Noncardiac Chest Pain

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Abstract: Noncardiac chest pain (NCCP) affects approximately 1 quarter of the adult population in the United States. The pathophysiology of the disorder remains to be fully elucidated. Identified underlying mechanisms for esophageal pain include gastroesophageal reflux disease (GERD), esophageal dysmotility, and visceral hypersensitivity. Aggressive antireflux treatment has been the main therapeutic strategy for GERD-related NCCP. NCCP patients with or without spastic esophageal motor disorders are responsive to pain modulators. The value of botulinum toxin injection, endoscopic treatment for GERD, and antireflux surgery in alleviating NCCP symptoms is limited.

Key Words: gastroesophageal reflux disease, noncardiac chest pain, nonspecific esophageal motility disorder, lower esophageal sphincter

Noncardiac chest pain (NCCP) is defined as recurring angina-like retrosternal chest pain of noncardiac origin. A patient's history and characteristics do not reliably distinguish between cardiac and esophageal causes of chest pain.[1] This is compounded by the fact that patients with a history of coronary artery disease (CAD) may also experience chest pain of noncardiac origin. The heightened awareness about the potentially devastating ramifications of chest pain may drive patients to seek medical attention despite a negative cardiac workup.[2] Furthermore, almost half of the NCCP patients are not convinced by their negative cardiac diagnosis, and reassurance alone has proved to be an ungratifying therapeutic strategy.[3] Compared with patients having cardiac angina, those with NCCP are usually younger, less likely to have typical symptoms, and more likely to have a normal resting electrocardiogram.[4] Additionally, levels of anxiety of NCCP patients seen in a rapid access chest pain clinic significantly exceeded those of patients with cardiac angina and remained above community norms for at least 2 months after clinic visit.[5] NCCP patients view their condition as significantly less controllable and less understandable than those whose pain is of cardiac origin.[5]

NCCP may be the manifestation of nongastrointestinal (GI) or GI-related disorders (Fig. 1). An important step toward understanding of the underlying mechanisms of NCCP was the recognition that gastroesophageal reflux disease (GERD) is the most common contributing factor for chest pain. Although chest pain has been considered an atypical manifestation of GERD, it is an integral part of the limited repertoire of esophageal symptoms. In patients with non-GERD–related NCCP, esophageal motility disorders and functional chest pain of presumed esophageal origin are the main underlying mechanism for symptoms.

The Rome III Committee uses the term "functional chest pain of presumed esophageal origin" to describe recurrent episodes of substernal chest pain of visceral quality with no apparent explanation. As with all other functional esophageal disorders, GERD and esophageal dysmotility should also be ruled out before the diagnosis is established.[6] Up to 80% of the patients with functional chest pain exhibit other functional disorders, primarily irritable bowel syndrome (27%), and abdominal bloating (22%).[7] The mechanisms responsible for functional chest pain include abnormal mechanophysical properties of the esophagus, central and peripheral hypersensitivity, and psychologic comorbidity (Table 1). The latter may include depression, anxiety, and somatization.

EPIDEMIOLOGY

Information about the epidemiology of NCCP in the United States and around the world is relatively scarce. The mean annual prevalence of NCCP in the general population is approximately 25%, making NCCP the most common atypical/extraesophageal manifestation of GERD. A recent nationwide population-based study from South America[8] found that the annual prevalence of NCCP was 23.5% and that NCCP has been equally reported by both sexes. In this study, frequent typical GERD symptoms (at least once a week) were significantly and independently associated with NCCP. Another recently published epidemiologic study demonstrated that the annual prevalence of NCCP in a Chinese population was 19%.[9]

Although females with NCCP tend to consult healthcare providers more often than men, the disorder affects both sexes equally.[10] Additionally, females are more likely to present to hospital emergency departments
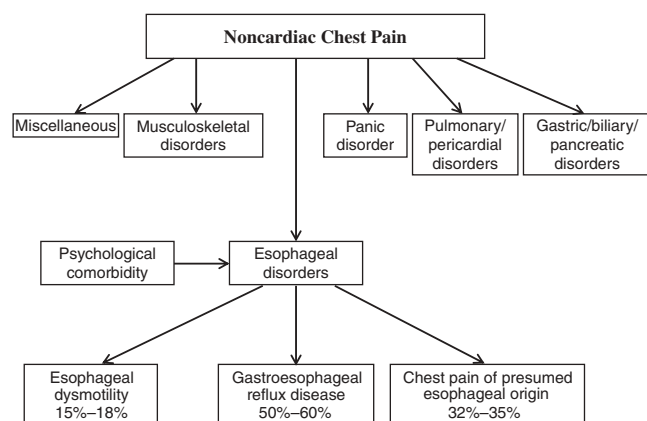
FIGURE 1. The different underlying causes for noncardiac chest pain.

with NCCP than males. However, there are no sex differences regarding chest pain intensity, although women tend to use terms like "burning" and "frightening" more often than men.[11]

Epidemiologic studies report a decrease in the prevalence of NCCP with increasing age. Women under 25 years of age and those between 45 and 55 years of age have the highest prevalence rates.[12] Patients with NCCP are younger, consume greater amounts of alcohol, smoke more, and are more likely to suffer from anxiety than their counterparts with ischemic heart disease. Patients with NCCP continued to seek treatment on a regular basis after the diagnosis was established for both chest pain and other unrelated symptoms, but few are in contact with hospital services.[13]

A recent US-based survey revealed that cardiologists manage by themselves about half of the patients who are diagnosed with NCCP. Of those NCCP patients who were referred, 45.9% were sent back to the primary care physician (PCP), and only 29.3% to a gastroenterologist.[14]

In a survey of PCPs, Wong et al[15] demonstrated that most NCCP patients were diagnosed and treated by PCPs (79.5%), without being referred to a gastroenterologist. The most preferred subspecialty for the initial diagnostic evaluation of a patient presenting with chest pain was cardiology (62%), followed by gastroenterology (17%). However, the mean percentage of such referrals was only 22%. The most preferred subspecialty for

TABLE 1. The Main Proposed Underlying Mechanisms of Functional Chest Pain of Presumed Esophageal Origin

Abnormal mechanophysical properties
  Hyperactive
  ↓Compliance
Visceral hypersensitivity
  Peripheral and central sensitization
  Altered central processing of visceral stimuli (altered autonomic activity)
Psychological abnormalities
  Panic attack
  Anxiety
  Depression

further management of NCCP was gastroenterology (76%), followed by cardiology (8%). However, the mean percentage of the actual referral rate was 29.8% for gastroenterologists and 14% for cardiologists.[15] Eslick and Talley[16] assessed the types of healthcare professionals consulted for chest pain. In their study, the main healthcare professionals seen were PCPs (85%), cardiologists (74%), and gastroenterologists (30%).

NATURAL HISTORY

The long-term prognosis of NCCP patients is excellent and very few eventually succumb to CAD or other cardiovascular-related disorders. In a study that followed 46 NCCP patients over a period of 11 years, only 4.3% died from a cardiovascular-related event.[17] However, most of the NCCP patients continue to report episodes of long-term chest pain. In the previous study, 75% of the surviving NCCP patients continued to report chest pain 11 years later, and 34% reported chest pain symptoms weekly.[17] Furthermore, studies have demonstrated that many NCCP patients have long-term impaired functional status and use healthcare resources because of their chest pain.[18] In one study, the rates of work absenteeism and interruption to daily activities were 29% and 63%, respectively, over a 1-year period.[16]

PATHOPHYSIOLOGY

GERD and NCCP

GERD is by far the most common cause for NCCP. Typical GERD symptoms were found to be significantly and independently associated with the presence of NCCP. NCCP was reported by 37% of the patients who experienced frequent heartburn symptoms (at least once a week) when compared with 30.7% of those with infrequent heartburn symptoms (less than once a week) and 7.9% of individuals reporting no GERD symptoms.[10] A recent population-based study confirmed this finding and demonstrated that the prevalence of NCCP among patients with frequent (at least once a week), occasional (less than once a week), and no GERD was 37.6%, 28.3%, and 12.2%, respectively.[8]

An abnormal pH test occurs in up to 50% of subjects with NCCP.[19,20] In patients with a normal pH test, a positive symptom index (percentage of symptoms that are associated with an acid reflux event) has been suggested to be indicative of GERD-related NCCP. However, Dekel et al[21] reported that a positive symptom index is a relatively uncommon phenomenon in NCCP, primarily owing to the lack of reported chest pain symptoms during the pH test.

Esophageal erosions during upper endoscopy are present in 10% to 70% of patients with NCCP. The wide range is likely because of the different patient populations assessed in these studies. Recently, Dickman et al[22] evaluated upper GI findings in patients with NCCP compared with those having GERD using a national endoscopic database (Table 2). Of the NCCP group, 28.6% had hiatal hernia, 19.6% had erosive esophagitis,

TABLE 2. The Value of Endoscopy in NCCP Patients From a Large Multicenter Consortium (14)

| Findings	Chest Pain Group N = 3688 (%)	Reflux Group N = 32,981 (%)	*P*
Barrett's esophagus	163 (4.4)	3016 (9.1)	< 0.0001
Esophageal inflammation	715 (19.4)	9153 (27.8)	< 0.0001
Hiatal hernia	1053 (28.6)	14,775 (44.8)	< 0.0001
Normal	1627 (44.1)	12,801 (38.8)	< 0.0001
Stricture/Stenosis	132 (3.6)	1223 (3.7)	0.69

NCCP indicates noncardiac chest pain.

4.4% had Barrett's esophagus, and 3.6% had stricture/stenosis. The prevalence of these findings was significantly lower in the NCCP group when compared with the GERD group. The authors concluded that most of the endoscopic findings in NCCP patients were GERD related but less common as compared with GERD patients.

Esophageal Dysmotility and NCCP

In patients with non-GERD–related NCCP, esophageal dysmotility is relatively uncommon. Studies have consistently demonstrated that approximately 70% of the patients with non-GERD–related NCCP have normal esophageal motility during esophageal manometry.[23,24] An exception to the rule is a recent study in 100 NCCP patients demonstrating that only 8% had normal esophageal manometry.[25]

Katz et al[24] reported that the most common esophageal motor disorder in NCCP patients is nutcracker esophagus (Fig. 2). However, Dekel et al[23] reported that hypotensive lower esophageal sphincter (LES) was the most commonly identified esophageal motor disorder (61%) in NCCP patients, followed by hypertensive LES, nonspecific esophageal motility disorder, and nutcracker esophagus (10% each). Rencoret et al[25] evaluated 100 newly diagnosed NCCP patients and demonstrated that 36% had nutcracker esophagus, 28% hypotensive LES, and 16% nonspecific esophageal motor disorder.
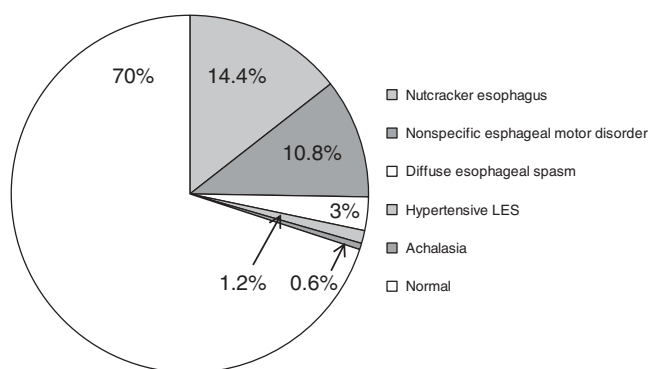
FIGURE 2. Distribution of esophageal motility abnormalities in patients (N = 910) with non-gastroesophageal reflux disease-related noncardiac chest pain (16).

Patients with NCCP and nutcracker esophagus respond symptomatically to antireflux treatment. However, using treatment outcomes as an indirect measure for normalization of esophageal motor function is expected to occur in only a minority of patients who respond symptomatically to antireflux treatment, suggesting that gastroesophageal reflux is the cause of symptoms rather than high-amplitude esophageal contractions.[26]

Overall, the relationship between non-GERD–related NCCP and esophageal dysmotility remains an area of controversy. This is primarily because of the common documentation of esophageal dysmotility in NCCP patients undergoing esophageal manometry without concomitant reports of chest pain symptoms.

Hypersensitivity and NCCP

Several studies using balloon distension or electrical stimulation protocols have demonstrated that patients with non-GERD–related NCCP have lower perception thresholds for pain.[27] Additionally, investigators have suggested that NCCP patients demonstrate altered central processing of intraesophageal stimuli.

Several studies from a research group suggested that a subset of patients with NCCP demonstrate autonomic dysregulation (increased vagal cardiac outflow).[28] The authors further hypothesized that increased perception of esophageal stimulation may also reflect an exaggerated brainstem response. However, in most cases in which both central and autonomic factors are involved, central factors will likely lead to autonomic dysregulation.

Repeated acid exposure of the distal esophagus in NCCP patients can lead to secondary allodynia in the proximal esophagus.[29] Additionally, pain thresholds for somatic pain (chest wall) are also reduced after distal esophageal acid exposure.[29] It is unclear what mechanisms are responsible for the development of visceral and somatic hypersensitivity in NCCP, but central sensitization is likely the cause. It is important to note that other studies[30] in NCCP showed no significant effect on esophageal pain thresholds after acid perfusion into the distal esophagus. Borjesson et al[31] also demonstrated that patients with NCCP have reduced sensitivity to esophageal balloon distension during simultaneous transcutaneous electrical nerve stimulation when compared with healthy controls.

In another study of NCCP patients with documented nutcracker esophagus, stepwise balloon distensions reproduced pain symptoms at a lower threshold in 90% of the NCCP patients when compared with 20% of the healthy controls.[32] This study suggests that patients with NCCP and nutcracker esophagus also exhibit visceral hypersensitivity. Additionally, the latter is likely the main underlying mechanism for patients' symptoms, rather than the presence of the high amplitude contractions (nutcracker esophagus).

Hollerbach et al[33], who studied 20 subjects (8 with NCCP, 12 healthy controls), demonstrated an abnormal cerebral processing of intraesophageal stimuli in patients with NCCP. Cortical-evoked responses were lower in

intensity during electrical esophageal stimulation in patients with NCCP in comparison with healthy controls. Because of the smaller cortical-evoked potentials, it has been hypothesized that the increased perception of esophageal stimuli might in fact be the result of enhanced cerebral processing of visceral sensory input rather than hyperalgesic responses of visceral afferent pathways.[33]

Recently, Sarkar et al[34] evaluated 14 patients with GERD-related NCCP and 8 healthy controls. All subjects underwent esophageal electrical stimulation in the proximal esophagus and those with NCCP demonstrated lower perception thresholds for pain when compared with normal controls.[34] After a 6-week course of high-dose proton pump inhibitor (PPI, omeprazole 20-mg twice daily); however, there was an increase in the perception thresholds for pain during electrical stimulation in the group of patients with NCCP.[34] This study demonstrated that patients with NCCP and evidence of GERD have a component of esophageal hypersensitivity that is responsive to potent antireflux treatment.[34]

NCCP and Psychologic Comorbidity

Psychologic comorbidity has been shown to be common in patients with NCCP. Between 17% and 43% of the patients with NCCP are estimated to suffer from some type of psychologic abnormality.[35] Studies reported a high prevalence of panic disorder (24% to 70%), anxiety (33% to 50%), and major depression (11% to 22%). However, men are less likely to report depression or anxiety when compared with women.[36] Recently, Cheng et al[37] demonstrated that patients with NCCP, when compared with patients with rheumatism and healthy controls, tended to monitor more, use more problem-focused coping, display a coping pattern with a poorer strategy-situation fit and receive less emotional support in times of stress. Additionally, monitoring perceptual style and problem-focused coping were associated with higher levels of anxiety and depression. Overall, studies have demonstrated that central factors, such as stress and psychologic disorders play an important role in enhancing perception of intraesophageal stimuli.[38]

DIAGNOSIS

Patients who present to the clinic or emergency department with chest pain should initially be evaluated for a cardiac cause for their symptoms. The use of the "nitroglycerin test" (repeated sublingual administration of 400 mcg nitroglycerin) to distinguish cardiac from NCCP has been shown to be an unreliable diagnostic tool with very low specificity.[39]

Differentiating the underlying mechanisms of NCCP on a clinical basis has not been a gratifying experience. A recent study could not find significant differences when comparing the quality and characteristics of chest pain in patients with and without GERD-related NCCP.[11] Symptoms evaluated included chest pain site, radiation, and relationship to food, exercise, and sleep. Only chest pain that was relieved by antacids and

the presence of classic GERD symptoms (heartburn and acid regurgitation) were predictive of GERD-related NCCP. The latter findings are supported by a Korean study demonstrating increased GERD-related findings in patients with GERD-related symptoms as compared with those without GERD-related symptoms.[40]

Upper endoscopy has limited value in NCCP patients because most of the mucosal findings are consistent with GERD.[22] In patients with NCCP and alarm symptoms such as dysphagia or odynophagia, upper endoscopy is indicated. Upper GI tumors, either benign or malignant, are extremely rare in patients with NCCP alone.[22] About 4.4% of patients with NCCP demonstrate Barrett's esophagus on upper endoscopy.[22] Thus, patients with GERD-related NCCP should be screened, like other GERD patients, at least once during their lifetime for Barrett's esophagus. The role of upper endoscopy in NCCP patients who failed medical therapy is unknown but is likely to be very low.

The PPI therapeutic trial has markedly changed the role of the 24-hour esophageal pH test in patients with NCCP. Presently, the pH test is used to assess NCCP patients who have failed an empirical therapy with a PPI. Calculating the symptom index was supposed to increase the sensitivity of the pH test. However, only the minority of patients will demonstrate a positive symptom index, because reports of chest pain symptoms are relatively uncommon during a pH test.[41] Prakash and Clouse[42] found that by extending the recording time to 48 hours, using the wireless pH system, the number of subjects recording symptoms during the test increased by 6.8% and the number of symptoms available for association with an acid reflux event was doubled. The study also demonstrated that patients with NCCP benefited the most from extending the duration of the pH test. In another study, the same authors demonstrated that the wireless pH system increased the detection of NCCP patients with an abnormal pH test and/or positive reflux-symptom association probabilities.[43]

A therapeutic trial with a PPI is an attractive diagnostic modality, because of its high sensitivity, simplicity, and availability. The trial uses a short course of high-dose PPI to diagnose GERD-related NCCP. The main requirement of a PPI therapeutic trial is to achieve a significant improvement in symptoms of as many patients as possible within a relatively short period of drug administration. The sensitivity of the PPI therapeutic trial ranges from 69% to 95% and the specificity from 67% to 86%.[44–47] The dosages of PPIs used ranging from 60 to 80-mg daily for omeprazole, 30 to 90-mg daily for lansoprazole, and 40-mg daily for rabeprazole, with a trial duration from 1 to 28 days.

Two recently published meta-analyses[48,49] assessed the performance of the PPI test in NCCP patients. Cremonini et al[48] demonstrated that PPI therapy reduces symptoms in NCCP and may be useful as a diagnostic test in identifying patients with abnormal esophageal acid reflux. However, the authors pointed out that most published studies are small and there is evidence of

publication bias or other small study effects. Wang et al[49] in their meta-analysis concluded that the use of a short PPI therapeutic trial as a diagnostic test for detecting GERD in patients with NCCP has an acceptable sensitivity and specificity and could be used as an initial approach for detecting GERD-related NCCP.

Patients who do not respond to antireflux treatment (non-GERD–related NCCP) are likely to undergo manometry. However, the usefulness of esophageal manometry in NCCP is likely limited to excluding achalasia as the underlying cause of patients' chest pain.

Provocative testing, like the balloon distension test, edrophonium test (Tensilon test), acid perfusion test, ergonovine test, and bethanechol test have all fallen out of favor because of their low sensitivity and potential side effects. Additionally, the introduction of the PPI test eliminated the need for the acid perfusion test.

The role of intraluminal, multichannel impedance, and brain imaging in patients with NCCP remains to be elucidated.

Some patients with NCCP require evaluation by an expert psychologist or psychiatrist because of the high prevalence of psychologic abnormalities in NCCP patients. Appropriate patients for referral are those who seem to be refractory to therapeutic interventions or those who display clear features of a psychologic disorder.

TREATMENT

Treatment for NCCP should be targeted toward the specific underlying mechanism responsible for patient's symptoms (Fig. 3). Table 3 provides general tips for the treatment of NCCP.

GERD-related NCCP

Lifestyle modifications include elevation of the head of the bed, weight loss, smoking cessation, avoidance of alcohol, coffee, fresh citrus juice, and other food products as well as medications that can exacerbate reflux such as narcotics, benzodiazepines, and calcium-channel blockers.[50,51] Although these lifestyle modifications are com-

TABLE 3. General Tips for the Treatment of NCCP

1. GERD-related NCCP	PPIs, double dose for at least 2 mo
2. Dysmotility-related NCCP	Achalasia–Medical, endoscopic, and surgical therapy
	Nutcracker esophagus–Treat for GERD first. If no response, treat with pain modulator
3. Chest pain of presumed esophageal origin	Pain modulators, low dose and at bed time (long term)

GERD indicates gastroesophageal reflux disease; NCCP, noncardiac chest pain; PPI, proton pump inhibitor.

monly advocated as first line treatment in GERD patients, there is no evidence to support their efficacy in GERD-related NCCP. Regardless, enthusiasm about lifestyle modifications is very high among physicians, and thus it is highly likely that GERD-related NCCP subjects will be instructed to follow them.

The efficacy of histamine-2 receptor antagonists (H_2 RAs) in controlling symptoms in patients with GERD-related NCCP has been shown to range from 42% to 52%.[52] In a study, cimetidine (unknown dose) and antacids were shown to be effective in only 42% of the patients with GERD-related NCCP who were followed for a period of 2 to 3 years.[53] Stepping down GERD therapy from a PPI to an H_2 RA has been a disappointing strategy in GERD-related NCCP patients.

Omeprazole (Prilosec) 20-mg twice daily or placebo were administered over a period of 8 weeks to GERD-related NCCP patients in the only fully published double-blind, placebo-controlled trial that has been performed.[54] Patients who received omeprazole had a significant reduction in both the number of days with chest pain and in their chest pain severity scores compared with the patients who received placebo. Thus far, most of the studies assessing the efficacy of PPIs in NCCP primarily used omeprazole. However, it is likely that all other PPIs would demonstrate similar efficacy. In fact, a recent open-label study with esomeprazole (Nexium) administered 40-mg once daily over a period of 1 month demonstrated complete resolution of symptoms in 57.1% of subjects with either NCCP or laryngeal manifestations of GERD.[55] In another open-label study, 85% of NCCP patients reported symptom relief or improvement after receiving PPI twice daily (different brands) for a period of 3 months.[56]

A retrospective review of patients' files revealed that PPIs reduce the number of chest pain episodes, emergency department visits, and hospitalizations owing to chest pain in subjects with documented CAD.[57] It is likely that GERD-related symptoms contribute to the medical-seeking behavior of this patient population.

Patients with GERD-related NCCP should be treated with at least double the standard dose of PPI until symptoms remit, followed by dose tapering to determine the lowest PPI dose that can control symptoms. As with other extraesophageal manifestations of GERD,
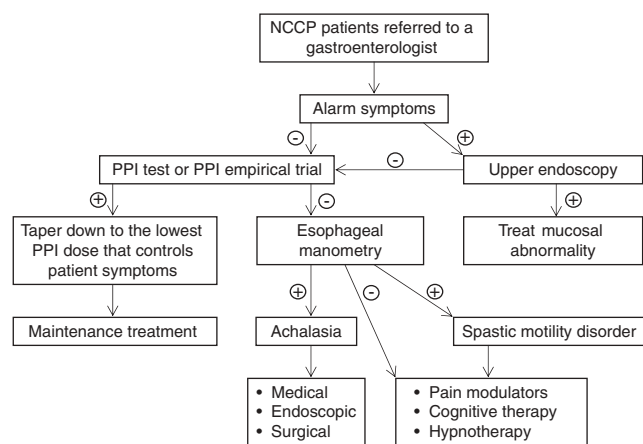
FIGURE 3. Proposed treatment algorithm for patients presenting with noncardiac chest pain.

NCCP patients may require more than 2 months of therapy for optimal symptom control. Long-term maintenance of PPI treatment has been shown to be highly effective.[38] Borzecki and colleagues[58] developed a decision tree to compare empiric treatments for NCCP patients with H_2 RAs or standard-dose PPI for 8 weeks with initial investigations (upper endoscopy or upper GI series). Empiric treatment was more cost effective in the initial investigation strategy, with a cost of $849 per patient versus $2187 per patient.

The value of antireflux surgery in GERD-related NCCP is unclear. Several studies have demonstrated a significant improvement in symptoms after laparoscopic fundoplication in patients with GERD-related NCCP. For instance, Patti and associates[59] reported improvement in chest pain symptoms after laparoscopic fundoplication in 85% of patients with GERD-related NCCP. In addition, Farrell and coworkers[60] reported that 90% of NCCP patients who underwent antireflux surgery experienced improvement in chest pain and 50% reported complete symptom resolution. In contrast, So and colleagues[61] reported that after laparoscopic fundoplication, relief of atypical GERD symptoms (eg, chest pain) was less satisfactory than relief of typical GERD symptoms (eg, heartburn). In their study, the authors evaluated symptom improvement with a questionnaire given 3 months and 12 months after antireflux surgery. Overall, heartburn was relieved in 93% of patients, whereas only 48% of patients reported relief of chest pain symptoms.

Non-GERD–related NCCP

The treatment of non-GERD–related NCCP is primarily based on esophageal pain modulation (Table 4). An important development in this field was the recognition that NCCP patients with spastic esophageal motor disorders (except achalasia), as documented by esophageal manometry, are more likely to respond to pain modulators than to muscle relaxants. Unfortunately, no large, well-designed studies to assess pain modulators in patients with non-GERD–related NCCP have been performed.

Several recent studies have shown that most NCCP patients are managed by cardiologists and PCPs who seem to know little about the role and treatment of esophageal hypersensitivity in NCCP.[14,15,62] Even gastro-

TABLE 4. Therapeutic Modalities for Non-GERD–related NCCP

Muscle relaxants (nitrates, calcium channel blockers)
Botulinum toxin
Pain modulators (trazodone, tricyclic antidepressants, serotonin reuptake inhibitors, theophylline)
Surgery for motility disorders
Cognitive-behavioral therapy/hypnotherapy

GERD indicates gastroesophageal reflux disease; NCCP, noncardiac chest pain.

enterologists seemed somewhat uninformed about the role of visceral hypersensitivity in NCCP.[63]

Nitroglycerin and long-acting nitrates cause relaxation of GI smooth muscles by stimulating cyclic guanosine monophosphate (GMP)-dependent pathways. Several open-label studies have reported that nitrates improve symptoms and esophageal motility patterns in patients with chest pain and esophageal dysmotility. Several investigators reported symptomatic improvement in patients with diffuse esophageal spasm (DES), accompanied by normalization of esophageal motility during treatment with nitrates.[64,65] In a small study, 5 patients with DES experienced a 4-year clinical and manometric remission.[66] However, other studies have failed to demonstrate similar efficacy.[67,68] Long-acting nitrates in doses of 10 to 20 mg, 2 to 3 times daily, as well as short-acting, sublingual nitrates for acute episodes of chest pain in NCCP patients, were used in these studies.

Overall, studies that evaluated the value of nitrates in NCCP have been limited by small number of patients and inconsistent results in regard to drug efficacy. A placebo-controlled trial that excludes patients with GERD has yet to be performed.

As calcium plays an important role in esophageal muscle contraction, the role of calcium channel blocking agents in patients with NCCP and esophageal spastic motility disorders has been the focus of investigation. Nifedipine (10 to 30 mg PO, t.i.d.) decreases the amplitude and duration of esophageal contractions in patients with nutcracker esophagus after only 2 weeks.[69] Unfortunately, the effect of the drug disappeared after 6 weeks of treatment with the complete recurrence of symptoms. Davies and associates[70] used a placebo-controlled trial to assess the efficacy of nifedipine in the prevention of symptomatic episodes of esophageal spasm in 8 NCCP patients over a 6-week period. The authors were unable to find statistically significant differences in symptom improvement between the 2 therapeutic arms. In contrast, symptom improvement was noted in 20 NCCP patients with various esophageal motility disorders, including hypertensive LES, nutcracker esophagus, DES, and vigorous achalasia, treated with nifedipine (10 mg PO, t.i.d.).[71] Nifedipine was also found to significantly decrease LES resting pressure, with a direct correlation to the plasma levels of drug.[72]

Diltiazem (60 to 90 mg PO, q.i.d.) for 8 weeks significantly improved mean chest pain scores and esophageal motility studies in patients with nutcracker esophagus when compared with placebo.[73,74] However, in a study evaluating 8 patients with DES, the effect of diltiazem in relieving chest pain was not different from the effect of placebo, probably because of the small number of patients who participated in the study.[75]

Other calcium channel blockers have been evaluated in patients with primary esophageal motor disorders including verapamil, fendiline, nimodipine (Nimotop, Bayer), and nisoldipine (Sular, Sciele), with various effects on LES resting pressure and esophageal amplitude contractions. Regardless, calcium channel blockers seem

to have a transient esophageal motor effect that translates to a short-lived improvement in symptoms, compounded by a variety of side effects such as hypotension, bradycardia, and pedal edema.

Sildenafil (Viagra, Pfizer) is a potent selective inhibitor of cyclic GMP-specific phosphodiesterase type 5, which inactivates the nitric oxide-stimulated GMP. Intracellular accumulation of the latter induces smooth muscle relaxation. The drug has been shown to improve esophageal motility in patients with nutcracker esophagus or hypertensive LES by lowering LES resting pressure, reducing distal esophageal amplitude contractions, and prolonging the duration of LES relaxation.[76,77] However, thus far, there have been no studies that specifically addressed NCCP patients, so the value of this compound in NCCP remains unknown. Additionally, the usage of this compound in NCCP will likely be limited by its cost and side effects.

The antispasmodic cimetropium bromide has been shown to be efficacious in 8 NCCP patients with nutcracker esophagus when taken intravenously,[78] but clinical data regarding the efficacy of an oral formulation are still lacking. Hydralazine, an antihypertensive compound that directly dilates peripheral vessels, was shown to improve chest pain and dysphagia by decreasing the amplitude and duration of esophageal contractions in a small study of only 5 patients.[68] Overall, evidence to support the therapeutic benefit of anticholinergic agents for the treatment of NCCP remains very limited.

Pain Modulators

Visceral hyperalgesia is thought to be the primary underlying mechanism of patients with non-GERD–related NCCP, regardless of the presence or absence of esophageal motor disorder. Consequently, drugs that can alter esophageal pain perception have become the mainstay of therapy in these patients.

Several drugs have been shown to have a pain modulatory or a visceral analgesic effect, thus alleviating chest pain symptoms. These drugs include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors, theophylline, and trazodone.

Several studies have demonstrated that antidepressants have a visceral analgesic effect,[79] but they also seem to inhibit calcium channels and thus may have an additional muscle relaxant-like effect.[80] TCAs have both central neuromodulatory and peripheral visceral analgesic effects. Several clinical trials have found favorable TCA-related effects on esophageal pain perception in both healthy subjects and patients with NCCP.

Imipramine, administered at a dose of 75-mg daily, significantly increases the pain threshold of healthy men during intraesophageal balloon distension as compared with baseline.[81] In another study, 60 patients with NCCP and normal coronary angiography were randomized to receive clonidine (0.2-mg daily), imipramine (50 mg nightly), or placebo for a period of 3 weeks. Patients who received imipramine had a significant (52%) reduction in the frequency of chest pain episodes, independent

of cardiac, esophageal, or psychiatric test results, suggesting that imipramine has a visceral analgesic effect on chest pain.[82] In contrast, amitriptyline failed to show an effect on both perception and esophageal compliance in subjects undergoing balloon distention protocol.[83]

Because of their anticholinergic side effects, TCAs are commonly administered at nighttime. On the basis of our experience, it is recommended that TCA doses are slowly titrated to a maximum of 50-mg daily. The incremental increase in dosing should be based on symptom improvement and development of side effects.

Trazodone (100 to 150 mg PO, q.i.d.) for 6 weeks, showed a significant improvement in the symptoms of patients with NCCP and esophageal dysmotility as compared with placebo.[84] However, esophageal motility abnormalities remained unchanged. A small, open-label study reported symptom control and improved esophageal motility in patients with NCCP and DES after the treatment with both trazodone and clomipramine.[85]

A randomized trial assessing the effect of sertaline in patients with NCCP demonstrated a significant reduction in pain scores, regardless of concomitant improvement in psychologic scores.[86] In addition, a recent study demonstrated that citalopram, given 20-mg intravenously in a single dose, reduced chemical and mechanical esophageal hypersensitivity without altering the esophageal motility.[87]

Octreotide, a synthetic analog of somatostatin, has been shown to increase rectal and sigmoid perception thresholds for pain in irritable bowel syndrome subjects, and healthy subjects.[88,89] It has been postulated that the effect of octreotide is mediated by the activation of somatostatin receptors at the spinal cord and/or the supraspinal level.

Octreotide, administered 100-mg subcutaneously, was found to significantly increase perception thresholds for pain as compared with placebo in healthy subjects undergoing intraesophageal balloon distention.[90] Unfortunately, because of the cost and the lack of an oral formulation, octreotide is rarely used for NCCP in clinical practice.

Theophylline, a xanthine derivative, has been shown to inhibit adenosine-induced angina-like chest pain and adenosine-induced pain in other regions of the body.[91] A study using an esophageal balloon distention protocol and impedance demonstrated that intravenous theophylline increased thresholds for sensation and pain in 75% of patients with functional chest pain.[92] Similar results were documented in functional chest pain patients receiving oral theophylline for a period of 3 months. In another study, the same authors showed that oral doses of theophylline 200-mg twice daily was more effective than placebo in preventing chest pain in 19 patients with functional chest pain.[93]

Alprazolam has been shown in a study to ameliorate chest pain at a mean dose of 4.3-mg daily in patients with NCCP and panic disorder.[94] In this study, 15 out of 20 patients reported at least a 50% reduction in panic attack

episodes and a corresponding decline in the frequency of chest pain episodes. Clonazepam, given 1 to 4-mg daily, was also shown to be effective in the treatment of patients with NCCP and panic disorder.[95] The treatment of a functional disorder such as NCCP with benzodiazepines has been greatly discouraged, primarily owing to the likelihood of becoming addicted to this class of drugs.

5-HT, also called serotonin, is a neurotransmitter present in the central nervous system, enteric neurons, and extrinsic afferents of the gut. It is involved in visceral perception and motor activity processes in the GI tract.[96] Ondansetron, a 5-HT$_3$ antagonist that is used as an antiemetic, has been shown to increase esophageal perception thresholds for pain in patients with NCCP.[96] The selective 5-HT$_4$ receptor agonist tegaserod (Zelnorm, Novartis) has been demonstrated to reduce both chemoreceptor sensitivity to acid and mechanoreceptor sensitivity to balloon distention in patients with functional heartburn.[97] Thus far, there are no studies assessing the value of tegaserod in patients with non-GERD–related NCCP.

Endoscopic Treatment and Surgery for NCCP

Botulinum toxin (BoTox, Allergan) interacts selectively with cholinergic neurons to inhibit the release of acetylcholine at the presynaptic terminals. Botulinum toxin injection into the LES has been used in several uncontrolled trials that included patients with NCCP and documented esophageal spastic motility disorder. Injecting botulinum toxin into the LES in a small, uncontrolled study resulted in 50% reduction of chest pain episodes in 72% of the subjects for a mean duration of 7.3 months.[98]

Laparoscopic fundoplication relieves heartburn and acid regurgitation in most patients with GERD, but its effect on chest pain is less clear. DeMeester and associates[53] identified a temporal correlation between chest pain and acid reflux events in 12 of 23 patients with NCCP. Chest pain resolved in all 12 patients treated either by surgery (8 patients) or acid-reducing agents (4 patients). Patti and coworkers[59] reviewed patients who complained of chest pain in addition to heartburn and acid regurgitation. Overall, chest pain improved in 85% of these patients after undergoing laparoscopic fundoplication for GERD. Improvement in chest pain increased to 96% in patients whose chest pain correlated with GERD most of the time. Farrell and colleagues[60] evaluated the effectiveness of antireflux surgery for patients with atypical manifestations of GERD. Chest pain improved in 90% of patients after laparoscopic fundoplication, with symptom resolution in 50% of patients. Although surgical studies demonstrated a high success rate of antireflux surgery in GERD-related NCCP patients, the patients included were carefully selected.

Very few studies to date have specifically evaluated the value of endoscopic treatment for GERD in patients with GERD-related NCCP. Liu et al[99], who treated 18 NCCP patients with endoluminal gastroplication, demonstrated short-term symptomatic response (6 mo) in 72% of them. During long-term follow-up (1 to 3 y), 75% of

nonresponders became symptom free, and 40% of responders became symptomatic.

Psychologic Treatment

Psychologic comorbidity, mainly depression and anxiety, is common in patients with NCCP. Psychotherapy may be helpful in the treatment of patients with NCCP, particularly those who also have hypochondriasis, anxiety, or panic disorder.

Several studies have demonstrated that patients with NCCP who are treated with cognitive-behavioral therapy report significant improvement in quality of life and reduction in chest pain symptoms. Additionally, cognitive behavioral therapy has been successfully used for the treatment of NCCP patients without an existing panic disorder.[100] A study evaluating patients who were treated with cognitive-behavioral therapy reported that 48% of these patients remained pain free at 12-month follow-up, as compared with only 13% of the patients in the nonintervention group. Other psychologic interventions that have been suggested to be effective in patients with NCCP include reassurance, education, relaxation techniques, breathing training, and biofeedback. Biofeedback was assessed in a study that compared it with primary care visits only in patients with NCCP.[101] Patients in the biofeedback group demonstrated a significantly lower symptom frequency and severity. However, a large group of patients assigned to the biofeedback arm (52%) did not complete the study.

Hypnotherapy has been recently evaluated in the treatment of NCCP patients. Jones and colleagues[102] reported an 80% improvement in symptoms, with a significant reduction in pain intensity, among patients who were receiving 12 sessions of hypnotherapy, compared with only a 23% symptom improvement in the control group. The study concluded that hypnotherapy seems to have a role in treating NCCP and that further studies are needed.

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