Medical Grand Rounds

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THE SYNDROME OF ANGINA PECTORIS: ROLE OF VISCERAL PAIN PERCEPTION

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THE SYNDROME OF ANGINA PECTORIS AND ABNORMAL VISCERAL PAIN PERCEPTION

Introduction

Angina pectoris is a syndrome of episodic chest pain with a choking, strangling, or suffocating quality. It is sometimes experienced as pressure, burning, or vague discomfort, rather than pain. Anxiety or a sense of impending death may be associated with the pain. Usually localized to the chest, it may also be felt in the neck, jaw, arms, or back. It may occur with exertion, or at rest, with strong emotions, or after eating.

In 1768 William Heberden distinguished this syndrome from other types of chest pain and termed it angina pectoris. Heberden did not suggest a cause for the syndrome of angina pectoris. Of the four patients he described, only one had an autopsy, and that patient's heart was described as normal.

Angina pectoris has come to be associated with coronary artery disease. In 1799 Caleb Parry proposed that angina pectoris is due to insufficient delivery of blood to the heart. The role of coronary artery insufficiency in angina pectoris was later confirmed by autopsy studies, including those by Blumgart in 1940 (1). The introduction of selective coronary arteriography in 1959 by Sones made possible direct evaluation of coronary arteries in patients with angina (2). Since then several studies have shown that 10 to 30% of patients undergoing cardiac catheterization for angina pectoris have angiographically normal coronary arteries (3,4). Coronary artery spasm, usually associated with atherosclerotic disease, causes angina in some patients with no apparent coronary stenosis (5). Cannon has described other patients who have angiographically normal epicardial coronary arteries, but who have angina due to dysfunction of the coronary microcirculation (6). In a significant fraction of patients with angina, however, no coronary abnormality can be demonstrated.

Angina pectoris with normal coronary arteries is common. In addition to the 10 to 30% of patients who have negative coronary arteriograms, there are others who do not have cardiac catheterization because they are deemed to be at minimal risk for coronary disease. Patients with chest pain and normal coronary arteriograms have little or no appreciable increase in mortality compared to normals (4,7). However, despite reassurance, many continue to have disabling chest pain and continue to believe that they have heart disease. They continue to visit physicians, take medication for chest pain, and are frequently hospitalized (8,9).

The purpose of this Medical Grand Rounds is to review the current understanding of the causes, evaluation, and treatment of angina pectoris not due to coronary disease. Recent evidence suggests that abnormal perception of visceral pain is an important contributing factor in this syndrome.

The differential diagnosis of angina pectoris, and thus of NCCP, includes a number of conditions, listed in the table below.

Differential Diagnosis of Angina Pectoris

- Cardiovascular
  - Myocardial ischemia
  - Microvascular angina
  - Pericarditis
  - Mitral valve prolapse
  - Dissecting thoracic aneurysm
- Pulmonary
  - Pneumonia
  - Pulmonary embolus
  - Pleuritis
- Chest wall*
  - Tumor
  - Thoracic outlet syndrome
  - Cervical or thoracic osteoarthritis
  - Costochondritis
  - Sternalis syndrome
  - Xiphoidalgia
  - Fibrositis
- Gastrointestinal
  - Esophageal
    - Gastroesophageal reflux
    - Dysmotility
    - Tumor
  - Peptic ulcer
  - Biliary colic
  - Pancreatitis, pancreatic cancer
- Panic disorder

* References (10-12) provide good reviews of chest wall and musculoskeletal chest pain.

In this review, special emphasis will be placed on esophageal causes of angina pectoris. Of the other conditions causing chest pain, microvascular angina and panic disorder will also be discussed in the context of abnormal visceral pain perception. Angina pectoris not due to coronary artery disease will be termed noncardiac chest pain (NCCP).

THE ESOPHAGUS AND CHEST PAIN

Characteristics of cardiac and esophageal chest pain

Proximity and shared innervation with the heart make the esophagus a natural consideration when no cardiac disease is found to account for chest pain. It has long been appreciated that esophageal pain may be anginal. Esophageal pain may be provoked by exercise or emotion, radiate down the left arm, and be relieved by nitrates. Certain features of the chest pain may suggest a greater likelihood of an esophageal cause, including pain that continues as a background ache after an acute onset, retrosternal pain without lateral extension, oral regurgitation of liquid, and provocation by swallowing (13,14). Associated dysphagia also suggests esophageal disease. However, no single characteristic or group of characteristics is infallible.

To further complicate the issue, both esophageal and cardiac disease are common, and often coexist (15,16).

Esophageal causes of NCCP

In standard textbooks of medicine and cardiology, gastroesophageal reflux (GER) and esophageal dysmotility are listed as the esophageal causes of anginal pain (1,17). Information accumulated over recent years suggests that this may be an oversimplification.

GASTROESOPHAGEAL REFLUX

Acid perfusion test (APT)

In 1958 Bernstein reproduced heartburn by perfusion of the esophagus with dilute HCl and later used this test to attempt to differentiate esophageal from cardiac pain (18,19). The Bernstein or acid perfusion test (APT) is done by infusing alternating solutions of normal saline and 0.1 N HCl through a nasogastric tube placed in the mid-esophagus. Normal saline is begun first at a rate of 6 to 8 ml per minute, and followed after 5-10 minutes by infusion of 0.1 N HCl at the same rate. The patient is asked to report any symptoms. If heartburn or chest pain are reported, the HCL is stopped, and saline is substituted. The test is considered positive if the typical symptom is replicated, particularly if symptoms are relieved by resumption of normal saline infusion.

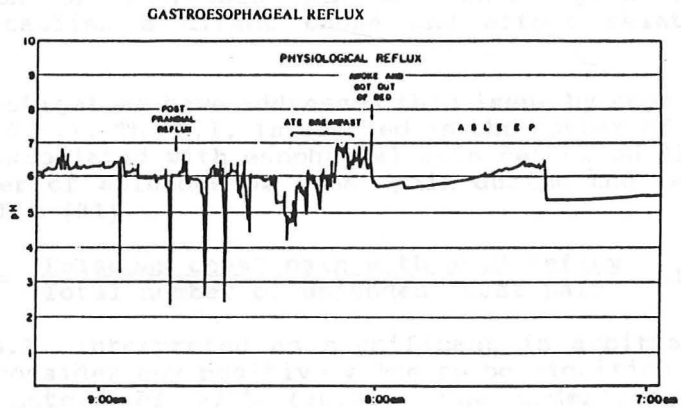
The prevalence of a positive APT among NCCP patients has varied greatly among series. DeCaestecker reported that 35% of 60 NCCP patients studied by his group had a positive APT (20). Other groups have reported a similar prevalence. However, in the largest series of NCCP patients reported to date, only 61 of 910 patients, or about 7% were found to have a positive APT (21).

Prevalence of +APT in NCCP

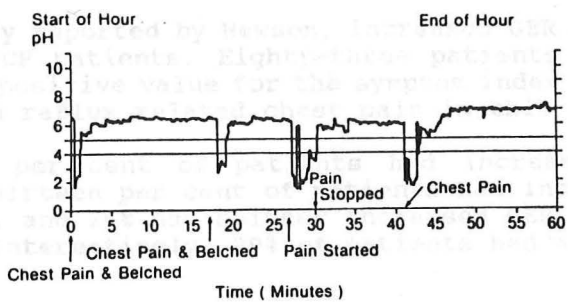
Author (ref)	N=	% +APT
DeCaestecker(20)	60	35
Hewson(22)	45	33
Ghillebert(23)	50	36
Katz(21)	910	7

Ambulatory esophageal pH monitoring

Since the mid 1970's it has been possible to monitor esophageal pH for up to 24 hours, using miniaturized electrodes and portable recorders (24). Patients may eat a normal diet, sleep, work, and exercise during monitoring. Ambulatory esophageal pH monitoring was first applied to the study of GER and esophagitis. GER occurs in nearly everyone, especially after meals. However, during a 24 hour period, the total duration of esophageal acid exposure does not normally exceed 4% (25,26).



When ambulatory monitoring is used in patients with suspected GER-associated NCCP, episodes of pain may be marked on the recorder, and correlated with evidence of acid reflux.



Using ambulatory esophageal pH monitoring, a number of authors have reported a high prevalence of increased GER in patients with NCCP. In 1982, DeMeester reported that of 50 NCCP patients who were studied with esophageal pH monitoring, 23 (46%) had increased GER. Thirteen patients with abnormal GER had chest pain during monitoring, and in 12 chest pain coincided with acid reflux (27). Other investigators have reported a similar prevalence of increased GER as shown in the table below.

Prevalence of Increased GER in NCCP

Author (ref)	N=	% Increased GER
DeMeester (27)	50	46
Janssens (28)	60	22
DeCaestecker (29)	30	47
Ghillebert (23)	50	38
Hewson (30)	100	48

The association of increased GER and chest pain does not necessarily establish a direct cause and effect relationship, however.

Other investigators have addressed this issue by reporting the symptom index (S.I.). The S.I. is defined as the number of episodes of chest pain associated with esophageal acid reflux pH divided by the total number of episodes of chest pain during the recording, multiplied by 100 (31).

$$\text{Symptom Index} = \frac{\text{Episodes chest pain with acid reflux}}{\text{Total number of episodes chest pain}} \times 100$$

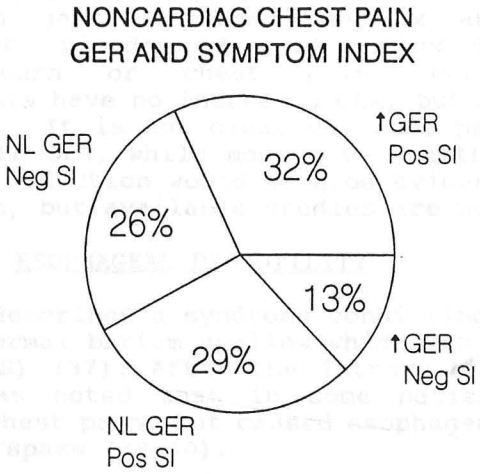
The value of S.I. interpreted as significant is arbitrary. Some investigators consider any positive value to be significant, while others use a cutoff of >75% (30,32). The underlying logical assumption is that the more often a symptom is associated with a physiological event, the more likely the event is to be the cause of the symptom. However, the higher the frequency with which acid reflux occurs, the more likely it is to be associated in time with chest pain. The S.I. does not take this into account (33).

Hypersensitivity to acid reflux

In the study reported by Hewson, increased GER was documented in 48 of 100 NCCP patients. Eighty-three patients had CP during monitoring. Any positive value for the symptom index was considered to indicate acid reflux related chest pain in this study.

Thirty-two per cent of patients had increased GER and a positive S.I. Thirteen per cent of patients had increased GER but a negative S.I., and 26% had neither increased GER nor a positive symptom index. Interestingly, 29% of patients had a positive S.I.

but no increase in GER. The finding of a positive S.I. for chest pain in patients with no increase in total esophageal acid exposure suggests that some patients are hypersensitive to acid (30), that is, few episodes of acid reflux occur, but these patients experience pain with the episodes.



In other patients, only a small proportion of episodes of acid reflux are associated with symptoms. In one study, only 10% of reflux episodes in patients with increased GER were associated with heartburn (34).

Treatment of GER-associated NCCP

If GER is the cause of NCCP in some patients, treatment should relieve the chest pain. Treatment trials to date have been small and inconclusive.

In an uncontrolled study reported in 1982 by DeMeester 11 patients who had NCCP associated with GER were treated by a surgical antireflux procedure. Ten of the 11 had complete relief of chest pain after a followup of 2-3 years (27).

Reports of medical treatment of GER-associated NCCP have been reported only in abstract form. Stahl used ranitidine (Zantac) to treat 10 patients with NCCP who had abnormal GER on ambulatory pH monitoring. Patients were started on a dose of 150 mg 3-4 times a day. The dose was doubled at 2 weeks if the patients were still symptomatic. All patients improved on these high doses of ranitidine. Seven had complete resolution of CP (35).

Richter used omeprazole 20 mg daily for 8 weeks to treat 16 patients with NCCP on abnormal GER on ambulatory pH monitoring. In

this single blind, placebo-controlled, crossover study 12 patients improved on omeprazole while 7 worsened on placebo (36).

Conclusions- gastroesophageal reflux and NCCP

GER is frequently found in patients with NCCP. However, the relationship between gastroesophageal reflux and CP is not straightforward. Most episodes of acid reflux do not produce symptoms of heartburn or chest pain. Conversely, some hypersensitive patients have no increased GER, but still have GER-associated chest pain. It is not clear why some patients seem to have anginal pain with GER, while most have heartburn. Relief of chest pain with acid reduction would be good evidence that GER is a cause of chest pain, but available studies are not conclusive.

ESOPHAGEAL DYSMOTILITY

In 1889 Osgood described a syndrome consisting of dysphagia, chest pain, and abnormal barium swallow which was termed diffuse esophageal spasm (DES) (37). After the introduction of coronary arteriography, it was noted that in some patients ergonovine infusion reproduced chest pain, but caused esophageal spasm rather than coronary artery spasm (38-40).

Baseline esophageal manometry

The development of low compliance, low flow rate, water-perfused manometry systems made accurate esophageal motility studies possible in the mid 1970s (41). Normal esophageal motility has been defined (42). A number of motility disorders have been found to be associated with NCCP.

Esophageal Motility Disorders: Manometric Definitions (21)

Nutcracker esophagus: Normal peristalsis with a mean contraction of distal esophageal contractions of ≥180 mm Hg; May also have increased duration (>5.5 sec.)

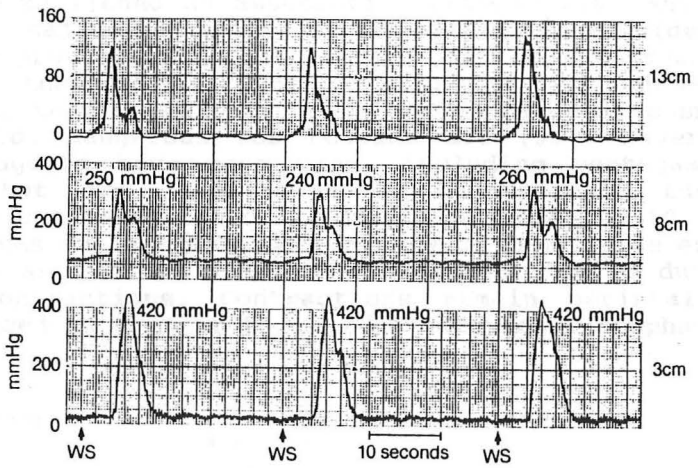
Diffuse esophageal spasm: Simultaneous contractions on >10% of wet swallows; May have repetitive contractions (> 2 peaks) or increased duration or amplitude

Achalasia: Aperistalsis of esophageal body; May have incomplete LES relaxation, elevated LES pressure

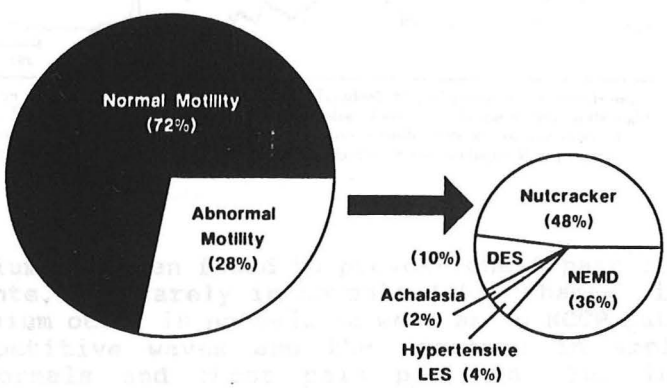
Hypertensive lower esophageal sphincter: LESP >45 mm Hg; normal relaxation, normal esophageal peristalsis

Non-specific esophageal motility disorders (NEMD): Abnormal motility other than those above; normal LES pressure; May have intermittent normal peristalsis with nontransmitted contractions on >20% of wet swallows; triple peaked contractions; retrograde contractions; intermittent incomplete LES relaxation

Contrary to expectations, DES has been found to be relatively infrequent in NCCP patients. In 1977, Brand reported that 14 of 43 (35%) patients with NCCP had abnormal manometry. He described high amplitude peristaltic esophageal contractions in 9 of the 14 (43). In 1983, Benjamin reported abnormal manometry in 23 of 34 (68%) of NCCP patients. Like Brand, he noted frequent high amplitude peristaltic contractions, and coined the term "nutcracker esophagus" (44).



The largest study of esophageal manometry in NCCP patients was reported in 1987 by Katz. Of 910 patients studied, 255 (28%), had abnormal baseline motility. Of those with abnormal baseline motility, only 10% had DES. Nutcracker esophagus, the most common abnormality, was found in 48%, while non-specific esophageal motility disorders were found in 36%, isolated high lower esophageal sphincter pressure in 10%, and achalasia in 2% (21).



Although esophageal motility disorders are present on baseline manometry in a substantial fraction of NCCP patients, it is very rare for patients to report chest pain during manometry. Thus, although these motility disorders are associated with NCCP, the relationship between dysmotility and chest pain is not straightforward.

Edrophonium provocation

Having established an association between NCCP and motility disorders on baseline manometry, it was natural to consider whether pharmacologic provocation might improve the yield of manometry and shed light on the nature of the association. Although ergonovine had been found to provoke chest pain and esophageal spasm, it was felt to be too dangerous for routine use (39). Several other provocative agents have been used, including pentagastrin and bethanecol, but are insensitive or nonspecific. Edrophonium (Tensilon), a cholinesterase inhibitor, in a dose of 10 mg IV, is safe, and causes an increase in frequency of repetitive esophageal contractions, as well as increases in amplitude and duration of esophageal contractions. Contractions remain peristaltic. The pattern produced is similar to that of nutcracker esophagus.

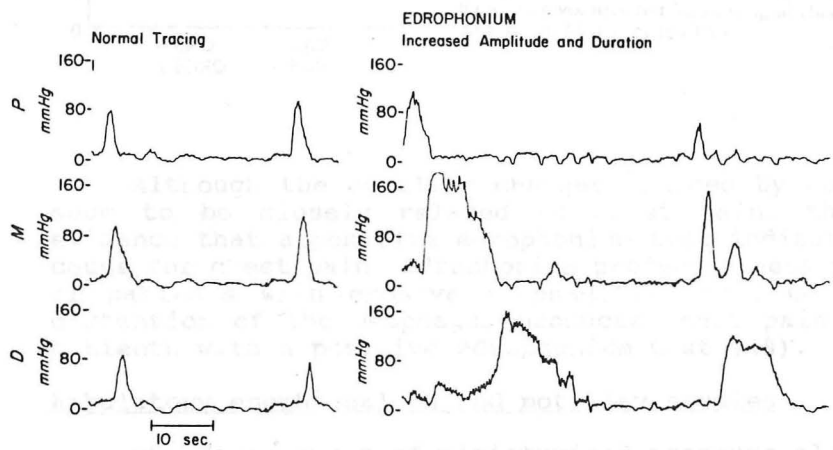


Fig. 35-2. The effects on esophageal manometry of edrophonium (Tensilon), 80 μg/kg in an intravenous bolus, in a healthy volunteer. Tracing on the left demonstrates normal esophageal motility, whereas tracing on the right demonstrates the cholinergic effects of edrophonium characterized by contraction waves of markedly increased amplitude and duration as well as repetitive peaks. D = distal esophagus; M = midesophagus; P = proximal esophagus.

Edrophonium has been found to provoke chest pain in up to 33% of NCCP patients, but rarely in normals (45). Changes in motility after edrophonium occur in normals as well as in NCCP patients. The number of repetitive waves and the increase in amplitude are similar in normals and chest pain patients. The increase in

duration of contractions is greater in NCCP patients than in normals, but there is a great deal of overlap between the two groups (46). Thus, although the edrophonium test may be useful for provoking esophageal pain, abnormal motility does not appear to be the mechanism.

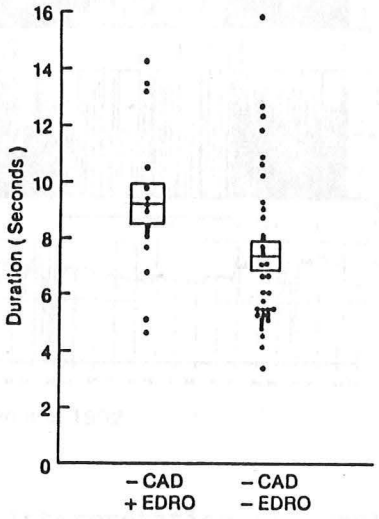


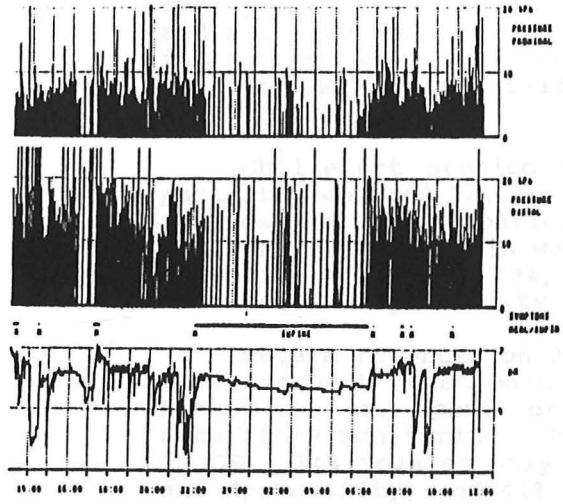
Fig. 35-3. Individual mean durations of distal esophageal contraction in the first five swallows after edrophonium injection in the two subsets of patients with noncardiac chest pain (–CAD). Bars represent mean plus or minus the standard error of the mean for the entire group. Considerable overlap was seen between individual mean durations of esophageal contractions after edrophonium in the patient groups with a positive (+EDRO) or negative (–EDRO) response. This prevented the establishment of a specific manometric criterion for a positive edrophonium test. (Reprinted with permission from JE Richter et al, Edrophonium: a useful provocative test for esophageal chest pain. Ann Intern Med 1985;103:18.)

Although the motility changes induced by edrophonium do not seem to be closely related to chest pain, there is indirect evidence that a positive edrophonium test indicates an esophageal cause for chest pain. Edrophonium produces chest pain in up to 40% of patients with erosive esophagitis (47). Conversely, balloon distention of the esophagus produces chest pain in up to 80% of patients with a positive edrophonium test (48).

Ambulatory esophageal pH and motility studies

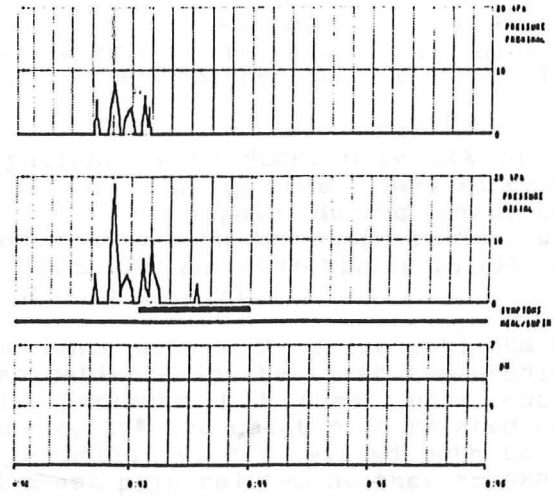
The development of miniaturized pressure electrodes and high capacity digital recorders has recently made possible prolonged ambulatory monitoring of esophageal motility as well as esophageal pH. As with esophageal pH monitoring, event markers allow correlation of episodes of chest pain with abnormal motility.

AMBULATORY pH & MOTILITY
24-Hour Plot



Lam, Gastroenterol 1992

MOTILITY ASSOCIATED CHEST PAIN



Lam, Gastroenterol 1992

Interpretation of ambulatory esophageal motility studies is complex. A large amount of information must be processed, usually by automated analysis as well as by visual inspection. There is a high frequency of abnormal contractions in normals studied with ambulatory esophageal motility monitoring, including high pressure contractions, prolonged contractions, and simultaneous contractions (49-51). Thus, investigators have used each patient as his/her own control to establish a baseline.

Several groups have recorded their findings with ambulatory pH and motility monitoring. The results of four of these studies are summarized in the table below.

AMBULATORY ESOPHAGEAL PH AND MOTILITY MONITORING IN NONCARDIAC CHEST PAIN- SUMMARY OF SELECTED STUDIES

Author (ref)	% patients with pain during study	% patients with pain related to acid reflux (GER) or dysmotility			
		GER	Dysmotility	Both	Neither
Bruemelhof (32)	57	8	8	16	68
Ghillebert (23)	42	57	19	14	10
Peters (52)	92	18	14	27	41
Soffer (53)	75	40	13	20	33

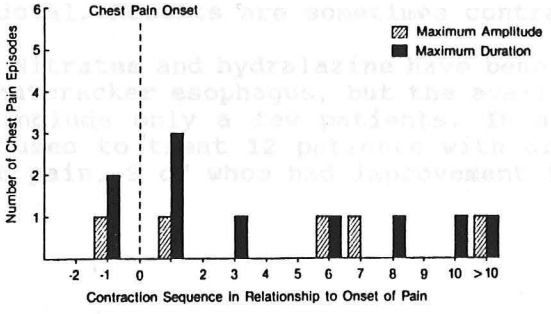
Breumelhof studied 41 patients admitted to the CCU for chest pain which was subsequently proved to be noncardiac. Fifty-five per cent of the patients reported having at least daily chest pain. Twenty-five (57%) had chest pain during ambulatory esophageal pH and motility monitoring. Chest pain was associated with GER alone in 8% of patients with pain during monitoring, dysmotility alone in 8%, both GER and dysmotility in 16% and neither GER nor dysmotility in 68% (32).

Ghillebert studied 50 patients with NCCP. Only 24% of the patients reported having chest pain at least once a day. Forty-two per cent of the patients had chest pain during ambulatory monitoring. Chest pain was associated with GER alone in 57%, with dysmotility alone in 19%, with both GER and dysmotility in 14%, and with neither dysmotility nor GER in 10% (23).

Peters reported on 24 patients with NCCP. These patients had more frequent chest pain than patients in the first two studies. Ninety-two per cent of the patients had chest pain during ambulatory monitoring. Of these, 18% had chest pain related only to GER, 14% related only to dysmotility, 27% related both to GER and dysmotility, and 41% had chest pain related neither to GER or dysmotility. There were 92 episodes of CP recorded. Of these, 20% were associated with GER, 12% with dysmotility, but 64% with neither GER nor dysmotility (52).

Soffer studied 20 NCCP patients, of whom 75% had chest pain during ambulatory pH and motility monitoring. Forty per cent had chest pain associated only with GER, 13% only with dysmotility, 20% with both, and 33% with neither. However, he drew different conclusions from his results. He noted that only 12 of 297 episodes of GER were associated with chest pain, and "only one patient... showed a consistent pattern." He was unwilling to consider episodes of chest pain to be caused by dysmotility if there were examples of similar or more dysmotility not associated with chest pain elsewhere in the tracing. Thus, he concluded that his study implicated GER or dysmotility as definite causes of chest pain in only 2 patients (53).

In the study reported by Peters, many of the abnormal contractions occurred several waves <u>after</u> onset of chest pain, and only 53% of abnormal contractions occurred within 5 contraction waves of the onset of chest pain.



Relationship of abnormal esophageal contractions (maximum amplitude or maximum duration) to onset of patients' chest pains. Note that only 8 of 15 (53%) abnormal maximum contractions occurred within five contraction waves of the onset of chest pain.

Ambulatory esophageal pH and motility monitoring- conclusions

Like other studies, ambulatory esophageal motility monitoring suggests that the relationship between abnormal motility and NCCP is complex.

1) Even with 24 hour ambulatory monitoring, motility associated chest pain is uncommon.

2) GER is the most common event associated with chest pain.

3) A substantial number of patients have the same type of chest pain with both GER and abnormal motility.

4) Even with prolonged ambulatory monitoring, a substantial proportion of episodes of chest pain are associated with neither GER nor abnormal motility.

The natural history of motility disorders and NCCP

Studies of the natural history of motility disorders and NCCP further emphasize the difficulties in assigning a direct cause and effect relationship.

Nutcracker esophagus, the most common motility abnormality associated with NCCP, seems to be quite variable. Dalton followed 17 patients with nutcracker esophagus for 2-1/2 years. On followup manometry only 4 had nutcracker esophagus on every study. Ten had it intermittently, while 3 had nutcracker esophagus documented only on the first study (54).

Non-specific motility disorders are also commonly associated with NCCP. Achem followed 23 patients with NEMD for a mean of 3 years. Seven of 23 reverted to normal on followup. Three evolved to DES and 13 remained unchanged. In 7 patients symptoms improved, in 6 they worsened, and in 10 remained unchanged. Most importantly, there was no correlation between changes in motility and change in symptoms (55)!

Treatment of motility disorders and NCCP

If motility disorders are a cause of chest pain, treatment with agents which relax smooth muscle should relieve symptoms. Unfortunately, most of the available studies are small and anecdotal. Results are sometimes contradictory.

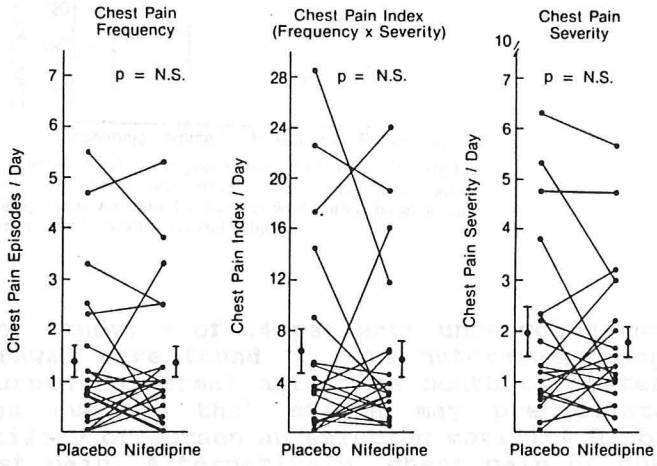
Nitrates and hydralazine have been used both for NCCP with DES and nutcracker esophagus, but the available studies are anecdotal, and include only a few patients. In an unblinded study nitrates were used to treat 12 patients with diffuse esophageal spasm and chest pain, 9 of whom had improvement in pain (56).

In another unblinded study, nitrates or hydralazine were used to treat 5 patients with motility disorders and chest pain, 3 of whom had diffuse spasm, one with nutcracker, and one who had chest pain with bethanecol provocation. Nitrates had no effect on pain or motility, whereas hydralazine improved both (57).

Calcium channel blockers inhibit contractions in the esophagus and decrease LES. They have been used in several trials for treatment of motility-associated chest pain.

In a placebo randomized, double-blind, crossover study, 9 patients with nutcracker esophagus were treated with diltiazem 60 to 90 mg qid. Diltiazem lowered contraction pressures and decreased chest pain, but the results were not statistically significant (59). In another placebo-controlled, randomized, blinded study 8 patients with diffuse esophageal spasm treated with diltiazem had no significant improvement in chest pain (60).

In a randomized, double-blind, placebo-controlled trial, nifedipine was used to treat 7 patients with nutcracker and 3 patients with diffuse esophageal spasm. Nifedipine decreased both contraction amplitude and frequency of chest pain (58). However, in another placebo-controlled trial, although nifedipine decreased esophageal contraction pressure in patients with nutcracker esophagus from 198 to 123 mm Hg., nifedipine was no better than placebo for relief of pain. Chest pain did improve on followup, as did esophageal pressures, but there was poor correlation between changes in pressure and improvement in symptoms (9).



Individual mean and group mean ± SEM scores for three measurements of daily chest pain (frequency, severity, and index) during the randomized 6-wk periods on placebo and nifedipine. There was no significant difference between placebo or nifedipine for any of the three chest pain parameters. n = 20 patients with nutcracker esophagus.

Interestingly, a recent study suggests that many patients with nutcracker esophagus may have chest pain due to acid reflux. Achem reported that 13 of 20 NCCP patients with nutcracker esophagus were

found to have abnormal GER on ambulatory esophageal pH monitoring. Endoscopy disclosed one additional patient with erosive esophagitis. Twelve of these 14 patients were treated with high dose or omeprazole for eight weeks, and 10 of the 12 treated patients had improvement in CP. Thus, in this study, acid reflux seemed to be at least a contributing cause of CP in 10 of 20, or 50% of patients with nutcracker esophagus (61).

Stress and esophageal motility

Stress may cause abnormal esophageal motility. Loud noise can induce simultaneous contractions or increase contraction amplitude (62). Difficult cognitive tasks have been shown to cause increases in esophageal contraction amplitude in normals and in patients with NCCP. The changes induced by stress are greater in patients with nutcracker esophagus than in normals (63).

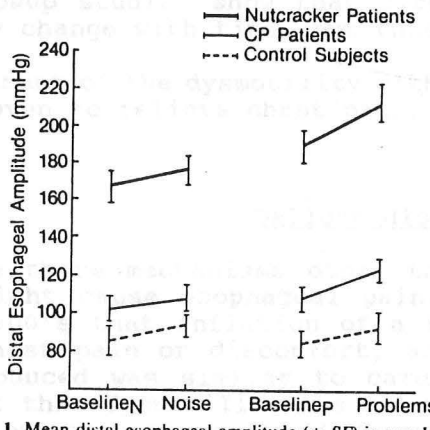


Fig. 1. Mean distal esophageal amplitude (± *SE*) in mm Hg for each stressor and baseline period for the group of 10 nutcracker esophagus patients, nine CP patients with normal baseline manometry, and 20 healthy control subjects.

In another study, 9 of 14 patients undergoing the stress of alcohol withdrawal were found to have nutcracker esophagus, but pressures returned to normal after one month of abstention (64). These findings suggest that stress may precipitate abnormal esophageal motility or worsen an existing motility disorder, which may cause chest pain. Alternatively, chest pain of unknown cause may act as a stressor, precipitating secondary esophageal motility changes.

Is abnormal esophageal motility a cause of chest pain?

The information accumulated makes it difficult to attribute NCCP directly to esophageal dysmotility in many cases.

1) Although esophageal dysmotility is commonly found in NCCP patients, chest pain is rarely present during the abnormal manometry.

2) Motility changes provoked by Tensilon do not correlate with chest pain.

3) Esophageal dysmotility is uncommonly associated with chest pain during ambulatory monitoring.

4) GER and dysmotility may be associated with identical pain in the same patient

5) Followup studies show that dysmotility patterns and symptoms commonly change with time, but these changes are not related.

6) Treatment of the dysmotility with smooth muscle relaxers has not been proven to relieve chest pain.

Balloon distention

Are there mechanisms other than acid reflux or dysmotility which might cause esophageal pain? It has been known since the early 1900's that inflation of a balloon in the esophagus could cause chest pain or discomfort, and it was later noted that the pain produced was similar to cardiac angina (65). As it became apparent that dysmotility was an uncommon cause of NCCP, balloon distention was revived. In 1986 Barish showed that distention of a balloon in the esophagus reproduced chest pain in 28 of 50 (56%) NCCP patients, compared to 6/30 (20%) of controls. Most NCCP patients had pain at volumes of 8 cc or less, while all volunteers with pain noted it at 9 cc or more (48, 66). These results have been reproduced by other investigators. Deschner found that balloon distention reproduced chest pain in 42 of 62 (68%) of NCCP patients (67). Barish found no differences between normals and controls in esophageal tone or contractions above the balloon. Deschner found esophageal motility consistent with spasm distal to the balloon in NCCP patients but did not attribute pain to the motility changes. Thus, many patients with NCCP are hypersensitive to esophageal distention.

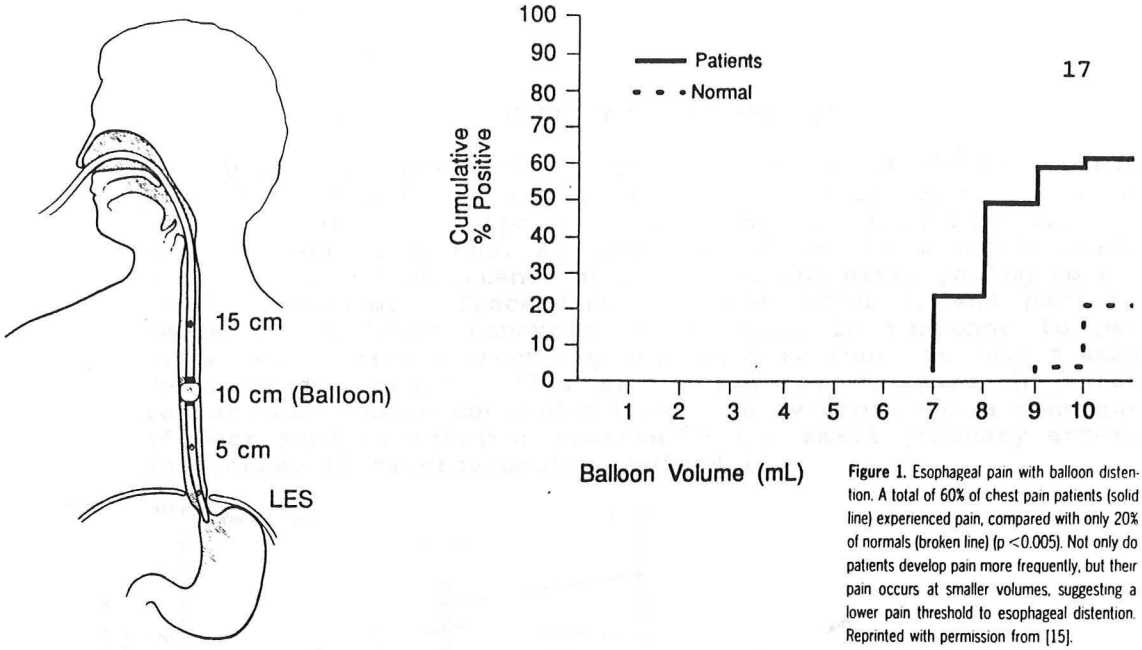


Figure 1. Esophageal pain with balloon distention. A total of 60% of chest pain patients (solid line) experienced pain, compared with only 20% of normals (broken line) ($p < 0.005$). Not only do patients develop pain more frequently, but their pain occurs at smaller volumes, suggesting a lower pain threshold to esophageal distention. Reprinted with permission from [15].

Irritable esophagus

As discussed previously, some NCCP patients seem to be hypersensitive to acid reflux, and many are hypersensitive to balloon distention. NCCP patients seem to be hypersensitive to other stimuli as well. Rosensweig reported 13 patients with NCCP who had reproduction of their symptoms by esophageal biopsy at the time of endoscopy, a stimulus that rarely causes chest pain in other patients (68). NCCP patients seem to respond to different stimuli with the same type of chest pain. As mentioned, a number of NCCP pain patients have identical episodes of chest pain in association with acid reflux or dysmotility. In Barish's study, 5 patients who had positive acid perfusion tests were also sensitive to balloon distention (48). These observations have led to the proposal that NCCP may be caused by an "irritable esophagus " (69).

NCCP, esophageal dysmotility, and irritable bowel syndrome

There are interesting parallels between NCCP and irritable bowel syndrome (IBS). Symptoms of IBS are more common in patients with esophageal motility disorders and in NCCP patients than in controls (70, 71). IBS has been associated with disorders of colonic motility, but the relationship between the motility abnormalities and symptoms is not clear, and treatment of abnormal motility does not have a clear effect on symptoms. Patients with IBS have an abnormally low threshold for pain with intraluminal balloon distention, and even experience discomfort with physiological intestinal motility (72, 73). Patients with IBS have been found to have pain not only with balloon distention, but also with perfusion of the colon with bile acids or fatty acids (74).

MICROVASCULAR ANGINA

During the early 1980's Cannon, working at the NIH, began to publish reports describing functional abnormalities of the coronary artery circulation in patients with anginal chest pain and normal coronary arteriography. At catheterization, he measured coronary artery flow and resistance at baseline, and after pacing to a rate of 150 beats/min. Ergonovine was then infused, and pacing was repeated. Patients reporting chest pain in response to pacing alone, or to pacing after ergonovine, were found to have a smaller decrease in coronary flow and a smaller decrease in coronary resistance. Cannon concluded that this syndrome was a consequence of decreased vasodilator reserve of the small coronary arteries, and termed it "microvascular angina" (6).

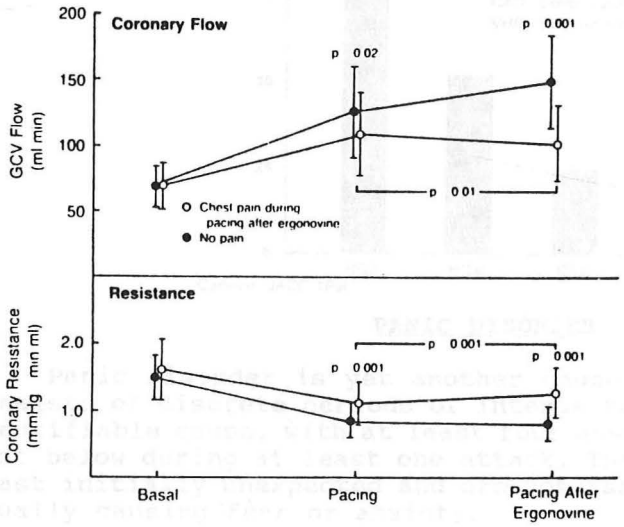


FIGURE 1. Great cardiac vein (GCV) flow (*top*) and coronary res tance (mean blood pressure/GCV flow) (*bottom*) in the basal sta during pacing at a heart rate of 150 beats/min and during rep pacing at the same heart rate after administration of ergonov 0.15 mg intravenously. *Open circles* denote the 87 patients w experienced chest pain during pacing following administration ergonovine and *closed circles* indicate the remaining 26 patie who experienced no chest pain during the entire pacing study. D are indicated as mean ± 1 standard deviation.

Patients with microvascular are most often women in their 40's with atypical angina. Some had abnormal resting EKG's or exercise tests. A minority had evidence of left ventricular dysfunction or increased myocardial lactate production with exercise or pacing (75).

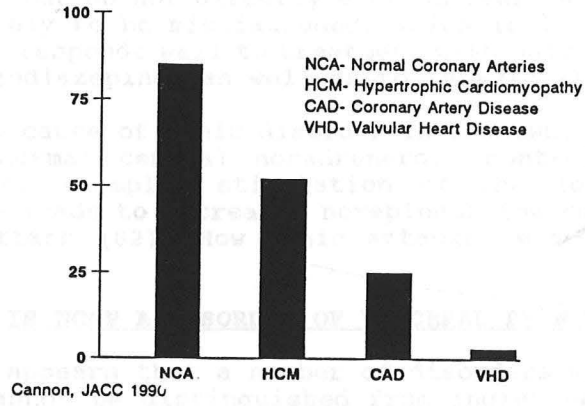
Microvascular angina and esophageal abnormalities

Interestingly, esophageal abnormalities are common in patients with microvascular angina. In a group of 87 patients with angina and angiographically normal coronaries studied at the NIH, 63 were found to have microvascular angina. Sixteen of these 63 (23%) patients were found to have esophageal motility abnormalities, including nutcracker esophagus in 9, NEMD in 5, and DES in 2. Eighteen of 38 patients had a positive esophageal balloon distention test, while 9 of 75 had a positive APT, and 17 of 86 had a positive edrophonium test (76).

Microvascular angina and altered cardiac sensitivity

A number of patients with microvascular angina have been found to have altered cardiac sensitivity. Two groups have reported provocation of typical chest pain in patients with normal coronary arteriograms by catheter pressure against the right atrium or by injections of saline or contrast (77, 78).

MICROVASCULAR ANGINA: CARDIAC SENSITIVITY
CHEST PAIN WITH RIGHT HEART STIMULATION



Cannon, JACC 1990

PANIC DISORDER

Panic disorder is yet another cause of NCCP. Panic disorder consists of discrete periods of intense fear or discomfort without identifiable cause, with at least four associated symptoms from the list below during at least one attack. The episodes of fear are at least initially unexpected and are not associated with a situation usually causing fear or anxiety.

Panic disorder: associated symptoms

1) shortness of breath (dyspnea) or smothering sensations
2) dizziness, unsteady feelings, or faintness
3) palpitations or accelerated heart rate (tachycardia)
4) trembling or shaking
5) sweating
6) choking
7) nausea or abdominal distress
8) depersonalization or derealization
9) numbness or tingling sensations
10) flushes (hot flashes) or chills
11) chest pain or discomfort
12) fear of dying
13) fear of going crazy or of doing something uncontrolled

(From DSM-III-R, ref. 79)

Pain typical of angina pectoris may occur in panic disorder. This pain, combined with other symptoms, such as sweating, shortness of breath, and anxiety, may simulate acute myocardial infarction.

Panic disorder is relatively common, affecting up to 1-2% of the population. Some investigators have found a high prevalence of panic disorder in NCCP. In one study, of 94 NCCP patients interviewed, 32 (34%) fit the criteria for panic disorder (80). Some patients with panic disorder present with a cluster of somatic symptoms but do not directly express fear (81). These patients are very likely to be misdiagnosed, which is important, because panic disorder responds well to treatment with polycyclic antidepressants and benzodiazepines as well as to behavioral therapy.

The cause of panic disorder is unknown, but there is evidence that abnormal central noradrenergic control plays an important role. For example, stimulation of the locus ceruleus in the midbrain leads to increased norepinephrine release and symptoms of panic attack (82). How panic attacks lead to chest pain is not clear.

IS NCCP A DISORDER OF VISCERAL PAIN PERCEPTION?

It appears that a number of disorders may lead to chest pain which cannot be distinguished from angina pectoris by history or examination. Furthermore, some of the disorders, such as GER, dysmotility, microvascular angina, and panic disorder, seem to overlap. Many of the features of NCCP suggest abnormal visceral pain perception (83). An understanding of the physiology of visceral pain may help to clarify some issues in NCCP.

PHYSIOLOGY OF VISCERAL PAIN

Characteristics of visceral pain.

Visceral pain is usually dull, aching, or boring. Often patients do not describe visceral discomfort as pain, but rather as pressure, tightness, or squeezing. It is usually poorly localized, and may be referred, or felt in areas far from the site of origin. It is often associated with malaise, anxiety, and strong autonomic reflexes (84).

Visceral pain receptors

Visceral pain from the gastrointestinal tract is mediated by free nerve endings, specialized as receptors, in the mucosa, muscle, and serosa. Visceral pain receptors respond to mechanical, chemical or thermal stimulation. Some are polymodal, that is, they will respond to more than one type of stimulation. Thus there are likely to be esophageal afferents which respond to acid, mechanical stimulation, or to both. Mechanoreceptors in the muscle respond

both to distention and contraction, and thus appear to be tension receptors. Visceral pain receptors may respond directly to stimulation, or indirectly, through mediators released from damaged tissue.

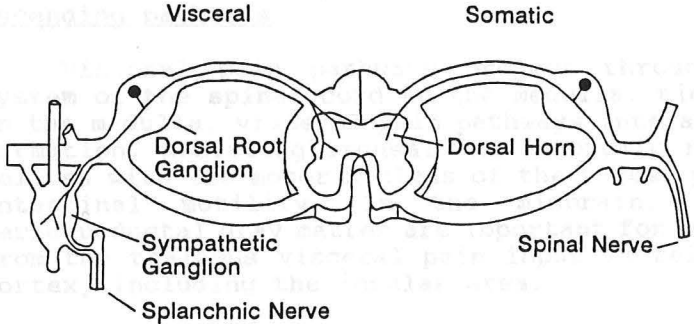
Visceral Pain Receptors
- Mechanical
- Heat
- Polymodal

- Mechanical
- Chemical
- Heat

Primary visceral pain fibers

Sympathetic afferent nerves mediate pain. Sympathetic afferent neurons have cell bodies in the dorsal root ganglia. The peripheral processes of visceral pain fibers reach the gastrointestinal tract with sympathetic efferent fibers, and collaterals synapse with efferents in the sympathetic ganglia. This arrangement is one mechanism whereby visceral pain may modulate motility. The central processes of visceral pain fibers synapse on interneurons in the dorsal horn of the spinal. Sympathetic afferents innervating the heart enter the spinal cord in segments which overlap those from the esophagus (85).

PRIMARY PAIN AFFERENTS

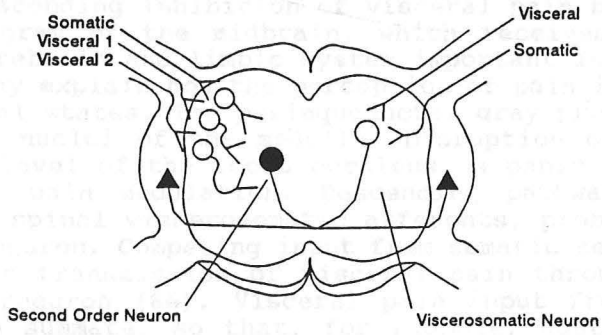


Spinal visceral pain pathways

Dorsal horn interneurons which receive visceral pain input are called viscerosomatic neurons. These neurons also receive somatic afferent input from skin, tendons, and muscle. There are no separate visceral pain interneurons. The convergence of visceral and somatic pain fibers on the same interneurons explains why visceral pain is often referred, that is, why it is often perceived in somatic areas remote from the involved organ.

Somatic afferent input, visceral afferent input of different types (chemical and mechanical, for example), and visceral afferent input from several organs also converge on second order interneurons in the dorsal horn. Thus, pain arising from different organs, such as the chest wall, esophagus, or the heart may be indistinguishable, as may pain arising from chemical or mechanical stimulation.

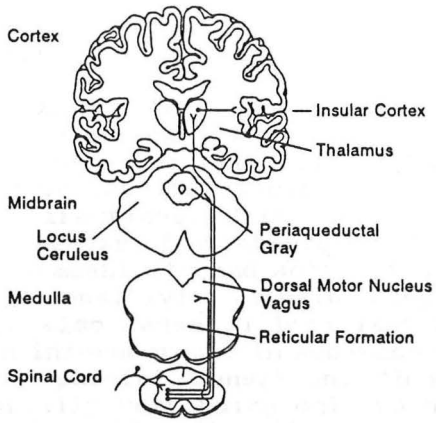
AFFERENT CONVERGENCE IN THE SPINAL CORD



Ascending pathways

Visceral pain pathways project through the anterolateral system of the spinal cord to the medulla, midbrain, and thalamus. In the medulla, visceral pain pathways interact with the reticular formation, mediating arousal and autonomic responses to pain, as well as with the motor nucleus of the vagus, potentially affecting intestinal motility. In the midbrain, projections to the periaqueductal gray matter are important for descending modulation. From the thalamus visceral pain input is relayed to areas of the cortex, including the insular area.

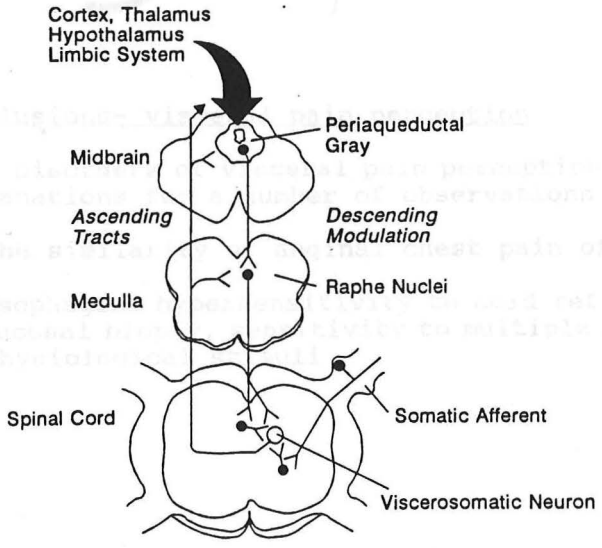
VISCERAL PAIN
ASCENDING PATHWAYS



Modulation of visceral pain

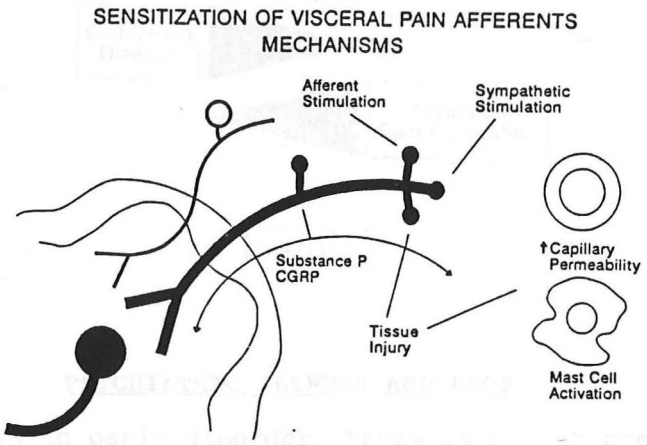
Modulation of visceral pain occurs through descending inhibition from higher centers as well as at the level of the spinal cord. Descending inhibition of visceral pain begins in the periaqueductal gray of the midbrain, which receives input from areas of the forebrain and limbic system important in controlling emotion. This may explain how the perception of pain is altered in certain emotional states. The periaqueductal gray projects to the medullary raphe nuclei of the medulla. Disruption of adrenergic control at the level of the locus ceruleus in panic disorder may affect visceral pain modulation. Descending pathways from the medulla inhibit spinal viscerosomatic afferents, probably through an opioid interneuron. Competing input from somatic sensory fibers can also inhibit transmission of visceral pain through a spinal inhibitory interneuron (86). Visceral pain input from different organs may also summate, so that, for example, gastroesophageal reflux might worsen angina pectoris of cardiac origin.

MODULATION OF VISCERAL PAIN



Sensitization

Sensitization to visceral pain may occur through a number of mechanisms. Both tissue damage and adrenergic stimulation increase sensitivity of visceral pain fibers. Visceral pain neurons transport neuropeptides substance P and CGRP in both central and peripheral directions. Stimulation of visceral receptors causes peripheral release of substance P and CGRP. These mediate increased capillary permeability and activation of mast cells, which in turn may increase sensitivity of pain receptors. Stimulation of visceral pain fibers also causes a long lasting increased excitability of dorsal horn interneurons. In addition to increasing transmission of the primary painful sensation, this facilitation could enable neurons normally responding only to noxious stimuli to respond to stimuli which would ordinarily not be painful (Textbook of pain, p. 136). Thus, for example, sensitization by acid reflux might cause esophageal pain with low levels of muscular tension.



Conclusions- visceral pain perception

Disorders of visceral pain perception could provide potential explanations for a number of observations in NCCP, including:

1) The similarity of anginal chest pain of different causes

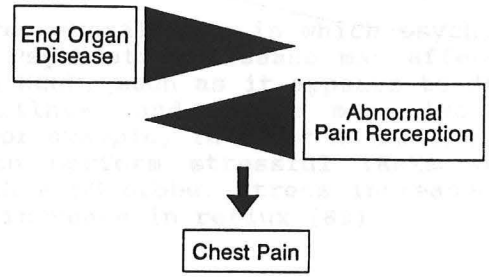
2) Esophageal hypersensitivity to acid reflux, balloon distention, or mucosal biopsy, sensitivity to multiple stimuli, and sensitivity to physiological stimuli

3) Esophageal dysmotility in NCCP. As mentioned, visceral pain fibers form reflex loops which modulate motility. Motility disorders might then be secondary to abnormal afferent modulation, rather than a primary cause of pain

4) Cardiac hypersensitivity in microvascular angina

5) Overlap among esophageal pain syndromes, microvascular angina, and panic disorder.

Although the concept of abnormalities in visceral pain perception is helpful in understanding NCCP, it is largely theoretical, and only one of several components of NCCP. NCCP may be considered a spectrum of disorders, with some patients having primarily severe end organ dysfunction, such as gastroesophageal reflux. Others have a combination of end organ dysfunction and abnormal visceral pain perception, yet others have primarily abnormal visceral perception.



PSYCHIATRIC ILLNESS AND NCCP

In addition to panic disorder, there is a high prevalence of other psychiatric illness in patients with NCCP. Clouse reported that 21 of 25 patients with symptomatic esophageal motility disorders had psychiatric diagnosis on a structured interview. The most common disorders found were anxiety, depression, and somatization (87). Using a behavioral inventory designed specifically for medical patients (Millon Behavioral Health Inventory), Richter studied patients with NCCP and IBS. NCCP patients were found to have high levels of anxiety about somatic symptoms as well as high gastrointestinal susceptibility, that is, a tendency to respond to psychological stress with an increase in frequency and severity of GI symptoms. In this respect, patients with NCCP were similar to patients with IBS (88).

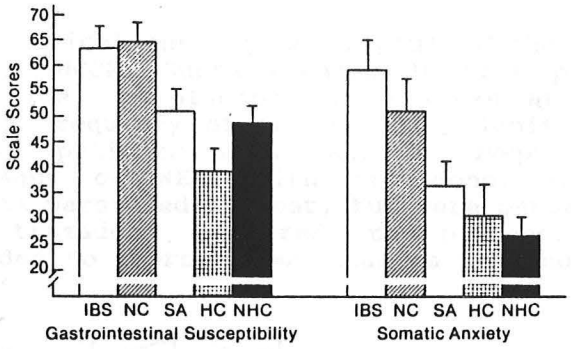
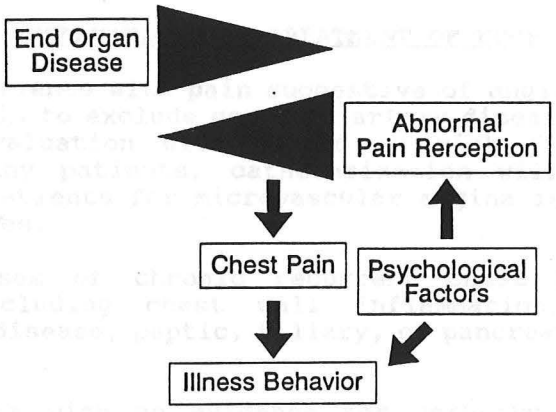


Fig. 35-6. Average score for values (plus or minus the standard error of the mean) on the Millon Behavioral Health Inventory scales of gastrointestinal susceptibility and somatic anxiety for five study groups: irritable bowel syndrome (IBS); nutcracker esophagus (NC); structural esophageal abnormalities—rings or esophagitis (SA); healthy hospital controls (HC); and healthy nonhospital controls (NHC). Subjects in the NC and IBS groups scored significantly higher ($p < .05$) on both scales than did all other subject groups. This pattern suggests that these patients react to psychologic stress with frequent and severe gastrointestinal symptoms and display hypochondriacal tendencies and unusual amounts of fear about bodily dysfunction. (Reprinted with permission from JE Richter et al, Psychological comparison of patients with nutcracker esophagus and irritable bowel syndrome. Dig Dis Sci 1986;31:135.)

There are several ways in which psychiatric disorders could affect NCCP. Psychiatric disease may affect illness behavior in patients with NCCP, much as it appears to do in IBS. Psychiatric illness and stress may also affect visceral pain perception. For example, in a recent study patients with heartburn were asked to perform stressful tasks while acid reflux was monitored with a pH probe. Stress increased symptoms even though there was no increase in reflux (89).



Psychotropic medications may be helpful in the treatment of some patients with NCCP. Gupta treated 30 NCCP patients with imipramine, clonidine, or placebo for 3 weeks and found that imipramine reduced frequency of CP episodes significantly (90). Clouse treated 29 patients with NCCP or dysphagia who had nutcracker esophagus or NEMD with trazadone. Interestingly, esophageal symptoms persisted in most, but were perceived as less distressing on trazadone compared to placebo. Manometric abnormalities tended to improve, but changes were not related to treatment (91).

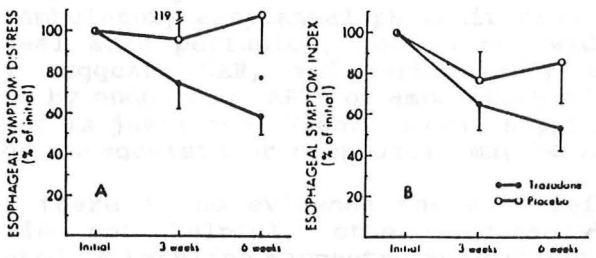


Figure 3. (*A*) Residual distress over esophageal symptoms compared to enrollment rating on the weighted esophageal symptom distress scale. *Closed circles* represent the trazodone group and *open circles* represent the placebo group in each panel. *p = 0.03 comparing the two treatment groups. (*B*) Residual objective esophageal symptoms compared to enrollment rating on the weighted esophageal symptom index scale. Differences between treatment groups were not significant. In both panels, *extensions* indicate SEM.

Cognitive and behavioral therapy has also been successful in the treatment of some patients (92).

EVALUATION AND TREATMENT OF NCCP

In most patients with pain suggestive of angina pectoris, the first priority is to exclude coronary artery disease. The extent of the cardiac evaluation will depend on risk factors for each patient. In many patients, catheterization will be necessary. Evaluation of patients for microvascular angina is impractical in most laboratories.

Other causes of chronic recurrent chest pain should be considered, including chest wall inflammation, cervical and thoracic spine disease, peptic, biliary, or pancreatic disease, and panic disorder.

In patients with no evidence for coronary disease, or in patients at low risk for coronary disease, esophageal causes of chest pain should be considered. A careful history may help. Although patients with NCCP of esophageal origin may complain only

of chest pain, many will have other esophageal symptoms if questioned carefully. In a study of 100 consecutive NCCP patients, 74% had a history of heartburn, 67% had regurgitation, 49% had dysphagia, and 14% had pain on swallowing (30). Upper GI endoscopy is a reasonable first examination. If esophagitis or peptic ulcer is found, a diagnostic trial can be initiated (93).

If no endoscopic esophagitis is found, an acid perfusion test is a reasonable next study, since it is safe, inexpensive, and easy to do. It is very helpful if positive, but insensitive, so GER-associated chest pain cannot be excluded on the basis of a negative study. Ambulatory esophageal pH monitoring is more sensitive than esophageal acid perfusion, but is not widely available. If the history suggests GER, and particularly if there is objective evidence by endoscopy, APT, or ambulatory pH monitoring, a trial of treatment is justified. Vigorous acid suppression with high dose H_2 receptor antagonists or omeprazole may be necessary.

If there is no evidence for acid reflux, or the treatment trial is not helpful, other esophageal studies should be considered. A baseline manometry and balloon distention test can be done at one visit in most GI laboratories. Ambulatory esophageal motility is primarily a research tool at this time. Manometry may disclose an unsuspected case of achalasia. Despite difficulties in establishing a cause and effect relationship, individual patients may indeed have pain due to dysmotility. If manometry shows DES, nutcracker, or NEMD, an agent such as nifedipine might be tried, and may be helpful in individual cases. However, we should remember that there is limited evidence of effectiveness, and treatment should be stopped if the benefit is not clearcut and sustained. Esophageal dilatation has been used for motility associated NCCP, but has only a placebo effect. A surgical myotomy should not be considered except in very severe or life-threatening cases.

A standardized balloon is commercially available for esophageal balloon distention, and is the single most commonly positive test for esophageal pain.

The major benefit of esophageal testing in patients with NCCP may be the reassurance that is provided to patients who are told that they have esophageal chest pain. In 1987 Ward reported a followup study of 91 NCCP patients who had been evaluated for esophageal disease and who responded to a followup questionnaire a mean of 22 months later. Of the 91 patients, 49 had been diagnosed as having an esophageal cause of their pain. Of these 49 patients, 27 recalled being told that their pain was esophageal, and 22 did not recall. Chest pain persisted in 89% of patients. There was no difference in the prevalence of persistent chest pain among the groups. However, those patients who recalled being told that their pain was esophageal reported significantly less disability, and fewer continued to require physician attention for diagnosis and management of pain (94).

In patients with persistent distress and disability, it may be helpful to consider psychological factors. In a patient with apparent depression, anxiety, or somatization, a trial of trazadone may be helpful. The most difficult patients may need psychological or psychiatric evaluation. Behavioral or cognitive therapy has been found to be helpful in some cases (92, 95). For most patients, however, thoughtful evaluation, identification of a source of chest pain when possible, support, and repeated reassurance is all that is required.

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