideal agents to use as a therapeutic trial to diagnose GERD as they are the most effective class of agents in reducing gastric acid secretion and treating symptomatic GERD and erosive esophagitis.[26]

Thus, the goal of the therapeutic trial, or what has evolved into the "PPI test," is to aggressively reduce gastric acid secretion over a short period of time with the intent to use improvement in symptoms as conclusive "proof" that they are due to acid. Although the optimal therapeutic trial for the diagnosis of GERD-related chest pain has not been fully determined—neither the PPI dose nor the length of therapy—clinical experience and the data available in the literature favor using a PPI twice daily for several weeks to make an initial assessment. The rationale for this is based on pharmacodynamic data evaluating control of intragastric pH (acid control) and a placebo-controlled trial of twice-daily omeprazole. Control of intragastric pH has been used as the surrogate marker for evaluating the potential efficacy of antisecretory therapy. Optimizing and/or maximizing outcomes in acid-related disease can be correlated with the number of hours of the day that intragastric pH is greater than 4.[27] For clinicians who do not regularly prescribe PPIs, a brief review of the pharmacology of these agents and the principles of optimizing therapy will serve them well in treating their patients.

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Optimizing PPI Therapy

Proton-pump inhibitors are weak protonatable bases that are absorbed incompletely, partly due to acid breakdown during their passage

through the stomach. They have short half-lives (< 90 min) and are accumulated and activated in the acidic milieu on the secretory canalicular surface of the gastric parietal cell. They covalently bind to cysteine residues on the alpha subunit of the hydrogen-potassium ATPase enzyme, and thus irreversibly inhibit acid production. Secretory capability is restored when new pumps are converted from their inactive status in the tubulovesicle to their active form, and move to the canalicular surface. Because not all pumps are active at any given time, and a single dose of PPI inhibits only 70% to 80% of active pumps, PPIs do not result in complete inhibition of acid secretion at any time and new pumps are generated constantly. Daily (or more frequent) dosing is therefore required to achieve an optimal antisecretory effect. Only actively secreting ATPase molecules are inhibited, so the timing of the dose in relation to meal stimulation is critical.[28]

The principal stimulators of parietal cell activity are the sight, sound, smell, and ingestion of food, which correspond to the cephalic and gastric phases of acid stimulation. Therefore, PPIs are most efficacious when taken with or directly before a meal. This is illustrated by the results of a study in which healthy subjects were randomly assigned to take 20 mg of omeprazole or 30 mg of lansoprazole each morning, either 15 minutes before a breakfast meal or without food or drink, except for water, until noon. Acid suppression was significantly more effective when the medication was taken before breakfast than when taken in the morning with no food until noon.[29] The choice to administer a PPI before a meal likely eliminates any decrease in bioavailability seen with omeprazole, lansoprazole, and esomeprazole when taken with food. This study also supports the strong opinion that delayed-release PPIs are less effective when given before bed.

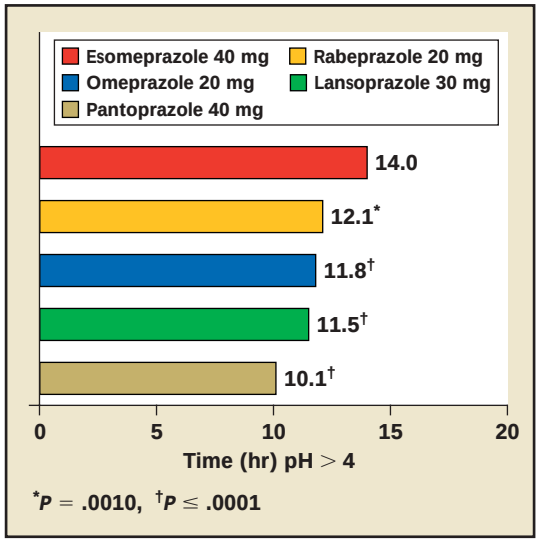


Figure 1. *An intragastric pH study comparing the effects of 5 proton-pump inhibitors given once daily, showing the number of hours (in a 24-hour period) that pH > 4. The results illustrate the potential for increasing pH above 4 for up to half of a 24-hour period. *P = .0010; †P ≤ .0001. Adapted with permission from Miner et al.*[30]

Once-daily PPIs are the standard of care in managing heartburn (as a symptom of GERD) and erosive esophagitis. Healing rates as high as 95% are seen with once-daily dosing of these agents.[26] Extending this to patients with chest pain and other so-called atypical presentations of GERD has been difficult, as the clinical response to once-daily PPI has not been as desired. Therefore, increasing the PPI dose for these patients has become the standard of practice. Intragastric pH studies provide the background for recommendation of a twice-daily dose to maximize initial therapy. A 5-arm, randomized, crossover study in 34 *Helicobacter pylori*–negative patients with symptoms of GERD compared esomeprazole 40 mg, rabeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, and omeprazole 20 mg, once daily, 30 minutes before the breakfast meal, for 5 days, with intragastric pH monitoring performed on day 5.[30] The study demonstrated the superiority of esomeprazole 40 mg compared with the other 4 PPIs in the number of hours and the percentage of the 24-hour period in which the pH was greater than 4 (Figure 1). The number of hours a day that intragastric pH is greater than 4, although sufficient for healing erosive esophagitis, seems somewhat low to effectively manage the majority of patients with chest pain. Thus, to achieve the increase in pH control needed for relief of chest pain and other atypical presentations, a higher dose is needed. This can be given either as a higher once-daily dose or by splitting the dose and giving it twice daily.

To achieve the increase in pH control needed for relief of chest pain and other atypical presentations of GERD, a higher dose of proton-pump inhibitor is needed.

A higher once-daily dose does achieve better control of intragastric pH, as demonstrated by the following

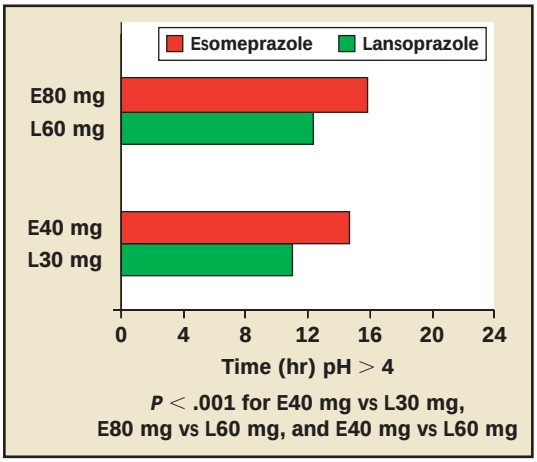


Figure 2. *An intragastric pH study showing an increase in the number of hours that pH > 4 with a double dose of proton-pump inhibitor (vs a single dose), esomeprazole (E) or lansoprazole (L), given once daily. The increase is a little over 1 hour. P < .001 for E40 mg versus L30 mg, E80 mg versus L60 mg, and E40 mg versus L60 mg. Data from Wilder-Smith et al.*[31]

study. *H. pylori*–negative healthy subjects were studied while taking esomeprazole 20 mg, 40 mg, or 80 mg versus lansoprazole 15 mg, 30 mg, or 60 mg once daily.[31] A 24-hour intragastric pH-monitoring study was performed on day 5, with results analyzed for median 24-hour intragastric pH. The study showed an increase in intragastric pH at the higher doses (esomeprazole 80 mg and lansoprazole 60 mg) (Figure 2).

Further studies have shown, however, that splitting the dose and giving the PPI before breakfast and before dinner offers better control than a double dose given once daily. A pharmacokinetic and pharmacodynamic study assessed intragastric pH control in 26 normal volunteers taking 40 mg of esomeprazole before breakfast, or 20 mg twice daily, or 40 mg twice daily.[32] The study showed a substantial increase in intragastric pH control when the second dose was added. A single daily dose of 40 mg controlled intragastric pH for 58% of the 24-hour period, whereas the 40 mg twice-daily dose controlled intragastric pH for 84% of the 24-hour period (approximately 19.5 hours). The 40 mg twice-daily dose seems to be superior to a single daily dose of 80 mg of esomeprazole in controlling intragastric pH; the latter controlled pH for only 15.8 hours in the study noted above.[31]

Another recent open-label, two-way cross-over study of 35 *H. pylori*–negative patients, comparing esomeprazole 40 mg twice daily with lansoprazole 30 mg twice daily (before breakfast and dinner) for 5 days, supports the superiority of twice-daily dosing (Figure 3).[33] The results show an increase in time during which intragastric pH exceeds 4 of about 4 to 5 hours with twice-daily compared with once-daily dosing. Our own database (> 400 intragastric pH studies) suggests that twice-daily PPI controls intragastric pH for 14 to 20 hours and that the twice-daily dose offers approximately 5 additional hours over a single daily dose.[34] Omeprazole-IR, a new formulation of omeprazole, twice daily was superior to pantoprazole twice daily in controlling nighttime pH,[35] and may be of use when high-dose PPI is needed.

Results of Clinical Trials

The therapeutic trials of PPIs for chest pain have assessed high-dose PPIs given for 1, 2, or 4 weeks to patients systematically studied for reduction of pain (Table 1). The first of these studies evaluated omeprazole 40 mg AM and 20 mg PM over 7 days, compared with placebo, in a cross-over study of 37 patients with chest pain at least 3 times per week, who were determined by cardiac evaluation to have noncardiac chest pain.[36] Endoscopy and ambulatory pH monitoring were performed on all patients, with those having an abnormal endoscopy or pH study

Figure 3. *An intragastric pH study showing an increase in the number of hours that pH > 4 when proton-pump inhibitor dose is doubled and given as a twice-daily dose. In this case, the increase is almost 5 hours, suggesting a twice-daily dose is the best way to control pH when increasing proton-pump inhibitor. Reproduced with permission from Johnson et al.*[33]

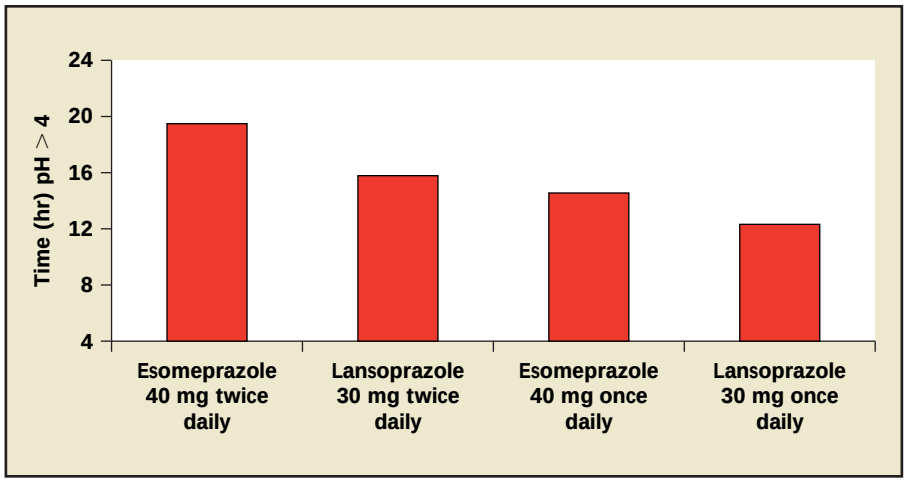


Table 1
Therapeutic Trial of Proton-Pump Inhibitors (PPIs) for Noncardiac Chest Pain

N	PPI	Dose	Duration (days)	Sensitivity (%)	Specificity (%)
37	Omeprazole[36]	40 mg AM / 20 mg PM	7	78	86
56	Lansoprazole[38]	60 mg AM / 30 mg PM	7	78	82
20	Rabeprazole[37]	20 mg bid	7	83	75
42	Omeprazole[39]	40 mg bid	14	71	82
68	Lansoprazole[18]	30 mg/d	30	92	67

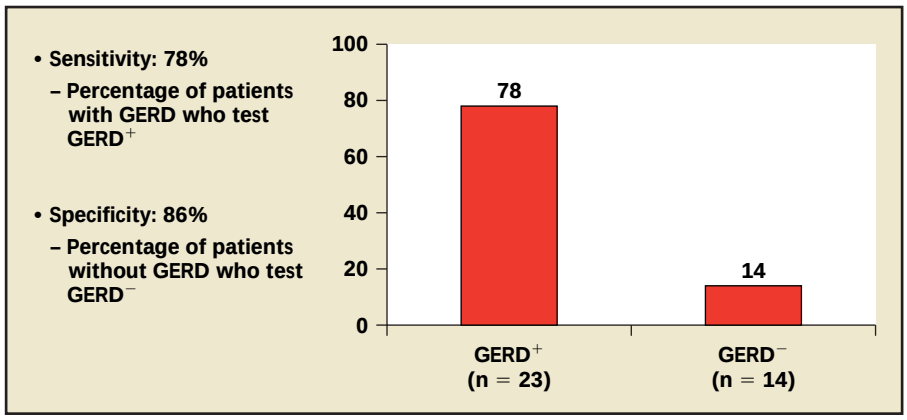
result, or both, determined to be GERD-positive, and those with all study results negative, GERD-negative. Patient chest-pain diaries were assessed daily for 1 week, while on therapy and on placebo, with a washout period in between. The authors found a sensitivity of 78.3% and a specificity of 85.7% for diagnosing GERD in these patients (Figure 4). The positive predictive value of the test was 90% and the negative predictive value, unfortunately, only 70.6%.

The study was repeated in 56 patients with lansoprazole 60 mg AM and 30 mg PM, and subsequently in 20 patients with rabeprazole 20 mg twice daily.[37,38] All 3 studies showed similar outcomes. Another study evaluated 40 mg of omeprazole twice daily for 2 weeks compared with placebo for patients with noncardiac chest pain as determined by a negative technetium sestamibi test. Patients first underwent endoscopy and pH monitoring, followed by the symptom trial with omeprazole 40 mg twice daily. The authors reported that patients with GERD, defined either by a positive result on 24-hour pH study or by the finding of esophagitis on endoscopy, responded to the omeprazole test in 95% of cases, whereas 90% of GERD-negative patients did not respond. However, in patients found to be GERD-negative by these interventions, 39% responded to therapy. Thus, the overall sensitivity was 71% and specificity 82% for the therapeutic trial.[39]

The final study worthy of comment evaluated 68 patients with noncardiac chest pain with 24-hour esophageal pH monitoring, and randomly assigned them to lansoprazole 30 mg once daily or placebo for 30 days.[18] Overall, 53% of patients receiving lansoprazole had improvement in chest pain, compared with 35% of those receiving placebo. The overall response to once-daily lansoprazole was lower than that to twice-daily. The authors found a clear relationship between an abnormal pH test result and a response to a PPI; however, the overall sensitivity and specificity of the 4-week test were 92% and 67%, respectively.

Overall, these studies suggest that a PPI trial is a reasonable first step in the management of these difficult cases. However, the outcome of the test will depend on optimizing the PPI therapy, as well as on the frequency of chest pain. Once-a-day therapy is probably too low, so I prescribe twice-daily in an attempt to maximize pH control. As many patients have pain infrequently (often only once a week or less), I prefer a trial lasting 8 weeks, and use this in my practice as the initial therapeutic and diagnostic intervention. This 8-week time frame is traditionally the one used to treat patients with erosive esophagitis and has been shown in one study of patients with noncardiac chest pain and GERD, documented by 24-hour pH monitoring, to be sufficient to demonstrate improvement over placebo.[40] This study, the only randomized,

Figure 4. *The sensitivity and specificity of a proton-pump inhibitor trial used as a diagnostic test for patients with noncardiac chest pain. GERD$^+$ (gastroesophageal reflux disease–positive) was judged by abnormal endoscopy and/or ambulatory pH findings; GERD$^-$ (GERD-negative), by normal endoscopy and pH findings. *Omeprazole 40 mg AM and 20 mg PM. Data from Fass et al.[36]*



double-blind, placebo-controlled treatment trial with PPIs, compared omeprazole with placebo for 36 patients with noncardiac chest pain and GERD, documented by 24-hour ambulatory pH testing. Patients received 20 mg of omeprazole twice daily or placebo for 8 weeks, and they kept a diary of chest pain frequency and severity. Omeprazole produced a significant decrease, versus placebo, in the fraction of chest-pain days (39% ± 7.2% vs 10% ± 6.9%; $P = .006$) and pain severity (40.7 ± 8.1 vs 14.8 ± 8.2; $P = .03$). Fifteen of 18 patients (83%) receiving omeprazole reported symptomatic improvement, in contrast to only 1 of 18 (6%) in the placebo group.

If the twice-daily trial is successful, the diagnosis of GERD can be considered correct and a long-term management strategy developed. No specific maintenance trials have been done for chest pain, so therapy is individualized. My practice is to continue twice-daily therapy for 6 months, then attempt to reduce therapy to once-daily PPI, as would be the case for patients with erosive esophagitis. If the trial is not successful, the patient should be evaluated (referred) with prolonged reflux monitoring and/or esophageal function testing to look for other continued reflux or etiologies of pain.

Summary

The cardiologist plays the primary role in establishing the etiology of chest pain. If the pain is noncardiac, GERD should be the first alternative etiology excluded. A proton-pump inhibitor trial of therapy seems to be a logical first step, and can be initiated by the cardiologist and followed up by appropriate physicians responsible for long-term care of the patient. ■

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Main Points

- The cardiologist is often the focal point of management of patients with noncardiac chest pain, even after cardiac disease has been ruled out, and can play an important role in their initial therapy.
- The spectrum of gastrointestinal reflux disease (GERD)-related abnormalities in patients with noncardiac chest pain is quite wide; they frequently include typical reflux symptoms of heartburn or acid regurgitation.
- Barium swallow and upper endoscopy have little value in the diagnosis of GERD if alarm symptoms such as dysphagia, weight loss, or gastrointestinal bleeding are absent.
- Prolonged ambulatory esophageal pH monitoring has several disadvantages for patients with noncardiac chest pain. Newly available wireless pH monitoring may afford improvements, but has not been systematically studied in large numbers of these patients.
- A trial of antisecretory (proton-pump inhibitor [PPI]) therapy is the favored mode of "diagnosing" GERD-related noncardiac chest pain while at the same time beginning treatment. This approach is simple, noninvasive, and potentially cost-effective.
- Once-daily PPIs, the standard of care in managing heartburn (as a symptom of GERD) and erosive esophagitis, are insufficient for patients with chest pain and other atypical presentations of GERD.
- Therapeutic trials of PPIs for chest pain have assessed high-dose PPIs given for 1, 2, or 4 weeks to patients systematically studied for reduction of pain. Overall, the results suggest that a PPI trial is a reasonable first step in the management of these difficult cases.
- A trial of twice-daily use of PPI over an 8-week time frame for patients with noncardiac chest pain and GERD is sufficient to demonstrate improvement over placebo. If the trial is successful, the diagnosis of GERD can be considered correct and a long-term management strategy developed.

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