Esophageal manometry with provocative testing in patients with noncardiac angina-like chest pain

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WG PATERSON, DA MARCIANO-D'AMORE, IT BECK, LR DA COSTA. Esophageal manometry with provocative testing in patients with noncardiac angina-like chest pain. Can J Gastroenterol 1991;5(2):51-57. In a five year period 238 of 594 esophageal manometric studies performed in the authors' laboratory were done on patients whose major reason for referral was noncardiac angina-like chest pain. Standard esophageal manometry was performed followed by an acid-antacid perfusion period (Bernstein test) and then subcutaneous bethanechol (80 µg/kg to a maximum of 5 mg) was administered. Baseline manometry was normal in 38% of patients and was diagnostic of 'nutcracker' esophagus, nonspecific esophageal motility disorder, diffuse esophageal spasm and isolated hypertensive lower esophageal sphincter in 24%, 19%, 16% and 3% of patients, respectively. Ninety-six of 238 patients (40%) experienced reproduction of their presenting angina-like chest pain during acid perfusion. In 80% of these patients there were associated esophageal motor abnormalities induced by the acid perfusion. Thirty-six of 212 (17%) experienced pain reproduction following the injection of bethanechol; however, 16 of these had already had their presenting chest pain reproduced during the acid perfusion study. In two-thirds of the patients with pain reproduction following bethanechol there was an associated bethanechol-induced esophageal motility disorder. Overall 49% of patients had their pain reproduced during provocative testing. The acid perfusion test reproduced the pain much more frequently than bethanechol stimulation. This study reaffirms the value of esophageal manometry and provocative testing in this group of patients. *(Pour résumé, voir page 52)*

Key Words: *Acid perfusion, Bethanechol, Chest pain, Esophageal*

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ONCE A CARDIAC ETIOLOGY HAS been excluded, patients with recurrent angina-like chest pain are frequently referred to a gastroenterologist for evaluation. This is because esophageal motor disorders or gastroesophageal reflux disease may be demonstrated in up to 60% of these patients (1,2), and a positive diagnosis of esophageal disease may not only alter medical management, but may also alleviate patient anxiety (3). Various investigations are performed in an attempt to define esophageal abnormalities in these patients, including barium x-ray studies, esophagoscopy, esophageal manometry and tests for acid reflux. These tests have relatively low sensitivity and specificity, the limitation being that the mere demonstration of an abnormality does not imply responsibility for pain. Ideally, one must demonstrate motor abnormalities or acid reflux that coincides with an episode of pain. Twenty-four hour ambulatory esophageal pH studies (2,4) and more recently combined 24 h pH and ambulatory esophageal manometry (4-8) are ideally suited for this, except that the patient must have

Manométrie oesophagienne et test de provocation chez les patients souffrant de douleur thoracique anginoïde non cardiaque

RESUME: Sur une période de cinq années, 238 des 594 études manométriques oesophagiennes qui ont été effectuées dans le laboratoire des auteurs l'ont été chez des patients se plaignant principalement de douleur thoracique anginoïde non cardiaque. Les auteurs ont procédé à une manométrie oesophagienne standard suivie d'un test de perfusion acide (ou test de Bernstein) et de l'administration sous-cutanée de béthanéchol (80µg jusqu'à 5 mg maximum). La manométrie initiale était normale chez 38% des patients et a permis de diagnostiquer un oesophage ['nutcracker'], des troubles de la motilité non spécifiques, une maladie des spasmes diffus de l'oesophagien inférieur chez 24%, 19%, 16% et 3% des cas, respectivement. Quatre-vingt-seize des 238 patients (40%) ont ressenti la douleur thoracique anginoïde qui avait motivé la consultation pendant la perfusion acide. Dans 80% de ces cas, on a également noté des anomalies motrices de l'oesophage induites par la perfusion acide. Trente-six des 212 patients (17%) ont ressenti de la douleur après une injection de béthanéchol mais cette douleur avait déjà été provoquée par la perfusion acide chez 16 d'entre eux. Chez deux tiers des patients dont la douleur a été reproduite après l'administration de béthanéchol, on a relevé des troubles associés de la motilité. Dans l'ensemble, 49% des patients ont ressenti une douleur thoracique au cours du test de provocation. Le test de perfusion acide a provoqué la douleur plus fréquemment que la stimulation par le béthanéchol. La présente étude confirme la valeur de la manométrie oesophagienne et du test de provocation dans le groupe de patients étudiés.

frequent pain episodes if there is going to be a reasonable likelihood that the patient will experience a pain attack during the monitoring period. Because many patients have less frequent symptoms and the equipment for ambulatory pH/motility studies is not widely available, standard esophageal manometry combined with 'provocative testing' continues to be the mainstay of the diagnostic work-up in these patients. Most laboratories performing these studies use acid perfusion (Bernstein test) and pharmacological stimulation with either edrophonium or bethanechol in an attempt to reproduce the patient's chest pain during esophageal manometry. Numerous investigators have reported their experience with this form of testing and the results have varied significantly, leading to some uncertainty regarding the best method of performing these studies.

In the authors' clinical motility laboratory, esophageal manometry with provocative testing has been performed for the past 24 years. In 1984 the authors established a standard protocol for the prospective evaluation of this diagnostic test. The protocol included completing a symptom questionnaire for all patients referred for esophageal manometry. In the present report the authors summarize their experience with esophageal manometry and provocative testing in patients with noncardiac angina-like chest pain.

PATIENTS AND METHODS

Patient selection: The records of all manometric studies performed in the authors' clinical motility laboratory from January 1, 1984 to December 31, 1988 were reviewed. Patients were included in the analysis if the primary reason for esophageal manometry was non-heartburn, angina-like chest pain. This decision was based on a requisition form completed by the referring physician and the pre-study esophageal symptom profile. Patients referred primarily for manometric evaluation of either dysphagia or documented gastroesophageal reflux disease were excluded, irrespective of whether they also complained of angina-like chest pain. All patients had undergone upper endoscopy prior to manometry, and those with ulcerative esophagitis (58 patients) were not included in this analysis.

Coronary artery disease was considered excluded as the cause of pain if at least two of the following criteria were met: consultant cardiologist believed that the pain was noncardiac in origin; normal ECG during spontaneous chest pain episode; negative stress ECG and/or stress thallium study; or normal coronary angiography.

Symptom profile: Prior to the study patients were interviewed by a gastroenterology fellow or a consultant gastroenterologist. A standardized form was completed which surveyed all esophageal symptoms and documented frequency, duration, response to previous treatment, etc. Details of heartburn-type pain and the presenting angina-like pain were also recorded.

Manometric studies: The authors' technique for performing esophageal manometry and provocative testing has been reported previously (9). Studies were performed after an overnight fast when done in the morning, whereas a light breakfast but no lunch was permitted prior to studies performed in the afternoon. One of two manometric catheters was used: from January 1984 to February 1988 a multilumen catheter with side holes spaced at 5 cm intervals was used (201 studies), whereas from February 1988 onward a standard configuration Dent sleeve catheter was used (37 studies). Both catheters were modified such that an antimony pH electrode was passed down the central core and exited from the catheter at a position 5 cm above the lower esophageal sphincter. This permitted continuous intraesophageal pH monitoring on the physiograph. Each catheter lumen used to record intraesophageal pressures was perfused with distilled water at 0.7 mL/min using a low compliance pneumohydraulic catheter system. The recording fidelity of this system was such that finger occlusion of a side hole resulted in a pressure rise of greater than 400 mmHg/s. A bipolar silver chloride surface electrode was attached to the submental region to record the electromyogram from the

TABLE 1
Manometric criteria for the diagnosis of esophageal motility disorders

Diagnosis	Manometric features
Normal	Mean resting lower esophageal sphincter pressure 10 to 35mmHg above intragastric pressure Mean peristaltic amplitude in distal esophagus 40 to 160mmHg Contraction duration in distal esophagus less than or equal to 7.5 s Greater than or equal to 80% of contractions are peristaltic in nature with single or double peak
Achalasia	Aperistalsis in the smooth muscle esophageal body Incomplete or ill-timed lower esophageal sphincter relaxation with or without elevated resting lower esophageal sphincter pressure May have increased intraesophageal baseline pressures relative to intragastric pressure
Diffuse esophageal spasm	Greater than or equal to 30% of contractions nonperistaltic with frequent high pressure (greater than 160 mmHg) prolonged multi-peaked (greater than or equal to three peaks) contraction waves Periods of normal peristalsis
Nutcracker esophagus	Normal peristaltic sequences with greater than one-third of contractions in distal esophagus of increased amplitude (greater than 160 mmHg) and/or increased duration (greater than 7.5 s)
Isolated hypertensive lower esophageal sphincter	Mean resting lower esophageal sphincter pressure greater than 35 mmHg without other associated manometric abnormalities
Nonspecific esophageal motility disorder	Manometric features outside the normal range without fulfilling criteria for above primary motor disorders

TABLE 2
Associated esophageal symptoms in patients referred for manometric evaluation of noncardiac chest pain

Dysphagia	49%
Heartburn	56%
Regurgitation	61%
Odynophagia	19%
Globus sensation	20%

TABLE 3
Baseline manometric diagnoses in patients referred for manometric evaluation of noncardiac chest pain

Normal	38%
Nutcracker esophagus	24%
Nonspecific esophageal motility disorder	19%
Diffuse esophageal spasm	16%
Isolated hypertensive lower esophageal sphincter	3%

suprahyoid muscles. Spike bursts from these muscles indicate the onset of deglutition (10). Respiratory excursions were measured using a belt pneumograph.

The catheter was passed per os and then positioned so that all perfusion ports were initially located in the stomach. A station pull-through of the lower esophageal sphincter was then performed and the catheter positioned so that either the most distal perfusion port or the Dent sleeve recorded lower esophageal sphincter pressure. With the standard side hole catheter, intraesophageal pressures were recorded 5, 10 and 15 cm above the lower esophageal sphincter, whereas with the Dent sleeve catheter pressures were recorded approximately 2, 5, 8 and 14 cm above the lower esophageal sphincter. Following a stabilization period in this position, an infusion of normal saline was begun at 3 mL/min through an unused catheter port 20 cm above the lower esophageal sphincter. The patient was then asked to perform at least five wet (5 mL water) and five dry swallows spaced at least 20 s apart. Once this 'baseline' study was completed, a 10 mL bolus of 0.1 N hydrochloric acid was administered over 15 to 20 s through the port 20 cm above the lower esophageal sphincter, and then a continuous infusion of 0.1 N hydrochloric acid was begun at a rate of 3 mL/min. The patient was unaware that a change in perfusate had been made. Acid perfusion was continued for 20 mins or until the patient experienced intolerable heartburn or chest pain. Following this, the perfusion was switched over to antacid (10 mL bolus followed by infusion at 3 mL/min of a 1:4 dilution of Mylanta II [Parke Davis Division of Warner Lambert Canada Inc]), again without informing the patient. This perfusion was performed for 10 mins. During this entire acid/antacid period the patient was asked to dry swallow at approximately 1 min intervals.

Following completion of the acid/antacid perfusion study the patients were briefly disconnected from the recording equipment and allowed to use the washroom. The recording was begun again and a baseline observation period of at least 5 mins was undertaken, during which time the patient dry swallowed at approximately 30 s intervals. If the patient had residual pain or disorganized motility from the acid perfusion period, the study was discontinued and the patient asked to return on a separate day for performance of the bethanechol provocation test. Otherwise, bethanechol at a dosage of 80 µg/kg (maximum dose 5 mg) was administered by subcutaneous injection. Bethanechol was not administered to patients in whom a contraindication for this medicine existed. Following this the recording was continued for 20 mins with the patient asked to dry swallow intermittently throughout.

Patients were instructed to report any symptom to the technician as soon as it was perceived. In addition, technicians questioned the patient at 2 min intervals throughout the test about the presence or absence of chest pain. If pain was experienced, a determination was made as to whether it was the same as or different from the presenting pain documented in the pre-study questionnaire. The intensity of pain was also

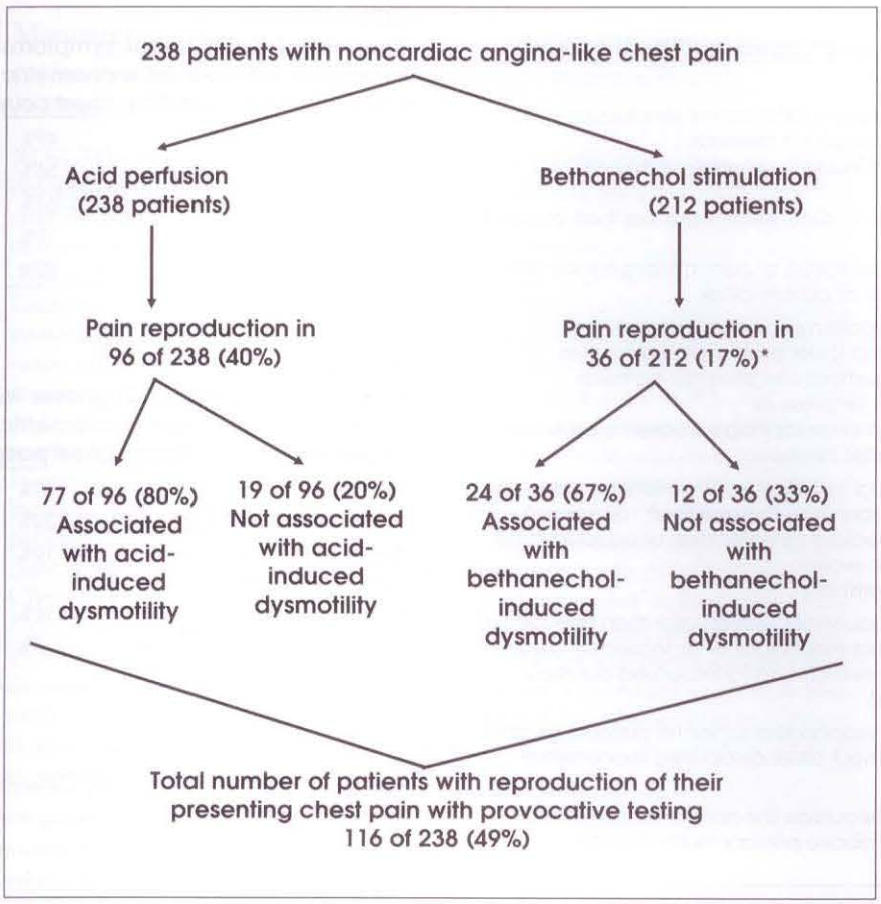

Figure 1) *Summary of results of esophageal manometry with provocative testing in 238 patients evaluated for noncardiac, angina-like chest pain. All patients underwent the acid perfusion test, but only 212 were given bethanechol stimulation. *Includes 16 who already had their presenting chest pain reproduced during acid perfusion*

graded on a scale of 1 to 10 (10 being most severe), and recorded with respect to time from the onset of acid perfusion or bethanechol injection, on a special form.

Tracing analysis and interpretation: The baseline manometric tracings were analyzed manually and a manometric diagnosis made based on normal values obtained previously in the authors' laboratory in healthy volunteers. Diagnostic criteria were similar to those reported by other groups (11,12), and are summarized in Table 1. The acid perfusion or bethanechol stimulation test was deemed positive only if the patient's presenting chest pain was reproduced during these provocative tests. Whether the acid perfusion or the bethanechol stimulation induced esophageal manometric abnormalities (ie, repetitive, nonperistaltic waves, triple peaked waves or prolonged high pressure waves) that were not present on the baseline tracing, was also noted.

RESULTS

Of the 594 esophageal manometric studies performed in the five year period, 238 were on patients whose major reason for referral was non-heartburn, angina-like chest pain. In 40 of these patients (17%), the clinical presentation was such that coronary angiography was used to exclude coronary artery disease. There was a marked female predominance (163/75) and the mean age was 49 years (range 14 to 76). As can be seen in Table 2, a significant number of patients had esophageal symptoms in addition to angina-like chest pain. Just under 50% of patients reported dysphagia, and over 50% had reflux symptoms of heartburn and regurgitation. The manometric diagnoses made on the baseline study are summarized in Table 3. The most common manometric abnormality found was nutcracker esophagus (hypertensive peristalsis).

The results of provocative testing are summarized in Figure 1. Ninety-six of 238 patients (40%) experienced reproduction of their presenting angina-like chest pain during acid perfusion. In the majority of these (77 of 96) the pain was associated with acid-induced abnormal motility. Seventy-four patients (77%) experienced pain reproduction within 10 mins or less of the onset of acid perfusion, whereas in the remaining 22 patients (23%) the pain was reproduced after 10 mins of acid perfusion. Seventy-three per cent of patients having their angina-like pain reproduced with acid perfusion also reported heartburn-type pain during the perfusion.

Two hundred and twelve of the 238 patients were given bethanechol. Bethanechol was not given in 10 patients because severe acid-induced dysmotility persisted despite antacid perfusion, and the patients declined to return on another day. In 13 patients the bethanechol study was declined by the patient because of severe acid-induced symptoms. In two patients the bethanechol study was not completed for technical reasons, and in one there was a medical contraindication (reactive airways disease). The incidence of pain reproduction was significantly less with bethanechol provocation than with acid perfusion. A total of 36 of 212 patients (17%) experienced pain reproduction following bethanechol, but in only 24 of these was there an associated esophageal motor disorder at the time of pain. Sixteen patients who had their presenting chest pain reproduced during bethanechol stimulation had already had their pain reproduced during the acid perfusion study. In 12 of these patients the intensity of pain was rated higher with acid perfusion than with bethanechol stimulation, whereas in four the intensity of pain was no different between the two types of provocation. Overall, 116 of 238 patients (49%) had their chest pain reproduced during either acid perfusion or bethanechol stimulation.

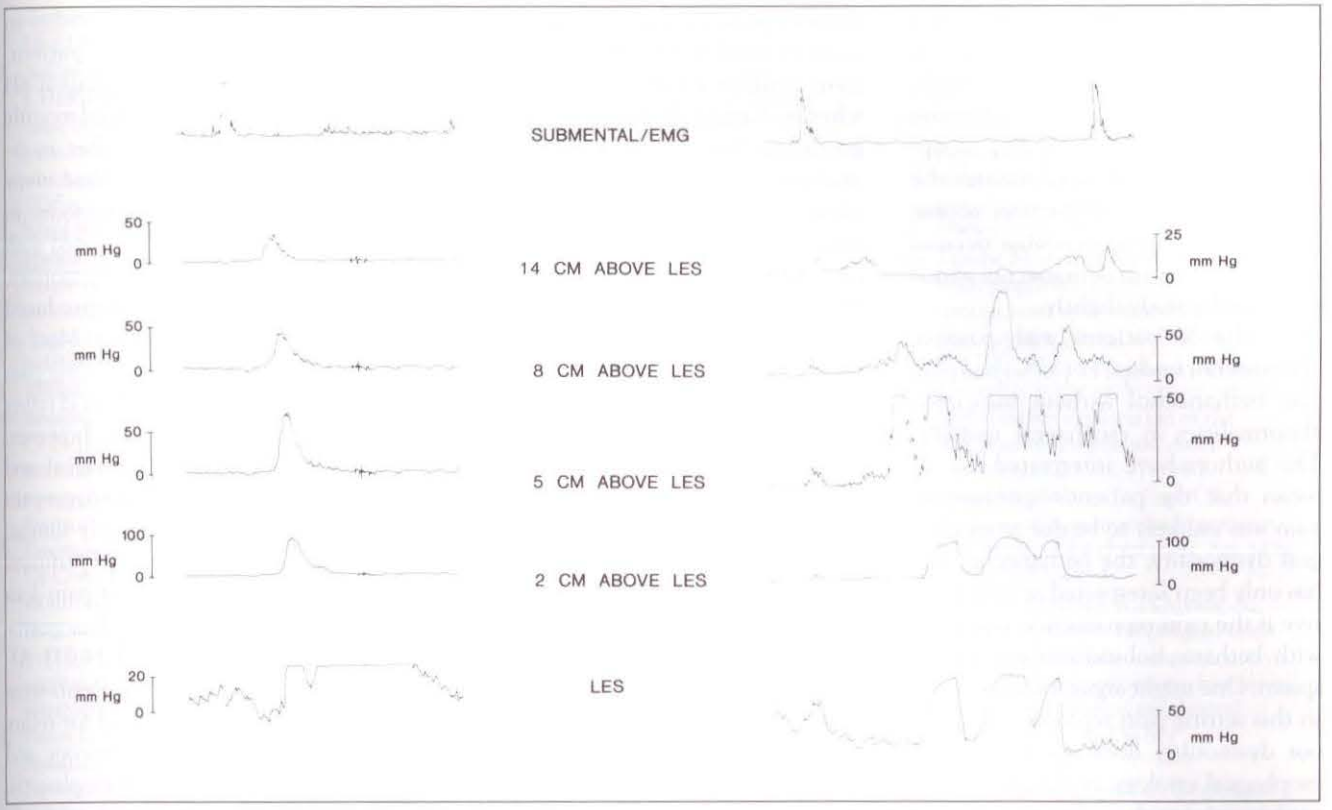

Figure 2) *Example of manometric tracing in a patient who had her angina-like chest pain reproduced during provocative testing. The baseline tracing* (**left**) *is within normal limits. During acid perfusion* (**right**) *a pattern of diffuse esophageal spasm was induced which coincided with the patient experiencing her presenting angina-like chest pain. Of interest is that marked esophageal spasm with pain also occurred following the injection of bethanechol (not shown). At that time atropine was administered which promptly alleviated both the pain and the esophageal spasm. The top tracing is the submental electromyogram (EMG), which records the onset of deglutition. This is followed in sequence by intraluminal side hole pressure recordings from 14, 8, 5 and 2 cm above the lower esophageal sphincter (LES). The lowermost tracing is the pressure recorded by the Dent sleeve, which straddles the LES*

The presence or absence of an abnormality on baseline manometry was not predictive of the subsequent response to provocative testing. Pain was reproduced in 43% of patients with normal baseline manometry and in 53% with an abnormal baseline study. Twenty-seven of 57 patients (47%) with nutcracker esophagus had their pain reproduced. Figure 2 is an example of the motility tracing of a patient with normal baseline manometry who experienced pain reproduction and esophageal dysmotility during provocative testing.

DISCUSSION

This review of a large group of patients reinforces the value of esophageal provocative testing and, in particular, the acid perfusion test, in the diagnostic evaluation of patients with noncardiac, angina-like chest pain. Almost 50% of the 238 patients studied had reproduction of their angina-like chest pain with provocative testing, a figure that compares favorably with that reported by others (1,4,11-15).

In the present patient population, acid perfusion reproduced the chest pain much more frequently than did bethanechol stimulation. Ninety-six of 238 patients (40%) had their pain reproduced during acid perfusion, whereas only 36 of 212 (17%) had their pain reproduced with bethanechol stimulation. Furthermore, 16 of the 36 patients (44%) with pain induced by bethanechol had already experienced pain reproduction during acid perfusion.

The baseline manometric diagnoses (Table 3) in the present patient group are similar to what others have reported (11,16-18), and reaffirms the relatively high prevalence of nutcracker esophagus in this patient population. In addition, the present results with bethanechol stimulation correspond to those reported by others. Using either bethanechol or edrophonium as a means of activating muscarinic receptors on esophageal smooth muscle, the average frequency of pain reproduction in noncardiac chest pain patients is about 20% (4,7,8,11-15,19). Improved diagnostic yields have been reported by groups using higher doses of these drugs (15,19). Deschner et al (12) recently compared bethanechol and edrophonium directly in patients with noncardiac chest pain and found the incidence of pain reproduction to be the same. A greater number of patients were reported to have side effects from bethanechol, leading these authors to conclude that edrophonium was the drug of choice. Unfortunately, the design of their study was flawed in that the patients always received bethanechol after edrophonium, and this may have partly explained the higher in-

cidence of side effects. Bethanechol does cause transient intense burning at the site of subcutaneous injection but in the authors' experience is otherwise well tolerated. Using this drug as opposed to edrophonium eliminates the need to establish intravenous access; however, there is a somewhat delayed onset of action with bethanechol which prolongs the study slightly.

Of the 36 patients with positive bethanechol studies, 12 (33%) had pain post bethanechol without associated abnormalities in esophageal motility. The authors have interpreted this to mean that the patient's spontaneous pain was unlikely to be due to esophageal dysmotility; the bethanechol test has only been interpreted as truly positive if the pain reproduction coincides with bethanechol-induced esophageal spasm. One might argue, however, that in this setting pain reproduction without dysmotility does not exclude an esophageal etiology of the pain. Muscarinic agonists also induce contraction of the esophageal longitudinal muscle (20) which is not apparent on intraluminal manometry; it is possible that an exaggerated contraction response in this muscle layer leads to angina-like pain.

The frequency with which intraesophageal acid perfusion reproduced the patient's angina-like chest pain in the present study is higher than in most previous reports. By far the largest published experience with provocative testing is that by Katz et al (11) using acid perfusion and edrophonium stimulation. In their patient group only 6.7% of patients had their angina-like chest pain reproduced with acid perfusion, whereas 23% had pain reproduction following edrophonium. There are several possible reasons for the differences between the present results and those of Katz et al (11). First, it is possible that the patient population studied is slightly different. The present patients had a high frequency of coexisting esophageal symptoms, including heartburn and regurgitation (Table 2). This was not specifically reported in Katz's study. A second explanation would be the different durations of acid perfusion used in the two studies. The authors perfused the esophagus for 20 mins or until severe angina-like chest pain and/or heartburn developed, whereas Katz et al only performed acid perfusion for 10 mins. On further analysis of the present data, however, most of the present patients (74 of 96) had pain reproduction within 10 mins of starting acid perfusion. Even if all of the patients who developed pain after 10 mins of perfusion were excluded, there would still be 31% (ie, 74 of 238) of all patients whose pain was reproduced with acid perfusion. A final reason for the discrepancy between the two reports is the length of esophagus that was perfused with acid. In the present study the perfusion catheter was positioned 20 cm above the lower esophageal sphincter, whereas Katz et al perfused acid 5 cm above the lower esophageal sphincter. Other groups with a similarly low yield with the acid perfusion test also perfused at this distal location (7,12). De Caestecker et al (14) recently reported results very similar to the present ones; 35% of their patients with noncardiac chest pain had their pain reproduced with acid perfusion, whereas the edrophonium test was positive in only 20%. All but one of the edrophonium-positive patients had pain reproduced by acid perfusion as well. These investigators perfused acid through two channels, one 5 cm and the other 20 cm above the lower esophageal sphincter, for 15 mins. It would thus appear that perfusing a greater length of the esophagus for longer durations is necessary if the acid perfusion test is to reproduce pain in a high proportion of patients.

Although the authors believe that esophageal manometry with provocative testing provides useful diagnostic information in patients with unexplained chest pain, one must be cautious about overinterpreting the results of these studies. Richter et al (1) state that a positive edrophonium or acid perfusion study proves conclusively that the patient's pain is esophageal in origin. This may not necessarily be true, however, in that pain reproduction with esophageal stimulation does not exclude the possibility that the patient's spontaneous pain is triggered by something else, yet perceived in an identical fashion by the patient. Prolonged ambulatory esophageal pH and motility studies performed recently by the authors (5) and other investigators (4,6-8) indicate that many spontaneous chest pain episodes in these patients are not associated with acid reflux or esophageal dysmotility, even though pain was reproduced during provocative testing. Most of these patients have at least one pain episode that correlates with acid reflux or esophageal dysmotility, however, suggesting that both esophageal and nonesophageal stimuli may trigger pain episodes that are qualitatively similar. In addition, the fact that acid perfusion reproduces angina-like chest pain does not mean that the patient has gastroesophageal reflux disease (4,14,21). Although all of the present patients were not extensively investigated for reflux disease, all underwent endoscopy and had no evidence of erosive esophagitis. It has been well documented previously that acid reflux events may trigger angina-like chest pain even though the patient does not have endoscopic, histologic, or 24 h pH probe evidence of pathological reflux (4).

Despite these limitations, esophageal manometry with provocative testing appears to be the best available diagnostic test in patients who have infrequent episodes of pain. Reassurance that the pain is not cardiac in origin is one of the mainstays of therapy in these patients and seems to influence the degree of future incapacitation (3). The authors believe that demonstrating to the patient that their pain can be reproduced by stimulating the esophagus is a powerful form of reassurance.

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