

# Provocation Testing in Noncardiac Chest Pain

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The ability to reproduce chest pain and to identify the esophagus as the source of this pain are the major reasons why provocation testing has become standard in the evaluation of patients with noncardiac chest pain. Recent studies that challenge the validity of performing provocation tests have polarized experts into two camps: those who would abandon such testing because of its low sensitivity and low specificity, and those who would use testing judiciously because of moderate increases in diagnostic yield. Use of 24-hour pH and pressure testing has shown a high number of chest pain events associated with acid reflux in patients with positive cholinergic stimulation tests and esophageal dysmotility, as well as pain with esophageal dysmotility in patients with positive acid infusion tests. Mechanisms of esophageal chest pain are not known. All provocation agents can decrease coronary flow reserve (i.e., induce microvascular angina), thus raising the question of a cardiac source of pain even in patients with positive presumed esophageal provocation. Acid infusion, cholinergic stimulation, and balloon distention are discussed in light of 24-hour pH and pressure monitoring. Esophageal distention and the role of acid in inducing chest pain are emphasized. The role of stress, the use of defined stressors to induce chest pain, and altered pain perception as a final common pathway for chest pain are examined.

Provocation testing has become standard in the evaluation of patients with noncardiac chest pain [1-3]. Acid infusion, cholinergic stimulation, and balloon distention are the most commonly used provocation tests. Provocation testing allows the physician to reproduce the spontaneous pain felt by the patient, thereby increasing the power of provocation testing over standard manometry, which rarely connects pain with a motility abnormality. Controversy over the role of provocation testing stems from a lack of knowledge of the mechanisms for spontaneous and provoked chest pain and from rapid proliferation of new pain provocation methods that do not have adequate confirmation from laboratories [4-6]. Other factors that complicate the interpretation of studies of noncardiac chest pain and provocation testing include problems in patient selection and an inadequate database of normal esophageal motility and acid exposure over long periods of observation. This article will review the controversies about provocation testing, discuss data on commonly used provocation agents and how they produce chest pain, and summarize how provocation testing is best used in evaluating patients with noncardiac chest pain.

## CONTROVERSIES IN PROVOCATION TESTING

The role of provocation testing is still poorly defined. Experts have decried the rapid proliferation of provocation tests without adequate corroboration and the lack of proof that a positive provocation test implicates the esophagus as the cause of chest pain [4]. Microvascular angina has been proposed as the cause of chest pain in most patients with presumed noncardiac chest pain [4,7,8]. Others have agreed that esophageal dysmotility is an uncommon cause of chest pain, but, because acid has produced chest pain [5,9], investigators have identified gastroesophageal acid reflux as a cause of chest pain in 35-50% of patients with chest pain and normal coronary arteries [5,6]. Other stimuli may also be important in producing chest pain. Distention through stimulation of mechanoreceptors may be an extremely common mechanism. Both esophageal dysmotility (by producing esophageal distention proximal to a functionally contracted segment) and acid reflux (by bolus esophageal distention) may produce pain through this mechanism rather than through smooth muscle contraction or acid sensitivity, respectively [2,3,10].

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Why is there so much controversy about the role of the esophagus in patients with chest pain and the role of provocation testing in eliciting this pain? The basis of the controversy lies in three questions: (a) What is the mechanism of esophageal chest pain? (b) Is provoked chest pain the same as spontaneous chest pain? (c) Does a positive provocation test implicate the esophagus as the cause of chest pain?

#### What Are the Mechanisms of Esophageal Chest Pain?

The precise abnormality in esophageal function that produces chest pain is not known. For a number of reasons, abnormalities in contraction amplitude and duration alone are unlikely causes: (a) they are frequently found in baseline recordings of asymptomatic patients [11,12]; (b) treatment that lowers pain scores in patients with noncardiac chest pain does so without changing esophageal motility parameters [13,14]; (c) calcium channel antagonists (which effectively decrease both esophageal body and lower esophageal sphincter pressures) frequently are ineffective in treating presumed esophageal chest pain [14,15]; (d) spontaneous high-amplitude, long-duration esophageal contractions have been associated with chest pain but occur as frequently without pain [16,17]; (e) an absence of contraction may be seen during chest pain [18,19]; and (f) esophageal dysmotility in association with chest pain occurs in only 10–25% of documented chest pain events during 24-hour esophageal pH and pressure recordings [20–22].

Acid reflux into the esophagus may induce chest pain by several mechanisms. Chemoreceptor stimulation by hydrogen ions is presumed to be the most common cause. In one study, acid-induced microvascular damage occurred early in the course of acid esophageal injury, before microscopically visible inflammation was present, and it increased with increasing acid loads [23]. This acid-induced damage may be associated with pain. Of 25 symptomatic gastric acid reflux patients, all had pain reproduced during infusion of highly acidic solutions (pH 1.0), whereas 50% reported pain after infusions of less acidic solutions (pH as high as 6) [24]. Other factors that influenced the incidence of chest pain were duration of acid exposure and the number of previous chest pain events: of patients with chest pain, 80% had acid exposure times >10 minutes and previous chest pain events. This raises the possibility that acid may induce pain by other mechanisms [24,25], such as volume distention of the esophagus or by increasing visceral pain perception.

The most common cause of chest pain during acid infusion was initially thought to be dysmotility [26]. Simultaneous and spontaneous distal esophageal contractions of increased amplitude and duration were seen in most patients during Bernstein test-

ing [26]. However, this has not been reproduced by other investigators [27,28]. Changes in amplitude and duration of contraction occurred equally in normal subjects and in patients with symptomatic reflux [27], and 24-hour pH and pressure monitoring studies have shown that most acid-induced chest pain events occur without dysmotility [9,20–22]. Other mechanisms for chest pain during esophageal acid perfusion, such as interactions between pepsin and other barrier breakers, as well as coronary and esophageal ischemia, have had some experimental support but have either not been studied adequately in chest pain patients or are unlikely to be sufficient to produce chest pain [5,10]. Recent studies have demonstrated that chest pain patients had a higher pain response after acid infusion (35%) than after cholinergic stimulation with edrophonium (20%) [25]. However, 11 of the 12 patients responding to edrophonium also responded to acid infusion, suggesting a common mechanism for pain other than chemoreceptor stimulation by hydrogen ions.

Distention of the esophagus is an effective means of producing chest pain. Chest pain patients may be more sensitive to distention than controls. Chest pain patients develop more chest pain and at lower distention volumes than do normal subjects [29]. This distention-induced pain occurred without a change in amplitude or duration of esophageal contraction proximal or distal to the distended segment.

Enhanced pain perception as a cause of chest pain has received increasing support [10,13,30,31]. Altered pain perception could bring together under a single mechanism all the known ways of producing esophageal pain, such as acid, inflammation, dysmotility, balloon distention, as well as food and temperature induction. Recent studies using esophageal balloon distention and electrical stimulation have shown definite and reproducible cerebral evoked potentials after stimulation [31–33]. Clinical studies in patients with chest pain are awaited.

#### Is Provoked Esophageal Chest Pain the Same as Spontaneous Chest Pain?

Baseline recordings of the esophagus in patients with chest pain have shown a high percentage of patients with abnormal baseline motility (25–33%). Of these patients, nonspecific esophageal dysmotility and “nutcracker esophagus” were observed in >80% [11,12]. Provocation testing increases the diagnostic yield by 20–55%, with cholinergic stimulation accounting for 80–90% of the increase, whereas acid perfusion increases the number of patients with definable esophageal chest pain by only 7% [11,12,34]. Unfortunately, baseline dysmotility does not predict a higher percentage of

patients with provoked chest pain, raising the question of the role of baseline esophageal dysmotility in producing chest pain [5,6,34]. Using criteria suggested by Lee *et al* [35], investigators reported that amplitude of contraction exceeded baseline levels by 20 mm Hg in 87% of chest pain patients during pain but also in 69% of chest pain patients who did not develop pain and 68% of normal subjects [35,36]. No clear-cut level of abnormality in any esophageal manometric parameter discriminated between patients with and without pain. Only duration of contraction consistently has been shown to increase after cholinergic stimulation; a lack of increases in duration of contraction after cholinergic stimulation is highly predictive of a chest pain patient who will not develop chest pain during provocation testing [11,12,36]. Some investigators have abandoned esophageal contractive response and use only pain reproduction as an end point for a positive provocation test [5,6,36].

Use of 24-hour pH and pressure monitoring allows physiologic evaluation of both normal subjects and patients with chest pain [17,20-22]. In one study, 36% of pain events were explained by abnormal motility or acid reflux, with the latter accounting for two thirds of all esophageal pain events [21]. Janssens and coworkers [22] have used 24-hour monitoring to show that up to 60% of pain events have a potential esophageal origin. In these studies, however, a high percentage of patients (33%) had true angina, and an even higher percentage (44%) had unequivocal esophageal symptoms such as heartburn or dysphagia. The incidence of exercise-induced angina pectoris in the study by Janssens and coworkers [22] was 33%, with 44 of 60 patients having symptoms of heartburn or dysphagia.

When standard esophageal testing was compared with 24-hour pH and pressure monitoring, there was discordance of testing [37]. Patients with nutcracker esophagus were equally likely to have dysmotility or acid as causes for their spontaneous chest pain events, whereas patients with normal manometry were significantly more likely to have chest pain related to acid reflux. A positive acid perfusion test was significantly associated with abnormal pressure events, while a positive edrophonium test was more commonly associated with acid reflux pain. Thus, ambulatory monitoring may give completely different mechanisms for chest pain than those predicted by standard motility testing and esophageal acid perfusion studies, despite the fact that patients felt the provoked pain was identical to their spontaneous pain. Others feel that standard manometry, Bernstein testing, and 24-hour pH and pressure monitoring add little to chest pain evaluation (<20% yield overall) [20].

### Does a Positive Provocation Test Implicate the Esophagus?

A positive acid perfusion or cholinergic stimulation study has been presumed to indicate an esophageal origin for pain [2-6]. Mellow *et al* [38] first suggested that esophageal acid perfusion could induce coronary ischemia. Of patients with infrequent reflux symptoms, 64% had angina during acid perfusion tests, and 56% of patients with coronary disease who developed chest pain during esophageal acid infusion could not distinguish that pain from their usual angina [38]. In 10 of 12 patients with known coronary artery disease, exertional angina threshold was lowered significantly after acid infusion compared with saline controls [39]. The decreased threshold was more pronounced in patients with regular esophageal symptoms than in those without symptoms. In addition, both esophageal dysmotility and acid decrease coronary flow reserve, which may lead to "microvascular angina," a syndrome that may be associated with chest pain [40]. During atrial pacing and ergonovine stimulation, 83% of patients with esophageal dysmotility had abnormal coronary flow resistance and 67% developed angina with provocation [40,41]. Thus, dysmotility may produce chest pain by decreased coronary blood flow, and both esophageal dysmotility and coronary flow resistance may be a generalized disorder of smooth muscle function. As stated, however, mechanisms of esophageal chest pain are not known.

### SPECIFIC PROVOCATION TESTS

#### Food and Temperature

Some patients state that certain foods or cold liquids precipitate their chest pain. Mellow showed that food ingestion could produce esophageal dysmotility not evident at baseline in chest pain patients [42]. Dysmotility was enhanced if bethanechol, a cholinergic agonist, was coadministered. The rate of positive examinations in patients with food-associated symptoms was 100%, even though standard esophageal manometry was negative in all patients. In a retrospective analysis of 100 consecutive patients with chest pain, dysphagia, or both, food ingestion produced significantly more dysmotility in patients with dysphagia than did water swallows (79 vs 43%), and dysphagia was reproduced in 47% of patients [43]. Chest pain rarely was reported after food ingestion.

Low-temperature liquids also can incite chest pain. Unlike food ingestion, which enhances nonperistaltic contractions and incomplete lower esophageal sphincter relaxation, ice water most commonly produces chest pain and a complete absence of motor activity in affected persons [43,44].

Esophageal cooling brings on a transient state of relative paralysis in the distal esophagus and lower esophageal sphincter, with increased nonperistaltic waves, reduced peristaltic strength, increased duration and reduced velocity of distal esophageal contractions, and reduced lower esophageal sphincter pressure [19,45,46]. In animal models, these factors have all been associated with esophageal distention. Esophageal wall ischemia may be another mechanism. A selective decrease in mucosal blood flow could allow increased acid back-diffusion or altered sensory receptor function. The time for esophageal wall rewarming after cold water challenge was longer in 9 patients with esophageal spasm or nutcracker esophagus than in 21 normal subjects (90 vs 44 seconds); only 1 patient had a normal esophageal rewarming time [47]. Age or gender did not affect the results. Whether true mucosal ischemia occurs awaits confirmation by techniques allowing study of blood flow in different layers of the human esophagus. As with food ingestion, cold liquid precipitation of chest pain is seen in <5% of chest pain patients [45,46].

Hyperosmolarity and stimulation of esophageal chemoreceptors as a mechanism for esophageal chest pain were first reported by Lloyd [47]. Hypertonic saline, sucrose, and, most recently, hypertonic glucose [48,49] have been used as provocation tests for chest pain, but comparative studies have shown that they clearly are inferior to standard agents [48,49].

#### Acid Infusion Test (Bernstein Test)

The acid infusion (Bernstein) test is used to detect patients with presumed gastroesophageal reflux and acid-induced pain [50,51]. Acid infusion studies are negative if the patient has no pain, positive if the usual pain is reproduced, and indeterminate if some discomfort occurs but does not simulate the patient's spontaneous pain [50–53]. Relief with saline is frequently used to confirm the diagnosis but requires a much longer examination and may be falsely negative even in patients with documented reflux [53]. Behar *et al* showed that, using heartburn as the end point, sensitivity and specificity approached 80% [52]; patients with esophagitis were invariably positive. False-positive rates of 10–20% were seen in both normal subjects and patients with peptic ulcer disease.

Recent studies cast doubt that positive acid infusion testing is either specific or sensitive for gastroesophageal reflux [2,9,25,50]. Acid infusion can induce chest pain in normal subjects with no definable reflux during 24-hour pH testing [9]. Anginal chest pain also can be induced by acid. Sensitivity of acid infusion with chest pain as the end point has an inci-

dence of 7–64% [50–53]. Hewson *et al* [9,50] demonstrated that acid sensitivity was uncommon in 100 consecutive chest pain patients (19%), while abnormal 24-hour pH reflux parameters and/or a positive symptoms index were positive in 46% and 60%, respectively; these results limit the role of acid infusion testing in laboratories with 24-hour monitoring capability. Preliminary studies in our laboratory have indicated that 24-hour pH monitoring is more predictive for antacid treatment response than Bernstein testing. Relief of chest pain after 4 weeks of acid-suppressive therapy (omeprazole 20 mg every morning) was the reference for response. Patients with endoscopically visible esophagitis or positive distal esophageal biopsies were excluded. A total of 70 patients with persistent noncardiac chest pain were treated empirically; clinical response occurred in 53 patients (76%) at 4 weeks. Of responders, 48 (90%) had abnormal 24-hour pH monitoring, but only 24 (45%) had a positive Bernstein test. Of the 17 patients not responding to empiric therapy, only 1 had abnormal pH monitoring and 5 had a positive Bernstein test. Bernstein testing frequently may be positive in patients with clear-cut esophageal dysmotility as a cause of their chest pain. Of the 5 patients with a positive Bernstein test, 4 had positive bethanechol provocation with documented simultaneous esophageal dysmotility.

#### Edrophonium Stimulation

Edrophonium chloride, an anticholinesterase, is the current cholinergic stimulant of choice for testing patients with noncardiac chest pain. In normal subjects, chest pain following edrophonium stimulation rarely is seen (<4%), but a rapid bolus infusion of edrophonium induces chest pain in 25–33% of patients with noncardiac chest pain. If both chest pain and manometric changes are required, the reported positivity rates decline to 3–9% [11,54,55], except in a study by Lee *et al*, who found a higher percentage of positive patients even if manometric changes were required (34%) [35]. Their use of dry swallows may have increased perceived motility abnormalities, since dry swallows frequently produce simultaneous and repetitive contractions [35,36]. A standard 10 mg dose rather than a fixed dose per kilogram will produce a greater duration of contraction, a slightly increased level of significant side effects (compared to a fixed dose), but a lower frequency of significant side effects when compared with bethanechol (33 vs 45%, respectively) [55].

Edrophonium has no effect on coronary artery diameter and decreases cardiac work, making a cardiac source for edrophonium-induced pain unlikely

[54,55]. Several investigators have confirmed these results [2,3,25,35].

One of the few studies comparing edrophonium with other provocation tests evaluated acid infusion, bethanechol, and edrophonium in consecutive patients with noncardiac chest pain [34]. Edrophonium was superior although the yield was low (18%); acid infusion was the least useful examination. Chest pain without manometric abnormalities was as frequent as that with motility abnormalities. In contrast, in a study of 60 consecutive patients, De Caestecker *et al* [25] demonstrated that acid infusion had a higher yield than edrophonium. Most responders to edrophonium also responded to acid infusion. Even those with primary motility disorders responded to acid infusion, suggesting a common cause for pain production during acid infusion and edrophonium challenge [25].

Patient selection strongly influences the rate of positive responses to edrophonium. Higher rates of positive responses are reported in coronary care-unit patients [56], those with exercise-induced chest pain [2,12,56,57], those with ergonovine positivity during cardiac catheterization [56-62], and those with positive gastrointestinal symptoms [2,3,11], whereas patients with no associated gastrointestinal symptoms had the lowest yield of positive results [12,25]. The presence of baseline esophageal dysmotility did not predict a higher rate of positive responses than that in patients with normal baseline motility [23].

At this time, edrophonium should be considered the standard cholinergic provocation agent because of its low side-effect profile and ease of administration. Unfortunately, cholinergic stimulation at the currently accepted doses will give low yields of positive responses and may be replaced by more physiologic systems such as 24-hour pH and pressure monitoring and esophageal balloon distention.

### Bethanechol

Bethanechol, a cholinergic agonist, was first described as inducing motor abnormalities in patients with documented primary esophageal motility disorders such as achalasia and diffuse esophageal spasm [2,3,62,63]. Subcutaneous injection of bethanechol at doses of 40-50  $\mu\text{g}/\text{kg}$  induces chest pain in 12-33% of chest pain patients [2,3]. Our group reported positive pain reproduction in 77% after two subcutaneous doses of bethanechol (50  $\mu\text{g}/\text{kg}$ ) [12]. Why was the yield in our study so much greater than that in previous studies and greater than in a recent study using a single dose of bethanechol 80  $\mu\text{g}/\text{kg}$  [64]?

Retrospective analysis identified three factors

that may have influenced the results. The first was patient selection. Patients with true angina and those with positive ergonovine testing have a higher rate of positive responses to cholinergic stimuli such as bethanechol. Using the criteria of Constant [65], 63 of 80 patients with chest pain had true angina pectoris, and 50 patients had positive ergonovine tests during cardiac catheterization without definable coronary spasm. A total of 55 of the 63 patients with true angina had positive responses to bethanechol, and 48 of 50 patients with positive ergonovine testing had a positive bethanechol test. Of the remaining 17 patients with chest pain, 8 had atypical angina and 9 had nonanginal chest pain (>2 nonanginal components). Chest pain was reproduced in 4 of 8 patients with atypical angina and 3 of 9 patients with nonanginal chest pain (50 and 33%, respectively).

A second factor was medication dosage. The mean bethanechol dose for each injection was 4.5 mg, for a mean total dose of 9.0 mg. Positive responses occurred in 48 of 51 patients receiving  $\geq 10$  mg.

A third factor was the definition of a positive response. Dysmotility was defined as a mean manometric score during each 15-minute observation period greater than the mean +2 standard deviations of the score for normal subjects for each bethanechol dosage, rather than a definable motility change at the exact time of chest pain. Using this definition, dysmotility was noted in 80% of patients before pain induction. Other authors have emphasized that motility parameters in the period preceding chest pain may be more predictive of a positive chest-pain response than motility at the time of chest pain [2,3,20-22].

We have examined 850 consecutive chest pain patients with bethanechol stimulation using similar patient selection criteria. The overall response rate has been 42%. Our standard dosage of bethanechol is now two 5 mg doses. Side-effect profiles have remained the same. There have been three cases of symptomatic bradycardia requiring atropine and one case of symptomatic hypotension. Pain at the injection site is universal but tolerable in almost all. Chest pain or abdominal discomfort requiring atropine occurs in only 10% of patients and is limited almost entirely to true angina patients. In 10 tested cases, simultaneous esophageal and heart recordings during cardiac catheterization have shown no significant alterations in heart rate, blood pressure, and electrocardiogram recordings, and no significant coronary artery narrowing. Richter has stated that bethanechol may induce an acute stress that precipitates pain by nonesophageal mechanisms [2,3], but the lack of chest pain in normal subjects

and the low incidence of chest pain in patients with acid-induced pain make this explanation less plausible.

### Ergonovine Stimulation Tests

Ergonovine maleate has been used during cardiac catheterization to induce chest pain by bringing on focal spasm in epicardial coronary vessels. The incidence of esophageal dysmotility is high in ergonovine-positive patients [58–61]. Caution is needed in using ergonovine because of the risk of coronary spasm and reports of myocardial infarction after testing [58]. Comparative studies between ergonovine and edrophonium have shown no advantage for ergonovine [59,60]. Ergonovine, therefore, cannot be recommended for standard esophageal testing.

### Balloon Distention

Graded esophageal balloon distention was reintroduced in 1986 as a provocation test for noncardiac chest pain [29]. This test allows a titratable means of provoking pain without the use of systemic agents. Barish *et al* [29] demonstrated that 48% of patients had reproduction of their pain at a balloon volume  $\leq 8$  mL; this balloon distention volume did not produce pain in any normal subjects. The diagnostic yield of balloon distention ( $\leq 8$  mL balloon volume) was twice that after acid infusion and edrophonium (48 vs 24%). A total of 11 of 12 patients positive by acid infusion or edrophonium testing were positive by balloon distention, and an additional 13 patients were positive only with balloon distention. The test was reproducible, with patients having recurrent pain at the same balloon volume  $\pm 1$  mL. There were no electrocardiogram abnormalities, and the pain immediately disappeared with balloon deflation.

The mechanism for pain production was initially thought to be increased esophageal muscle tone [29,65–68]. For both primates and humans, intraballoon  $dP/dV$  (ratio of change in pressure to change in volume) curves showed linear changes at lower balloon volumes; incremental changes decreased with increasing balloon volumes [66–69]. No distinctive pattern was seen in chest pain patients. Bethanechol and edrophonium stimulation did not change the difference between  $dP/dV$  curves (a crude measure of esophageal muscle tone) with balloon distention *ex vivo* or *in vivo*; thus, bethanechol and edrophonium most likely do not produce chest pain by increased esophageal muscle tone [65–68]. Other authors have shown a high positivity rate (87.5%) with balloon distention in patients with nutcracker esophagus [70]. Patients

with baseline dysmotility may have a higher positive response rate to esophageal balloon distention compared with the total population of noncardiac chest pain patients.

Location of the balloon in the esophagus during distention determines the pattern of manometric changes as well as the number of patients positive with balloon insufflation [66,67]. Amplitude and duration of contraction of the esophagus, as well as pain scores, are higher proximal to balloon distention 16 cm above, compared with 6 cm above, the lower esophageal sphincter [66]. Atropine, an anticholinergic, significantly decreased orad contraction amplitudes after distal esophageal distention but had no effect when balloon insufflation occurred 16 cm above the lower esophageal sphincter [66,67]. Atropine decreased pain scores after distal esophageal distention but not after proximal balloon insufflation. There was no discernible pattern of balloon  $dP/dV$  curves at each distention site. The authors concluded that orad contractions had some effect on pain perception, but esophageal muscle tone did not appear to be a major factor in distention-induced pain. Studies of the stomach using true Barostat balloons, which record continuous muscle tone, have shown differences compared with noncontinuous  $dP/dV$  curves, and true muscle tone may not be measured by static  $dP/dV$  curves [71,72].

### Stress Provocation Testing

A direct relationship between emotional state and esophageal motility was suggested by the observation that patients with esophageal dysmotility had a high incidence of psychiatric abnormalities (predominantly depression and anxiety neurosis) [2,3,30,31,73]. Patients with chest pain or irritable bowel syndrome have a greater fixation on gastrointestinal symptoms and frequently relate stress to gastrointestinal upset [31]. Patients using mood-altering medications have lower pain scores compared with patients taking placebo despite no change in esophageal manometric parameters [13]. The effects of stress on visceral afferent input are being studied.

Anderson *et al* [74] recently demonstrated that both noise stress and difficult cognitive problems induced motor abnormalities in patients with noncardiac chest pain and in normal subjects. Cognitive problem-solving produced a greater increase in contraction amplitude and anxiety behavior than did noise stress. Patients with nutcracker esophagus had greater increases in contraction amplitude than normal subjects or patients with normal baseline motility. These investigators also showed that the level of symptom severity is greater in patients

with documented acid reflux during times of stress compared with no stress; however, there was no objective change in any reflux parameter induced by stress. Patients with the highest levels of anxiety measured by psychological testing had higher levels of reflux severity compared with low-anxiety patients. Autonomic hyperactivity (increased blood pressure, pulse, and anxiety state) was consistently observed during stress times in both high-anxiety and low-anxiety groups [73-76].

From these studies and others, it seems apparent that patients with noncardiac chest pain, irritable bowel syndrome, and possibly nonulcer dyspepsia have a decreased threshold for visceral sensory stimulation [78,79]. A total of 56% of noncardiac chest pain patients were found to have symptoms of irritable bowel syndrome [31]. Visceral afferent endings in the gastrointestinal tract are involved in vasodilation, increases in vascular permeability, contraction and relaxation of smooth muscle, and depolarization of autonomic efferent neurons in paravertebral ganglia [78]. Electrical stimulation of mesenteric nerves to the intestine elicits a cholinergic contraction that is resistant to guanethidine but sensitive to the sensory neurotoxin capsaicin [78,79], suggesting that afferent input could have terminals on intrinsic cholinergic neurons [77]. This intrinsic cholinergic activity could allow changes in esophageal motility and visceral sensation [78-81] and could partially explain the pain-producing effects of all provocation agents including acid, cholinergic stimulation, and esophageal distention. Recent studies in normal subjects have demonstrated reproducible cortical evoked potentials that may be the end point of afferent-induced perception [32,33].

## CONCLUSION

Esophageal provocation testing has a useful place in the evaluation of patients with noncardiac chest pain. Pain induction assures the physician and patient of a good prognosis in those patients with normal coronary arteries. In long-term follow-up studies, patients with a negative cardiac evaluation and positive provocation test(s) for presumed esophageal pain have a low mortality, less disability if the source is known, and use medical resources to a lesser degree than those without a definable pain source [82]. Where the pain is coming from and how it is produced are still matters of serious debate.

Specific provocation tests should be individualized to the patient. Patients with food- or temperature-induced symptoms might best be served by motility testing after these stimuli. The role of acid perfusion is decreasing with the advent of 24-hour pH testing, which is significantly more sensitive

and specific and appears to predict clinical response. Cholinergic stimulation using edrophonium or bethanechol allows some increased diagnostic yield but with significant side effects. Balloon distention offers a more physiologic stimulus that captures most if not all patients with positive cholinergic and acid perfusion tests and gives incremental positive results. The effects of balloon distention on pain perception should be studied. Recent studies using cerebral and spinal evoked potentials offer a promising new way to look at pain perception at the spinal column or cortical level. Modification of spinal and cortical input may be the best means of reducing pain in patients with noncardiac chest pain. Further research into the mechanisms of esophageal chest pain and further technical developments in prolonged monitoring most likely will disclose the cause(s) of noncardiac chest pain and offer positive solutions to this problem.

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