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Preface

Noncardiac chest pain



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Guest Editor

Noncardiac chest pain (NCCP) represents a diverse patient population with different underlying mechanisms for chest pain. Gastroesophageal reflux disease (GERD) is by far the most common cause. A subset of patients who have non-GERD-related NCCP displays a variety of esophageal motility disorders, but most fall into the category of functional chest pain of presumed esophageal origin. In this issue of *Gastroenterology Clinics of North America*, we have assembled an esteemed group of experts in the field of NCCP. Authors addressed cutting-edge issues related to NCCP including epidemiology, global distribution, diagnostic modalities, and current and future treatment. This issue also attempts to address esophageal pain mechanisms, the role of visceral hyperalgesia in patients who have NCCP, and central assessment of esophageal pain. The contribution of psychological comorbidity to the phenotypic presentation of NCCP and the role of psychological intervention in these patients are also addressed in this issue.

While NCCP remains an area of intense research, many recent developments in diagnosis and treatment have improved our current clinical approach significantly. Furthermore, research into the underlying mechanisms of esophageal pain will help direct us to better and more specific

therapeutic modalities. Many questions remained unanswered, however, leaving a fertile field for research opportunities.

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Noncardiac chest pain: epidemiology, natural history, health care seeking, and quality of life

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Chest pain is a symptom, not a disease. Noncardiac chest pain (NCCP) is essentially a diagnosis by exclusion of other acute and potentially fatal conditions such as acute myocardial infarction (AMI). The epidemiology and natural history of NCCP are poorly understood, and there are few well designed epidemiologic studies to assess NCCP and patient outcomes. In addition, the number of individuals with NCCP who consult a physician and the reasons why these individuals seek health care are uncertain. In the United States, it has been estimated that more than six million patients present to hospital annually with chest pain at a cost to the health care system of approximately US\$8 billion dollars [1,2]; this high cost is due in part to the large number of deaths from missed myocardial infarction (MI) among patients who are sent home and the associated litigation [3]. Moreover, the economic cost of NCCP in the long-term is unknown. The indirect costs of NCCP have not been determined; however, based on other functional gastrointestinal (GI) disorders (irritable bowel syndrome and non-ulcer dyspepsia), these costs are likely to be substantial [4,5].

Definition

NCCP is a complex disorder that is difficult to define. Part of the difficulty in defining NCCP can be related to the numerous synonyms used in describing this heterogeneous condition. There is considerable overlap in the terms used among different medical specialties (Box 1). Although it can be all inclusive of all chest pain that is not related to ischemic heart disease

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Box 1. Synonyms for NCCP

- Effort syndrome
- Soldier's heart
- Irritable heart
- Sensitive heart
- Neurocirculatory asthenia
- DaCosta syndrome
- Chest pain of undetermined origin
- Chest pain of unknown etiology
- Unexplained chest pain
- Gorlin-Likoff syndrome
- Cardiac syndrome X (microvascular angina)
- Chest pain with normal coronary angiograms
- Functional chest pain

(IHD), it can also be specific enough to constitute a subset of patients with chest pain that seems to have no organic origin at all (ie, functional chest pain). It is uncertain what proportion of patients belongs in each diagnostic group, and previous investigations have been biased by the selection of their subjects or by the selection of the investigations used.

Because of the diverse number of possible causes of NCCP [6], the pathophysiology remains inadequately understood. Indeed, the pathophysiology of NCCP is a complex and continuously developing area of gastroenterology and is beyond the scope of this review [7–9]. A majority of pathophysiologic studies relate to esophageal disorders [10–15], some studies are related to comparisons in cardiac and noncardiac chest pain [16–19], and others take a more general approach to the pathophysiology of pain [20].

In this article, NCCP is defined as chest pain that is not angina (retro-sternal pain precipitated by exertion and relieved by rest) and is not chest pain due to IHD. The term NCCP is a misnomer because some the possible pathogenic mechanisms may be cardiac related (eg, cardiac syndrome X). There seems to be a lack of consistency in the classification of NCCP. In the future, a more appropriate term may be “non-ischemic chest pain.”

Epidemiology*Population-based studies*

There is a dearth of population-based studies on NCCP. There are only a few studies that have estimated the population prevalence of NCCP [21–26]. In the United States, a population-based survey assessing the clinical spectrum of gastroesophageal reflux disease (GERD) in Olmsted County,

Minnesota reported an overall prevalence of NCCP (which was defined as “those who reported chest pain but did not have a history of cardiac disease”) among 1511 individuals of 23% (24% among males and 22% of females) [21]. Drossman et al [22] conducted a survey on functional GI disorders in 8250 households in the United States with 5430 respondents (66%). The sample was not representative of the US population because of a lack of data on minority groups. However, self-reported functional chest pain (based on the Rome I criteria) was reported by 13.6% of this group, and functional chest pain decreased with age (15–34 years, 18.4%; 35–44 years, 13.9%; > 45 years, 9.9%). There was no significant difference between males and females (12.1% versus 13.4%, respectively). In another population-based study of 7735 randomly selected men between 40 and 59 years of age, the prevalence of “other chest pain” was reported to be 24%; the selection criteria were based on the Rose Angina questionnaire, examination by a nurse, and previous cardiovascular diagnoses [23]. Brattberg et al [24] reported the prevalence of “chest pain” in a population-based longitudinal study of 321 Swedish individuals 53 to 87 years of age to be 28%, but cardiac and noncardiac cases were not distinguished. Another cross-sectional survey was conducted in Sweden on a population of 3000 people between 25 and 55 years of age to determine the prevalence of esophageal dysfunction (a proxy for NCCP). The study used a nonvalidated questionnaire (the contents of which were not mentioned or referenced in the article) and esophageal investigations (esophageal manometry and acid perfusion testing). The prevalence of esophageal dysfunction based on esophageal investigations and survey was 24.3% [25]. Recently, a study specifically designed to determine the population prevalence of NCCP was conducted in Australia [26]. This population-based study involved the mail-out of a specifically designed Chest Pain Questionnaire (CPQ) to 1000 randomly selected individuals in the Sydney suburb of Penrith and obtained a 73% response rate. The study found slightly higher prevalence rates of NCCP than the studies mentioned previously; the prevalence of NCCP was 33%, and the gender-specific prevalence rates were similar in males and females (32% versus 33%, respectively) [26]. Furthermore, this study showed that the population prevalence of NCCP decreases with increasing age (Fig. 1).

These studies differ in many respects in terms of how NCCP is defined, geography, sample size, sampling frame, and possible ethnic disparities. However, there are some important and consistent findings among these population-based studies. These include high prevalence rates of NCCP (mean prevalence of the above six studies ~24%) and little if any difference in the prevalence of NCCP between males and females.

To put the population prevalence of NCCP in perspective, if the attributable risk is calculated based on a conservative prevalence estimate for NCCP of 25% in the US population (~260 million people), approximately 65 million individuals can be estimated to have NCCP.

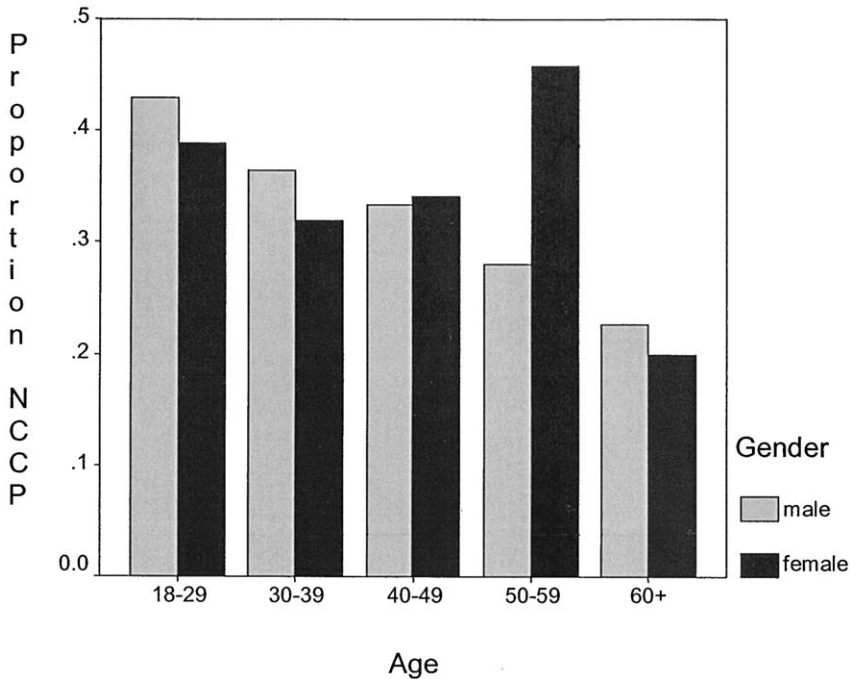


Fig. 1. Prevalence rates (as proportions) of NCCP by age and gender. Note the increase in NCCP prevalence among females aged 50 to 59 years. (From Eslick GD, Jones MP, Talley NJ. Non-cardiac chest pain: prevalence, risk factors, impact and consulting – a population-based study. *Aliment Pharmacol Ther* 2003;17:1115–24; with permission.)

Therefore, the public health implications of NCCP are enormous because a large proportion of NCCP is treatable. The public health importance will become more apparent when health care seeking is reviewed.

Hospital-based studies

Hospital-based studies have focused on determining the prevalence of NCCP among acute chest pain patients presenting to hospital emergency departments or outpatient clinics. One of the most comprehensive diagnostic assessments of chest pain patients was undertaken in a study of 204 non-acute MI patients where an extensive diagnostic examination was conducted to determine the cause of their acute chest pain [27]. The diagnostic work-up included an electrocardiogram (n = 204), exercise electrocardiogram (n = 148), myocardial scintigraphy (n = 144), Holter monitoring (n = 136), hyperventilation test (n = 123), echocardiography (n = 146), chest radiograph (n = 204), pulmonary scintigraphy (n = 175), esophagogastroduodenoscopy (n = 133), pH monitoring in the esophagus (n = 125), Bernstein test (n = 87), physical examination of the chest wall (n = 147), bronchial histamine provocation test (n = 147), and ultrasonic

examination of the abdomen ($n = 148$). The main clinical conditions reported were gastroesophageal diseases (42%, $n = 85$), IHD (31%, $n = 64$), and chest-wall syndromes (28%, $n = 28$); pericarditis, pneumonia, pulmonary embolism, lung cancer, aortic aneurysm, aortic stenosis, and herpes zoster infection made up the remainder of diagnoses. The majority (89%) of patients in the gastroesophageal diseases group had an esophageal motility disorder or GERD. This study had limitations in that older patients (> 70 years) with severe heart failure were excluded, thus reducing the prevalence of those with IHD. Moreover, coronary angiography was not routinely used in this study; a subset of patients ($n = 56$) received an incomplete diagnostic evaluation, and therefore other possible diagnoses may have been missed; and no attempt was made to specify which diagnosis was important in terms of chest pain.

A study from the United Kingdom of 250 individuals admitted to hospital for chest pain attempted to determine the cause of each patient's chest pain [28]. Each patient was assessed as part of routine care, and diagnosis was based on the discharge diagnosis from the medical records. Initial classification of the 250 patients grouped them into cardiac chest pain (57%, $n = 142$) and "atypical chest pain" (43%, $n = 108$). Those with atypical chest pain consisted of the following: 25% ($n = 25$) musculoskeletal, 19% ($n = 21$) cardiac, 11% ($n = 12$) gastrointestinal, and 9% ($n = 10$) respiratory; 37% ($n = 40$) were discharged without a diagnosis. A major limitation of this study is the lack of a specific definition for "atypical chest pain," with the data based on medical records and a follow-up questionnaire 1 year after admission. Issues regarding the accuracy of medical records and potential recall bias associated with using a questionnaire that was sent 1 year after admission should be considered in terms of validity of the data reported.

There are many causes of NCCP, and the diagnoses of patients presenting with chest pain are diverse (Table 1). Reasons for variation among these studies include possible geographic and ethnic differences in the prevalence of conditions like IHD and GERD where the major presenting symptom is chest pain, the diagnostic protocol used to assess patients, and the treating physician's own experience with chest pain patients. In addition, the investigations used often reflect the specialty of the investigators concerned. Often, other causes for chest pain are not considered. For example, Katon et al [29] investigated a population undergoing cardiac catheterization from a psychiatric point of view. They found that a high proportion of the patients with normal coronary arteries had panic disorder. However, Jannsens et al [30], primarily using gastroenterologic investigations, found that over 90% of their patients had either "likely," "probable," or "suspected" esophageal causes for their chest pain. Evidently some overlap must occur, yet neither set of investigators considered this possibility. Different again was the study by Wise et al [31], who investigated NCCP patients for the presence of musculoskeletal pathology. They found

Table 1
Hospital or population-based studies that have classified noncardiac chest pain into clinical groups

Study	Study design	IHD	GERD	Psychiatric disorders	Musculoskeletal disorders	Microvascular disease	Others
Cannon et al (n = 87) [108]	Hospital-based	§	*	*	*	73%	27%
Janssens et al (n = 60) [30]	Hospital-based	§	88%	*	*	*	12%
Rouan et al (n = 772) [109]	Out-patient clinic	8%	9%	1%	23%	*	59%
Katon et al (n = 74) [29]	Hospital-based	§	*	79%	*	*	21%
Wise et al (n = 100) [31]	Hospital-based	§	*	*	16%	*	84%
Fruergaard et al (n = 204) [27]	Hospital-based	31%	42%	*	28%	*	12%
Eslick et al (n = 672) [26]	Population-based	7%	54%	24%	11%	*	12%

Abbreviations: GERD, gastrointestinal reflux disease; IHD, ischemic heart disease.

* Not considered.

Panic disorder or current major depression: 10.8% in group with CAD = current psychological diagnosis.

§ Already excluded.

Forty-two patients (out of 204) had more than one diagnosis.

From Eslick GD, Coulshed DS, Talley NJ. Review article: the burden of illness of non-cardiac chest pain. *Aliment Pharmacol Ther* 2002;16:1217–23; with permission.

this to be present and to be the likely cause of the symptoms in 16% of their patients ($n = 100$). Thus, the apparent prevalence of a particular disorder is related to the degree of enthusiasm with which it is sought, and causes may act synergistically to produce the symptoms.

Pediatric chest pain

Chest pain among children and adolescents is rarely associated with fatal disease [32]. Chest pain is the second most common symptom for referral to a pediatric cardiologist [33,34]. As with adults, chest pain among children and adolescents has various causes (Table 2) [35–48]. Several studies suggest that most of the chest pain among children and adolescents is noncardiac in origin [49–52]. Recently, a prospective study of 50 children (5–21 years of age; mean 13 years) referred to a cardiology clinic for assessment with the main complaint being chest pain to determine the causes of the chest pain [50]. Diagnoses included musculoskeletal pain (76%, $n = 38$), exercise-induced asthma (12%, $n = 6$), GI causes (8%, $n = 4$), and psychogenic causes (4%, $n = 2$). Thus, all causes of chest pain in this group were noncardiac in origin. A 4-year follow-up study on 55 children and adolescents (27 girls and 28 boys) with a mean age of 14 years (range 6–20 years) that presented to a cardiology clinic for chest pain [51] found that, at diagnosis the causes of chest pain were idiopathic (30%), musculoskeletal (32%), GERD (15%), supraventricular tachycardia (8%), anxiety (2%), mitral valve prolapse (2%), GERD with anxiety (2%), GERD with musculoskeletal (2%), and GERD with hyperventilation (2%). At follow-up, 27 (51%) of patients had no chest pain, whereas 26 (49%) had recurrent episodes of chest pain, with 12 of these patients reporting pain only sporadically. All the patients in this follow-up study had NCCP, with almost half reporting recurrent chest pain. Sabri et al [52] evaluated 132 children who presented with chest pain, of which 44 had epigastric tenderness to light palpation. These patients underwent endoscopy. Endoscopic findings included gastritis (75%, $n = 30$); duodenitis (13.6%, $n = 6$); gastro-duodenitis (11.4%, $n = 5$); and esophagitis, which was always with gastritis

Table 2
Causes of chest pain in children and adolescents

Chest pain cause	Prevalence range (%)
Idiopathic	12–85
Musculoskeletal	15–31
Pulmonary	12–21
Gastrointestinal	4–7
Cardiac	4–6
Psychiatric	5–17
Other	4–21

Data from [35–48].

(11.4%, $n = 5$). Only three (6.8%) had a normal endoscopy, and another three patients were positive for *Helicobacter pylori* based on urease test results. The findings of this study suggest that epigastric tenderness may be useful in the diagnosis of children with NCCP.

Risk factors

There is little information on the risk factors associated with NCCP. The risk factors for NCCP are as diverse as the conditions that cause NCCP. The major risk factors include the GI conditions (heartburn, acid regurgitation, dysphagia) and psychological conditions (depression, anxiety, neuroticism) [26]. These were recently assessed in a population-based study of NCCP [26] that found that all GI risk factors were univariately significantly associated with NCCP (heartburn: odds ratio [OR] 2.13, 95% confidence interval [CI] 1.50–3.02; dysphagia: OR 2.43, 95% CI 1.54–3.84; and acid regurgitation: OR 1.54, 95% CI 1.11–2.14). In a logistic model that included gender, age, heartburn, acid regurgitation, and dysphagia, only heartburn had an independent predictive effect on the presence of NCCP [26]. The study also investigated psychological risk factors associated with NCCP and, using univariate analysis, found that significant differences existed for neuroticism (OR 1.14, 95% CI 1.08–1.21) and anxiety (OR 1.12, 95% CI 1.08–1.17) but not for depression (OR 1.05, 95% CI 0.99–1.10). In a logistic model that included gender, age, neuroticism, anxiety, and depression, none of these variables had an independent predictive effect on the presence of NCCP [26].

A telephone interview study of 1200 adults asked about factors that trigger heartburn [53]. A range of “triggers” was reported by the respondents that included spicy foods (50.7%), greasy/rich foods (46.4%), stress (34.4%), alcohol (21.0%), overeating (36.8%), pregnancy (4.9%), smoking (9.6%), food allergy (14.0%), coffee (17.9%), other (19.5%), and don’t know (3.3%). The study found that heartburn was more common among married people (37.4%) compared with those who are unmarried (28.3%), whereas employment status was not reported as a significant trigger of heartburn. These findings have also been supported by Oliveria et al [54], who assessed risk factors among 2000 individuals with heartburn and found that certain foods, alcohol consumption, work habits, and lifestyle were associated with heartburn. A cross-sectional study of 1524 individuals reported that the main risk factors for GERD were obesity (OR 2.8, 95% CI 1.7–4.5) and family history (OR 2.6, 95% CI 1.8–3.7); other risk factors included alcohol consumption (OR 1.9, 95% CI 1.1–3.3), past history of smoking (OR 1.6, 95% CI 1.1–2.3), and a higher psychosomatic symptom score (OR per 5 units 1.4, 95% CI 1.3–1.6) [55]. Recently, a study was conducted on 1000 adults who experienced heartburn at least once a week, and 79% ($n = 791$) of them reported experiencing heartburn at night; heartburn affected the sleep of 75% ($n = 593$) of individuals [56].

Menopause has been proposed as another risk factor for NCCP. Rosano et al [57] found higher rates of NCCP (cardiac syndrome X) among 107 women in the perimenopausal period or after menopause (age 53 ± 9 years) compared with men in the same age group. It was proposed that a deficiency of estrogen may initiate cardiac syndrome X in these women, although this has not been substantiated. More support has recently been given to this finding with data from a population-based study (Fig. 1) that shows that women 50 to 59 years of age have a statistically significant increase in the prevalence of NCCP compared with men [26].

Gastrointestinal, psychological, and lifestyle risk factors play an important role in the development of NCCP (Box 2). However, risk factors for NCCP require further examination because elimination of these risk

Box 2. Potential indicators and risk factors for NCCP

- Younger age
- Family history
- GI conditions
 - Heartburn
 - Dysphagia
 - Acid regurgitation
- Psychological conditions
 - Neuroticism
 - Anxiety disorders
 - Depression
- Menopause (estrogen deficiency)
- Alcohol
- Stress
- Food allergy
- Greasy/rich foods
- Spicy foods
- Overeating
- Smoking
- Pregnancy
- Obesity
- Citrus fruits or juices
- Tomato products
- Chocolate
- Peppermint
- Caffeinated beverages (ie, coffee)
- Carbonated beverages
- Prescription medication

factors, in particular modifiable lifestyle risk factors, benefits patients who are prone to attacks of NCCP.

Quality of life

There are few studies assessing quality of life (QOL) among individuals with NCCP. One of these has been population based, whereas two others have been hospital based in design [26,58,59]. Atienza et al [58] assessed a newly developed QOL instrument (specifically for patients with syndrome X) among 90 patients with syndrome X (chest pain and normal coronary arteriograms) and reported that QOL was significantly impaired in patients with syndrome X. This study had no comparison group with which to compare the QOL instrument and scores. In a recent study conducted in Hong Kong, NCCP patients undergoing endoscopy ($n = 78$) and healthy control subjects ($n = 20$) completed the SF-36 QOL questionnaire [59]. In all SF-36 domains, NCCP patients reported lower scores than the control subjects. Significant domains included physical functioning, role-physical, and general health. The hospital-based studies have evaluated patients with NCCP and have shown that these patients had a poor QOL and that their QOL profiles worsened in accordance with increasing severity of their chest pain [58,59]. A recent population-based study found similar results with significant differences in the mean QOL scores between individuals with nil pain, non-severe NCCP, and severe NCCP, with those experiencing severe NCCP having the worst QOL (Fig. 2) [26]. These results highlight the fact that NCCP can be a highly incapacitating condition if severe.

Health care seeking

Little is known about health care use among people experiencing NCCP. There is a paradox associated with individuals consulting for chest pain; that is, too many people present with chest pain, yet still not enough. Chest pain is the second most common presentation to hospital emergency departments. However, studies suggest that only 25% of individuals with chest pain actually present to hospital [75].

Reasons for health care seeking

The perception and verbal report of NCCP is a complex process, probably mediated by a number of factors, including symptom severity, anxiety, depression, individual cultural values, and secondary gain [60–64]. Little is known about the factors that drive health care seeking among people experiencing NCCP, and it is unknown whether health care seeking behavior for NCCP patients is qualitatively or quantitatively different from health care seeking for cardiac chest pain patients. Data from a population-based study have reported that almost one quarter of individuals with

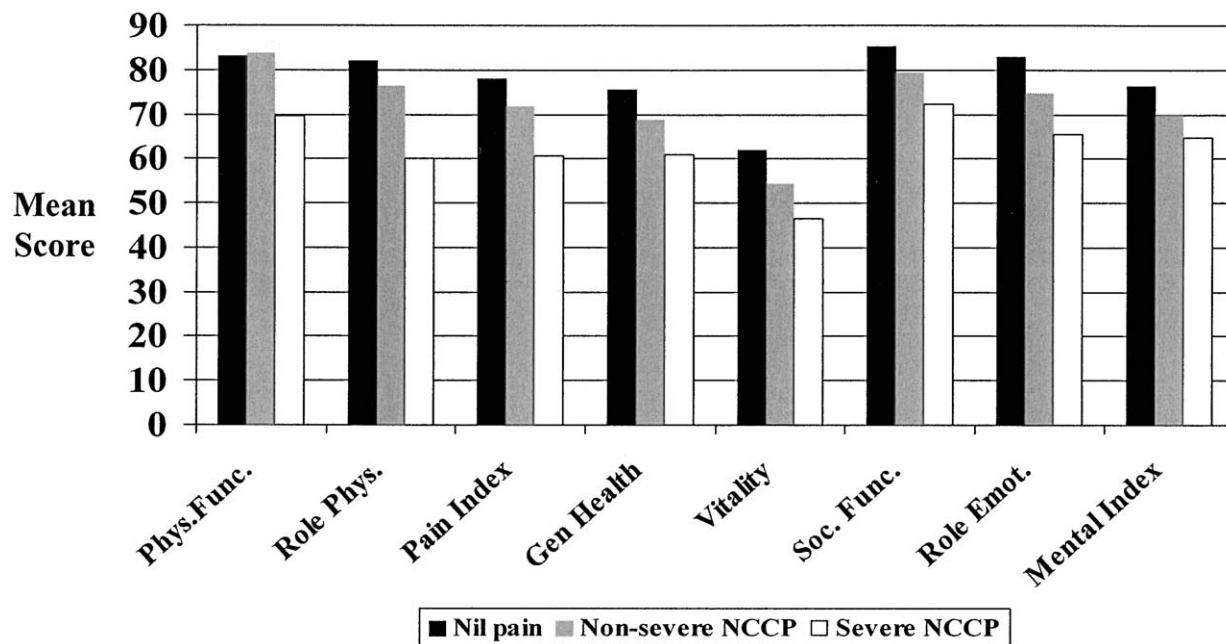


Fig. 2. QOL among individuals with NCCP. Those with severe NCCP have a much worse QOL compared with those with nonsevere or mild NCCP. (Data from Eslick GD, Jones MP, Talley NJ. Non-cardiac chest pain: prevalence, risk factors, impact and consulting – a population-based study. *Aliment Pharmacol Ther* 2003;17:1115–24.)

NCCP had sought health care primarily about their chest pain within the previous 12 months [26] and that the most common reason for health care seeking was anxiety about symptoms. An unusual finding was made in this study when comparing health care seeking between severe and nonsevere NCCP. Individuals with nonsevere NCCP were five times more likely to consult a physician than those with severe NCCP (OR 5.11, 95% CI 2.30–11.34), and this was not accounted for by psychological distress. This result seems counterintuitive, but a possible explanation may be that nonsevere NCCP could be more chronic over time, and this persistence of symptoms may lead to health care seeking.

A small hospital-based prospective study reported that patients with “non-specific” chest pain more frequently sought medical care than patients with IHD [65]. Studies have shown that among patients with heartburn, psychological factors are strongly associated with health care seeking behavior [66]. This study also reported that among those with heartburn, health care seekers and non-health care seekers differed significantly in terms of increased symptom severity and greater levels of psychological distress (eg, phobia, obsession, and somatization) [66]. Thus, this study concluded that health care seeking behavior was influenced by the interaction of heartburn severity and psychosocial factors.

Predictors of health care seeking for NCCP require further examination. Koloski et al [67–69] have described the predictors of health care seeking for other related functional GI disorders (irritable bowel syndrome and non-ulcer dyspepsia). Whether the results of these conditions can be extrapolated to NCCP is uncertain.

Who presents with noncardiac chest pain?

Kennedy et al [70] reported that females are more likely to present to hospital emergency departments with NCCP than males. Another study reported that in the age groups of less than 25 years and between 45 and 55 years, females were more likely to present to hospital for chest pain (Fig. 3) [26]. In addition, males overall were almost two times more likely to present for chest pain (OR 1.74, 95% CI 1.02–3.00) and were more likely to present in the age groups 25 to 35, 35 to 45, 55 to 65, and over 65 years [26]. The reason why health care seeking for chest pain was more common among males and older people is most likely because these groups are at a perceived “higher” risk for having a possible acute ischemic event.

A study in the United Kingdom involved 2000 individuals who were selected from general practitioners’ lists and were sent a questionnaire that included a fictional case history of a person with chest pain and questioned the respondents on how they would react if they experienced the chest pain [71]. The study reported that Asians (Hindu and Sikhs) would be more anxious about the chest pain than Europeans. Of the male respondents, 47% Sikhs, 38% Hindus, and 23% Europeans said they would seek immediate

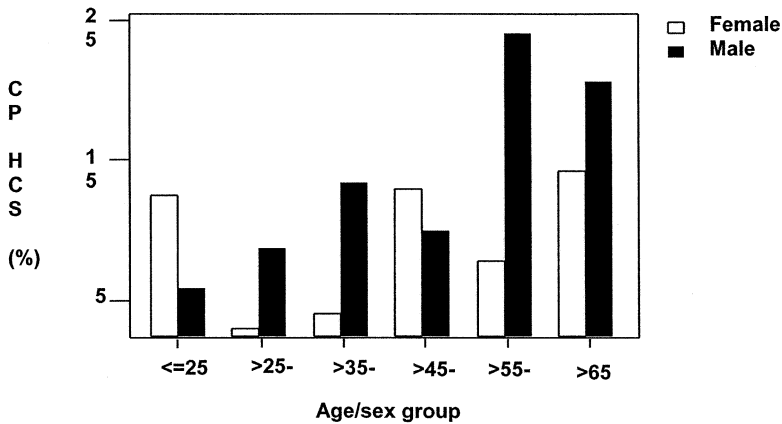


Fig. 3. Age and gender of individuals that consulted for chest pain. Women < 25 years of age or between 45 to 55 years are more likely to present for NCCP as are men over 55 years of age.

medical care, whereas among the female respondents, 46% Sikhs, 35% Hindus, and 24% Europeans would seek immediate health care. This suggests that Asians are more likely than Europeans to seek health care for assessment of chest pain symptoms.

Studies comparing African Americans and whites indicate that African Americans are inclined to report fewer painful chest pain symptoms and ascribe their symptoms to noncardiac causes, which in turn may be related to differences in health care seeking for acute chest pain [72,73]. Furthermore, differences in health care seeking behavior for African Americans are related to access to health care, socioeconomic status (SES), and gender [73]. A recent qualitative study that explored the socio-economic variations in perceptions and behavioral responses to chest pain found that patients from low SES felt more vulnerable to heart disease (because chest pain is associated with IHD and an unhealthy lifestyle) [74].

Which health care professional?

Which health care providers do individuals who present with acute chest pain most commonly use? A recent study attempted to determine the health care seeking behaviors of those with acute chest pain [75]. This was a prospective cohort study of 212 (84 women and 128 men) individuals 18 to 90 years of age (mean 57 years) who presented to a hospital Emergency Department with acute chest pain. In the previous 12 months, 78% of patients had seen a health care professional for chest pain. The types of health care professionals seen for chest pain in the 12 months before presentation to the Emergency Department were 85% general practitioner,

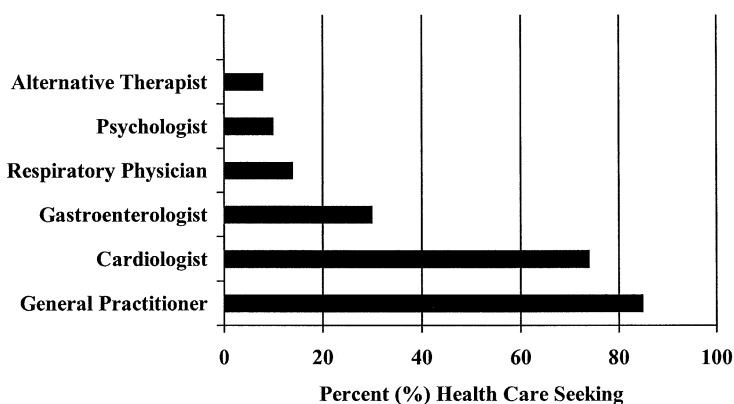


Fig. 4. Types of health care professional seen by patients with NCCP. (Data from Eslick GD, Jones MP, Talley NJ. Acute chest pain and health care seeking behaviour: role of reflux symptoms. *J Gastroenterol Hepatol* 2001;16(Suppl):A329.)

74% cardiologist, 30% gastroenterologist, 14% respiratory physician, 8% alternative therapist, and 10% psychologist (Fig. 4). Increasing chest pain severity and frequency was related to visiting a cardiologist ($P < 0.001$), and increased symptom frequency was also associated with consulting a psychologist ($P = 0.01$). A multiple logistic regression analysis found that patients with chest pain suffering heartburn were 16 times more likely to see a general practitioner (OR 16.40, 95% CI 1.98–135.99) and more than three times more likely to consult a gastroenterologist (OR 3.10, 95% CI 1.26–7.62). Patients with acid regurgitation were four times more likely to consult a general practitioner (OR 4.40, 95% CI 1.36–14.20) than any other type of medical professional. Therefore, consulting for chest pain is common in this group of select patients. The type of health care professional seen seems to be moderated by the frequency and severity of reflux symptoms among patients with chest pain [75].

Reasons for delay in health care seeking for chest pain

The reasons for delay in health care seeking by individuals with chest pain remain unclear and need to be established if education campaigns, health promotion activities, and health care policy are going to target those most at risk and those least likely to present to hospital with chest pain. Factors that bring individuals with chest pain to hospital can also discourage others from presenting for medical care. Furthermore, these factors often overlap and may include symptom severity, anxiety, depression, individual cultural values, and secondary gain [60–64]. There have been studies conducted to assess patients' delay in response to heart attack symptoms [76–80]. One study found that over 50% of AMI patients ($n = 317$) delayed in seeking treatment by 6 hours or more and that

cognitive and social factors contribute to this delay in health care seeking [79]. An interview-based study on patients ($n = 2314$) who were admitted for suspected AMI found that the main reasons for delay in health seeking included the following [77]:

- The patient thought that the symptoms would go away
- Symptoms were not severe enough to seek care
- The patient thought that symptoms were those of another illness (mainly indigestion)
- Worry about cost of medical care
- Fear of hospitals
- Fear of embarrassment
- The patient did not want to find out what was wrong
- The patient wanted to wait until a better time

Meischke et al [76] examined 426 individuals who presented to a hospital emergency department with a chief complaint of chest pain to assess their experiences and intention to delay health care seeking in response to symptoms. They found that less-educated patients were unsure if going to the emergency department was the right thing to do and that the more embarrassed patients felt the more likely they were to delay health care seeking. An important finding was that patients who were prompted by health care professionals to go to the emergency department were less likely to delay health care seeking for future symptoms.

Delay in health care seeking is also related to pre-hospital factors. A recent Canadian study reported that overcrowding of hospital emergency departments was associated with substantial delays in response by ambulance transport for patients with chest pain [80].

It has been proposed that the reason an individual may delay seeking treatment for chest pain is related to the immense resistance and rationalization that occur early on when symptoms are mild or minimal and that only when severe (and potentially fatal) chest pain develops does a patient feel the need to present to hospital [81]. It has been suggested that the symptom “chest pain” itself should be a risk factor because when “meaningful chest discomfort” commences, a patient is more at risk of sudden death than by having elevated cholesterol levels or a history of smoking [81]. A recent study compared acute chest pain outcomes between city and country hospitals in Sweden and found that complications were reported more often in country hospitals, use of medical resources was mixed between the two settings, and 2-year mortality was similar between the two settings (3.2% city and 3.0% country) [82]. This study had several limitations, including differences in baseline patient characteristics because country patients were older and had a higher prevalence of prior heart failure and hypertension, whereas individuals from the city had a higher prevalence of smoking and previous revascularization [82]. The findings highlight that a patient admitted with chest pain has a 1 in 8 chance of dying within 2 years [82,83].

Chest pain centers

The first chest pain center (CPC) opened in January 1981 at St. Agnes Hospital in Baltimore, Maryland, and was pioneered by Raymond Bahr [81,84]. CPCs were initially developed to facilitate rapid assessment of chest pain patients and the subsequent treatment of patients with AMI [85–87]. CPCs have generally been accepted as a safe and cost-effective method of assessing low-risk patients presenting with acute chest pain [86,88,89]. In the United States, the number of CPCs has increased steadily, and it was recently estimated that one third of all hospitals have a CPC (~1200 centers) [90–93]. The major purpose of CPCs is to improve outcomes for individuals with a suspected AMI [94]. However, this has recently been questioned. Eslick and Coulshed [95] have suggested that CPCs should not place too much emphasis on excluding cardiac ischemia. The focus should be on achieving a definite diagnosis that explains for NCCP patients the symptoms they are experiencing because this is often the most important part of the care of such patients [96]. CPCs have become an important part of assessing all patients who present to hospital with cardiac or noncardiac acute chest pain. They play a role in the immediate assessment of those admitted with AMI; however, in the future CPCs may be more involved in determining a “cause of chest pain” among patients with NCCP in the form of an outpatient clinic. CPCs are rapidly evolving not only in the United States but also in Australia, the United Kingdom, Brazil, and other countries around the world.

Natural history of noncardiac chest pain

The natural history of NCCP remains largely unexplored. Before a group of individuals with NCCP can be identified, there must be agreement on the definition of NCCP. Because there is considerable overlap and disparity in the definitions used for NCCP, there will be significant variations between studies. To assess the natural history of NCCP, a population-based study would offer the benefits of reduced bias (referral bias) and a randomly selected sample. However, persuading individuals from the community to undergo diagnostic testing is difficult, which explains why no population-based natural history studies of NCCP have been reported. A few hospital-based (patient-based) studies have addressed the long-term outcome of patients with NCCP [97–106].

One study conducted an 11-year follow-up on 46 chest pain patients with normal coronary arteries; only four patients had died; the causes of death were stroke, cancer, suicide, and ischemic heart disease [97]. At follow-up, 74% ($n = 31$) of the surviving 42 patients reported chest pain in the preceding 6 months, and 39% ($n = 18$) had chest pain at least once a week. In another follow-up study, patients with chest pain ($n = 821$) with normal coronary arteries (determined by coronary angiography) were assessed in

terms of mortality and morbidity [98]. After 1 year, 67% continued to experience some degree of chest pain (39% less pain, 26% same pain, 2% worse pain), and the mortality was 0.3% ($n = 3$), with these patients dying due to nonischemic events. Longer follow-up studies have also reported that patients with “atypical” chest pain followed for 5 years continue to experience chest pain (74%) and continue to have associated impaired functional status and health care seeking because of their chest pain [99,100]. Other studies have reported similar findings [101–105].

Wilhelmsen et al [106] in a 16-year follow-up study found that mortality (cardiac and noncardiac) was high among men aged 51 to 59 years ($n = 6488$) with chest pain who did not have angina pectoris. The relative risk of coronary heart disease mortality among men with “non-specific” chest pain was 2.77 (95% CI 2.20–3.50). This study was limited by the fact that it included only men aged between 51 and 59 years. The results of this study are not generalizable because there is no comparison with women or those from younger age groups.

Recently, a 2-year prospective cohort study assessed the natural turnover of NCCP and related symptoms and QOL [107]. The sample consisted of individuals who presented to a hospital emergency department with acute chest pain. At initial presentation, patients who elected to undergo further diagnostic tests were assessed according to a standard protocol. All patients, including those who do not wish to undergo further diagnostic procedures, were asked to fill out the CPQ. Two years after first presentation, the patients were sent another CPQ that measured symptoms, risk factors, psychological distress, QOL, and general demographics. At baseline, 212 acute chest pain patients were recruited into this study. Sixty-one percent ($n = 129$) were diagnosed with NCCP and were followed over 2 years. Over the 2-year period, NCCP disappeared among 19% ($n = 23$) and remained unchanged for 70% ($n = 86$) of the NCCP patients. Other chest pain risk factors were measured in this cohort (Table 3). Patients with changing heartburn symptoms had a significantly lower QOL (physical function, $P = 0.007$; role physical, $P = 0.03$). Moreover, patients with changes in heartburn symptoms also had higher levels of neuroticism ($P = 0.04$).

Table 3

Natural history of risk factors and indicators for noncardiac chest pain

Symptoms	Appear	Disappear	No change
Heartburn	14% ($n = 16$)	19% ($n = 22$)	68% ($n = 80$)
Acid regurgitation	13% ($n = 15$)	13% ($n = 15$)	74% ($n = 84$)
Dysphagia	6% ($n = 7$)	8% ($n = 10$)	85% ($n = 100$)
Angina pectoris	6% ($n = 6$)	5% ($n = 5$)	88% ($n = 82$)
Acute myocardial infarction	5% ($n = 5$)	4% ($n = 4$)	91% ($n = 95$)

Data from Eslick GD, Jones MP, Talley NJ. Stability of gastrointestinal symptoms, psychological and quality of life risk factors among patients with non-cardiac chest pain (NCCP): a prospective cohort study. *Gastroenterology* 2002;122(Suppl 4):A466.

Change in heartburn symptoms was negatively correlated with increased depression ($r = -0.18$, $P = 0.04$), whereas anxiety symptoms were positively correlated with acid regurgitation ($r = 0.19$, $P = 0.03$). Patients with NCCP showed some change in heartburn, acid regurgitation, and dysphagia, but when compared with other risk factors, the majority of changes were not statistically significant. Overall, GI symptoms and psychological and QOL factors remained stable (unchanged) among NCCP patients in the course of this 2-year follow-up study.

Although the prognosis for patients with NCCP is generally considered to be excellent, this has not been adequately assessed in the general population and deserves further attention. Most studies report the persistence of chest pain in the majority of patients and its association with impaired functional status, chronic use of cardiac drugs with repeated admissions to the hospital, and cardiac catheterizations. Therefore, the levels of health care use and the costs associated with NCCP are high.

Summary

The epidemiology of NCCP is poorly described, and the available data are conflicting. Population-based studies on the prevalence of NCCP are rare; most studies have been hospital based. According to the limited studies available, the annual prevalence of NCCP is approximately 25%. Despite this significant burden, the impact and natural history of NCCP in the community has not been adequately explored. NCCP is presumed to be a heterogeneous condition. Hospital-based studies have suggested that GERD, esophageal spasm, psychiatric disease (including panic attacks), and musculoskeletal pain explain many cases of NCCP. However, unrecognized coronary artery disease and microvascular angina (cardiac syndrome X) also explain an unknown proportion of cases in the general population. Current studies suggest that NCCP is common in the general population and significantly affects QOL, yet only a minority seeks medical attention. The epidemiology of NCCP requires further study in the general population and in those attending the Emergency Department.

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Esophageal perception and noncardiac chest pain

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Recurrent chest pain is among the most common clinical complaints because of an appropriate concern that it may reflect serious, possibly life-threatening, heart disease. Although most patients with such complaints are eventually referred to a cardiologist for definitive workup, ~30% have a negative cardiac catheterization examination indicating the absence of significant coronary artery disease. Based on this negative evaluation, these patients are described as having noncardiac chest pain (NCCP) [1,2]. NCCP is a symptom complex that, in its broadest context, includes patients with heartburn, odynophagia, and pleurisy. In most instances, patients with these complaints are readily diagnosed and treated successfully for the underlying disease (eg, reflux esophagitis, infectious or pill-induced esophagitis, or upper respiratory infection). Nonetheless, a significant number of patients remain with undiagnosed NCCP. Typically these patients complain of pain that resembles angina (substernal squeezing or pressure with or without radiation to neck, jaw, arm but with negative coronary angiography) or heartburn (substernal burning with or without oral radiation or relationship to meals or body position but with negative upper endoscopy and esophageal pH monitoring studies) [3]. In most instances, the source for the NCCP is believed to emanate from the esophagus. Why this is so speaks to the location of the organ, its repertoire of responses to noxious stimuli, and the complexity of the neuroanatomic pathways that enable pain perception. These areas are the subjects of this article.

Pain and perception

Pain and its perception irrespective of site of origin represents a series of events: (1) a localized pathophysiologic sequence leading to activation of

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pain-sensing neurons known as nociceptors, (2) the transmission of this nociceptor activation to the central nervous system (CNS), and (3) its recognition by the sensory cortex in the brain. These events are highly complex and variable. For instance, the local and central determinants of pain perception vary with the intensity, duration, and nature of the peripheral stimulus and with the speed and type of the neuroanatomic pathways involved for its transmission, localization, interpretation, and reaction. Moreover, reactions to pain may differ with the same stimulus based on psychologic factors such as personality, ethnicity, culture, and circumstances of the injury.

Origin of esophageal pain

Esophageal pain originates from the activation of nociceptors within its wall. Nociceptors can be one of two types: chemoreceptors, which respond to chemical or thermal stimulation; or mechanoreceptors, which respond to wall stretch [4,5]. Chemosensitive nociceptors are found predominantly within the esophageal mucosa and submucosa and are activated by tissue injury and inflammation. A host of substances mediate this activation, including hydrogen ions, potassium ions, histamine, serotonin, bradykinin, substance P, neurokinin A (NK-A), calcitonin gene-related peptide (CGRP), glutamate, prostaglandins, and leukotrienes. In contrast, mechanosensitive nociceptors are located predominantly within the submucosa, muscularis propria, and adventitia and are activated principally by wall distension. None of the esophageal nociceptors respond to acute cutting, tearing, or crushing of tissue, which in part explains the lack of discomfort associated with obtaining endoscopic esophageal mucosal biopsies. When activated, chemosensitive and mechanosensitive nociceptors transmit their impulses through small, unmyelinated C-fibers or myelinated A δ -fibers. C-fibers are known to transmit their signals relatively slowly, and pain perception transmitted by them is usually perceived as dull, burning, gradual, and poorly localized. In contrast, A δ -fibers transmit signals quickly, and the perception of the pain transmitted is typically sharp, sudden, and well localized. Because the number, rate, and type of fiber activated by a given stimulus can materially change the pain response, it is easy to appreciate how esophageal balloon distension in humans may be perceived as chest pain in most but as heartburn in others and how esophageal acid perfusion may be perceived as heartburn in most but as chest pain in others.

Neuroanatomic pathways of esophageal pain

Once nociceptors within the esophageal wall have been activated, their impulses are transmitted peripherally and centrally (Fig. 1). Peripheral transmission involves local reflex arcs for activation of afferent and efferent

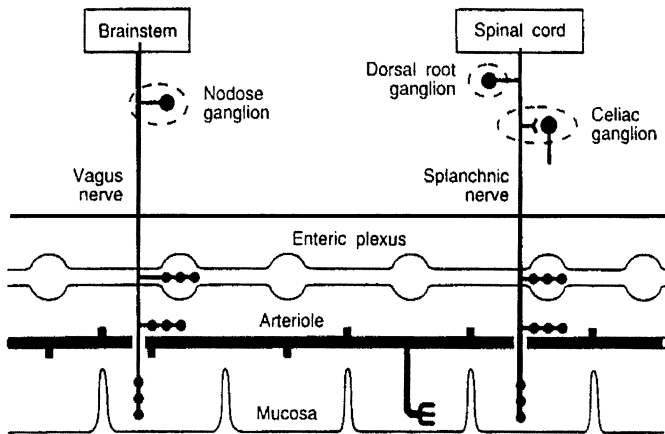


Fig. 1. Innervation of the mammalian upper digestive tract by extrinsic primary afferent neurons. Afferent neurons in the vagus nerves originate from the nodose ganglia, whereas afferent neurons in the splanchnic nerves have their cell bodies in the dorsal root ganglia. (Modified from Holzer PR. Neural emergency system in the stomach. *Gastroenterology* 1998;114:823–39, with permission.)

signals to muscle, glands, and blood vessels; these can lead to adaptive, possibly protective, responses in the form of altered motility, secretion, and blood flow. Central transmission is required for pain perception, and this occurs via peripheral spinal and vagal afferent nerves. Spinal afferents, which are the predominant means for transmission of pain, send their information to the spinal cord via the sympathetic nerves, and vagal afferents, which are principally involved with pain modulation, send their information to the CNS (medulla) via the vagus nerve (see Fig. 1) [6].

The detailed neuroanatomic pathways by which spinal afferents transmit pain to the brain include transmission via first-order neurons located in the dorsal root ganglia and second-order neurons in the dorsal horn of the spinal cord, each distributed over several spinal segments. After reaching the spinal cord, pain signals cross the midline and ascend via the spinothalamic and spinoreticular pathways to synapse with third-order neurons in the thalamus and reticular nuclei, the latter transmitting the signals to the somatosensory cortex for localization and interpretation, including intensity. Only spinal afferents transmit pain signals to the somatosensory cortex for recognition, whereas spinal afferents and vagal afferents transmit signals to the limbic system for affective and motivational assessment and to the frontal cortex for evaluation of pain. The detailed neuroanatomic pathways by which vagal afferents send impulses to the brain for pain modulation include transmission via first-order neurons located in the nodose ganglia and second-order neurons located in the nucleus tractus solitarius within the medulla, the latter then transmitting impulses to the limbic system and frontal cortex. There is considerable overlap between the

neuroanatomic pathways for the esophagus with those of the heart, lungs, trachea, and bronchi. For instance, vagus nerve impulses from the cardio-pulmonary region converge with those of the esophagus before passing to the medullary centers in the brainstem (Fig. 2). Similarly, there is overlap of pain

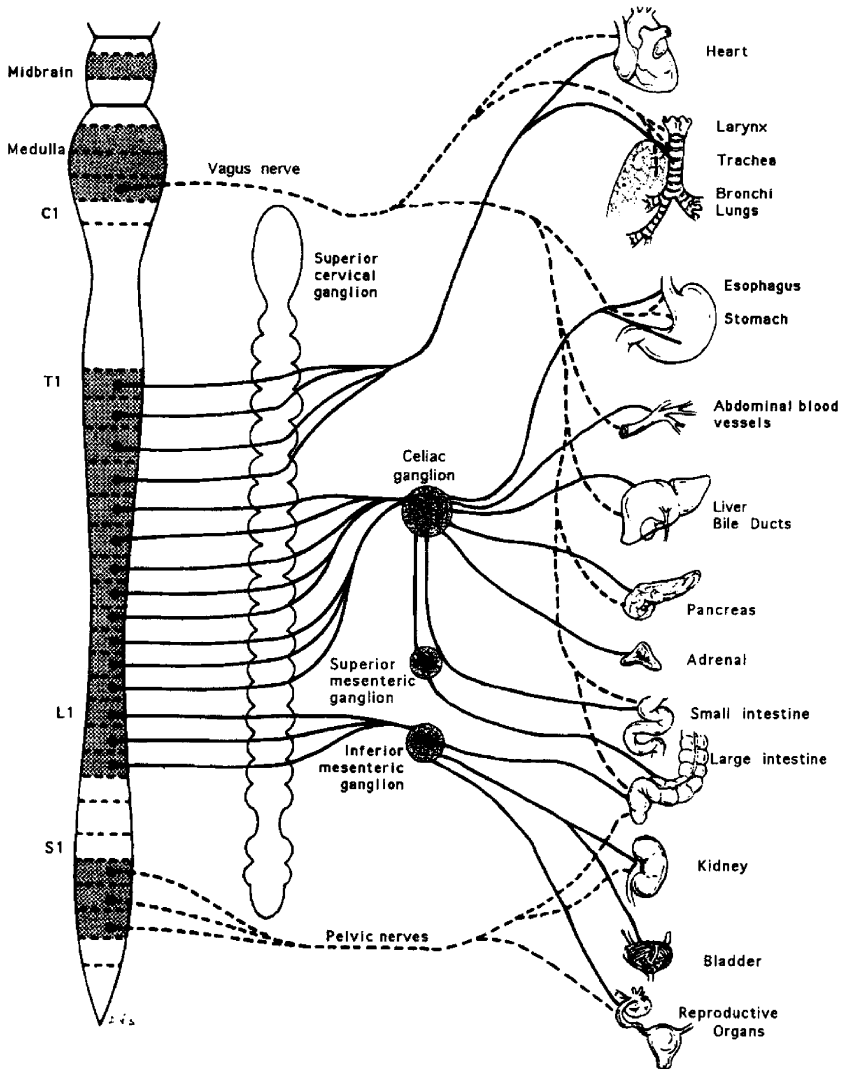


Fig. 2. Esophageal pain pathways are traced from the periphery via the sympathetic nervous system and vagus nerve to the CNS. For the vagus nerve, there is overlap between impulses arising within the esophagus and passing to the CNS and that arising in the heart, lungs, trachea, and bronchi. Overlap also exists for impulses that travel via the sympathetic nervous system (not shown). (Modified from Heimer L. The human brain and spinal cord: function neuroanatomy and dissection guide. New York: Springer-Verlag; 1983. p. 125; with permission.)

transmission pathways via sympathetic nerves from the cardiopulmonary and esophageal regions (not shown). It is therefore not surprising why the localization of NCCP to esophagus, heart, trachea, bronchi, or lungs may not be possible in many situations [7].

Esophageal pain modulation

Esophageal nociceptor impulses transmitted to the brain eventually ascend to and activate neurons of the anterior cingulate cortex, somatosensory cortex, and insula (Fig. 3) [8–10]. From these areas, afferent pain-inhibitory impulses are transmitted through descending fibers. These impulses, coupled with the descending pain-inhibitory impulses arising from neurons within the periventricular and periaqueductal gray matter, pons, and medullary nuclei, constitute the endorphin-mediated analgesia system (EMAS). Fibers within the EMAS descend and synapse with the second-order neurons within the dorsal horns of the spinal cord where they inhibit afferent pain impulses

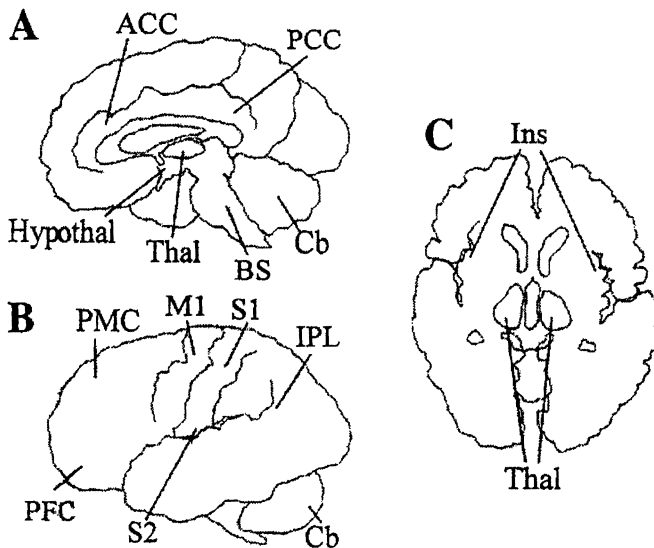


Fig. 3. Principal cerebral structures activated in functional imaging studies of somatic and visceral stimulation. (A) Medial view of right cerebral hemisphere. (B) Medial view of left cerebral hemisphere. (C) Cerebral cross-sectional view at the level of the insulae and thalami. ACC, anterior cingulate cortex; BS, brain stem; Cb, cerebellum; Hypothal, hypothalamus; Ins, insula; IPL, inferior parietal lobule; M1, primary motor cortex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; PMC, premotor cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; Thal, thalamus. (From Ladabaum U, Minoshima S, Owyang C. Pathobiology of visceral pain: molecular mechanisms and therapeutic implications V. Central nervous system processing of somatic and visceral sensory signals. *Am J Physiol Gastrointest Liver Physiol* 2000;279:G1–6; with permission.)

through the release of opioids, serotonin, and norepinephrine, which act on μ -opioid, 5-hydroxytryptamine (types 1,2,3), and α_2 -adrenoreceptors, respectively. Adding to the complexity of the system, there is cross-talk among central neurons (including, for example, impulses arising from the periaqueductal gray matter) that when transmitted to the rostroventral medulla facilitate pain transmission in some instances while inhibiting pain transmission other circumstances [11].

A central player in pain modulation is the neurons within the dorsal horn of the spinal cord. These neurons may be altered biochemically and physiologically to increase pain impulse transmission and perception or to decrease pain impulse transmission and perception; these modifications are known as the “gate control theory.” This theory suggests that pain perception can be enhanced if enough neurotransmitters—especially glutamate and small peptides (substance P, CGRP, NK-A)—are released by repeated peripheral nociceptor activation to subsequently activate the N-methyl-D-aspartate (NMDA) channel in the second-order neuron membrane (Fig. 4). When activated, the NMDA channel, through loss of inhibition by magnesium ions and influx of calcium ions, depolarizes the neuronal membrane, making it more excitable and susceptible to amplification and prolongation of received impulses. This process, which is referred to as “wind-up,” is likely responsible for the phenomena known as allodynia (nonpainful stimuli perceived as painful) and hyperalgesia

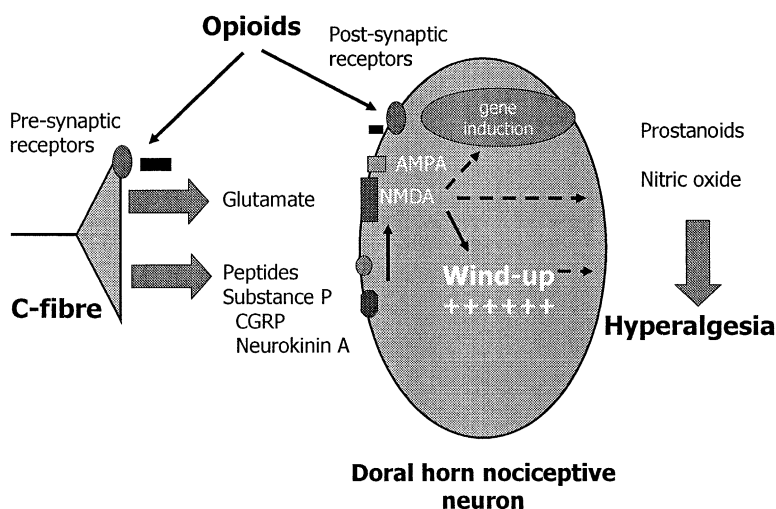


Fig. 4. A schematic diagram illustrating the release of the excitatory transmitters from C-fibers and the subsequent effects on a dorsal horn nociceptive neuron. The predominant synaptic action of opioids (reducing the release of these transmitters) and the post-synaptic action (reducing neuronal activity) are shown (From Dickenson AH. Spinal cord pharmacology of pain. *Br J Anaesth* 1995;75:193–200; with permission.)

(painful stimuli perceived at exaggerated levels) [12–17]. Moreover, the durability of allodynia and hyperalgesia has been explained by the fact that the calcium ions entering the NMDA channel bind to calmodulin and by so doing stimulate nitric oxide (NO) synthase to produce NO. NO generation increases pain transmission short-term by increasing the second-order neuron's membrane excitability via a feed back loop that stimulates the release of excitatory neurotransmitter from the synaptic membrane of the first-order neuron. NO generation also increases pain transmission more long-term by upregulating the genes for c-fos and dynorphin, which have been reported to increase membrane excitability for days to weeks (see Fig. 4) [12,13,18].

Esophageal symptoms and visceral hypersensitivity

The majority of patients with reflux symptoms (ie, heartburn) have a damaged esophageal epithelium on endoscopic or microscopic examination. Because breaks in the epithelial barrier permit luminal acid access to the sensory neurons, such defects seem to explain the origin of symptoms [19]. In support of this, Fass et al [20] found that patients with well documented reflux disease were not hypersensitive to esophageal balloon distension even though they exhibited a sensitivity to acid perfusion that paralleled the degree of tissue injury. Moreover, hyperalgesia to balloon distension in these patients was not induced by prior esophageal acid perfusion as has been reported to occur in healthy subjects [21,22]. Trimble et al [23] also noted that patients with reflux symptoms and pathologic reflux and those with Barrett's esophagus showed no evidence of visceral hypersensitivity to esophageal balloon distension. However, Trimble et al did identify a subgroup of patients with reflux-like symptoms and normal esophageal pH monitoring that responded to balloon distension at lower thresholds than did healthy subjects. These data indicate that reflux symptoms are one way that patients with visceral hypersensitivity present clinically, but the pathogenesis of such symptoms in patients with visceral hypersensitivity are fundamentally different from those of patients with reflux esophagitis [23].

NCCP is another presenting symptom in patients with visceral hypersensitivity. This is supported by the studies of Mehta et al, Sarkar et al, and Rao et al [21,24,25], in which patients with NCCP exhibited hyperalgesia to esophageal acid perfusion, electrical stimulation, or balloon distension. Moreover, Sarkar et al [24] showed that acid perfusion of the lower esophagus in those with NCCP was followed by hyperalgesia to electrical stimulation in the upper esophagus, indicating that this phenomenon is of central (brain or spinal cord) rather than peripheral origin. Yet, just as reflux symptoms do not identify a pure population with reflux disease, visceral hypersensitivity is not the only—or even necessarily

the major—cause of NCCP. For instance, Mehta et al [21] noted visceral hyperalgesia to esophageal balloon distension only in a subset of patients with NCCP—specifically those that responded with chest pain to prior intravenous edrophonium or esophageal acid perfusion. Moreover, the pain thresholds to esophageal balloon distension in this group did not decline after esophageal acid perfusion in contrast to what was observed in healthy subjects and in patients with NCCP that had negative intravenous edrophonium and esophageal acid perfusion tests.

Summary

Symptoms arising from the esophagus are produced generally in one of two ways: through stimulation of chemosensitive-nociceptors (eg, through excess esophageal exposure to refluxed gastric acid or the resulting inflammation arising in acid-damaged tissue) or through stimulation of mechanosensitive nociceptors (eg, through repeated deformation or distension of the esophageal wall resulting from peristaltic or lower esophageal sphincter dysfunction). These symptoms are usually attributed in most patients to such well recognized conditions as reflux esophagitis, achalasia, etc. that subsequently result in the delivery of specific and effective treatment. However, a subset of patients exists in which the etiology of “similar-sounding symptoms” remains obscure and their responses to standard specific treatments poor. Now recognized as among this group of patients are those with visceral hypersensitivity. Visceral hypersensitivity is not itself a disease but a definable aberrant sensory response (allodynia or hyperalgesia) to end-organ stimulation. Such an aberrant sensory response is neither specific for nor limited to the esophagus, and the etiopathogenesis for its development within this organ is unknown. Nonetheless, esophageal symptoms as a manifestation of visceral hypersensitivity are increasingly recognized and worthy of attention because they identify a disorder that responds to treatment aimed at the end organ’s nociceptors or their neuroanatomic pathways within the CNS.

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Evaluation of chest pain: a cardiology perspective for gastroenterologists

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A cardiologist is often the first physician to see a patient with chest pain, whether the origin is cardiac or noncardiac. As many as 55% of patients who report to an emergency room with chest pain or other symptoms suggestive of acute cardiac ischemia have noncardiac problems [1], and approximately 30% of patients evaluated for chest pain by coronary angiography each year show no evidence of coronary artery disease [2].

The cardiologist's first responsibility is to exclude any acute life-threatening condition. Then, an evaluation for chronic ischemic heart disease is conducted. Once these have been ruled out as possible causes of chest pain, a diagnosis of noncardiac chest pain (NCCP) is made, and the patient is treated for NCCP or referred to a gastroenterologist or other specialist for follow-up. An understanding of NCCP from the cardiology and gastroenterology perspectives is necessary for effective management of this disorder. Many of these patients repeatedly return to the emergency room if the gastrointestinal disorder is not adequately treated or if they do not understand that their symptoms are not signs of an impending heart attack [3]. On the other hand, a missed diagnosis of a cardiac event can have tragic consequences. The overlap in symptoms for cardiovascular disease and NCCP can make accurate diagnosis difficult and highlights the need for collaboration on the part of both these specialties.

The cardiac esophageal connection and the cardioesophageal reflex

Cardioesophageal reflexes seem to be responsible for a number of clinically important phenomena. There is strong evidence that events that occur in the esophagus can alter cardiac function, particularly the coronary

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circulation [4]. There is also evidence that coronary events can alter esophageal function [5].

Stimulation of the esophagus by acid, distention, or hot or cold liquids can produce changes in the coronary vasculature and in cardiac rhythm. The change in rhythm is vagally mediated, and the bradycardia that results can be sinus bradycardia or atrioventricular nodal block of varying degrees. More difficult to explain is that acid infusion can decrease coronary blood flow in normal coronary arteries. This does not seem to be the result of a vagal mechanism. Ischemic pain that is triggered by digestive factors has been termed “linked angina.”

Linked angina was explored by Chauhan et al [4] in 35 patients with syndrome X and 24 patients who had received a heart transplant. Patients with syndrome X have typical angina and objective evidence of cardiac ischemia but have angiographically normal epicardial coronary arteries. The presumed explanation is that these patients have normal large coronary arteries but that there is an abnormality in the function of the small coronary arteries, the microvasculature. An array of abnormalities, including nitric oxide deficiency, endothelial cell malfunction, angiotensin II type 1 receptor up-regulation, and increased sympathetic tone, may be present in these patients.

In the Chauhan study, esophageal infusion of hydrochloric acid significantly reduced coronary blood flow in the syndrome X group as measured by an intracoronary Doppler flow catheter but had no effect on coronary blood flow in the heart transplant group [4]. Twenty (57%) of the 35 syndrome X patients experienced ischemic pain provoked by the infusion of acid, but there were no changes in heart rate or blood pressure, eliminating a hemodynamic response as the cause. In the 15 patients who did not experience pain, no change was noted in coronary blood flow. In the 20 patients with pain, a significant decrease in flow was observed—from 85 mL per minute to 36 mL per minute [4]. No change was seen in the angiographically measured size of the left anterior descending coronary artery, so coronary artery spasm was not involved [4]. Thus, microvascular dysfunction was implicated as the cause of reduced blood flow and chest pain in 57% of these patients with syndrome X. Furthermore, on the basis of its absence in patients who had transplanted, denervated hearts, linked angina would seem to be a neurally mediated cardioesophageal reflex mechanism that occurs only in susceptible patients (Figs. 1 and 2) [4].

Cardiac events may have an effect on esophageal function. During coronary angiography and angioplasty, changes in esophageal function often occur. In 30 stable patients undergoing elective cardiac catheterization to determine the cause of chest pain, of whom four required angioplasty, esophageal manometry and pH were monitored throughout the cardiac procedure [5]. Afterward, esophageal provocation with ice water, hydrochloric acid, and balloon inflation was performed along with observation of cardiac rate and rhythm. Five of 13 patients with normal coronary arteries developed esophageal spasm during coronary angiography, as did 5 of 17

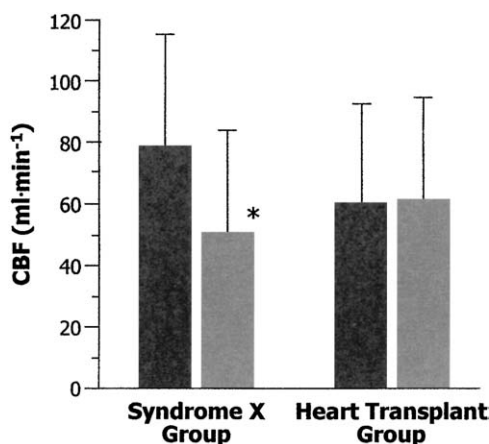


Fig. 1. The effect of acid infusion on coronary blood flow in syndrome X and heart transplant patients. (Black bars), before infusion; (gray bars), after infusion. (From Chauhan A, Petch MC, Schofield PM. Cardio-oesophageal reflex in humans as a mechanism for “linked angina”. *Eur Heart J* 1996;17:407–13; with permission.)

patients with abnormal coronary arteries [5]. The esophageal pain threshold was significantly lower in the four patients undergoing angioplasty than in those who had angiography only. No changes in esophageal pH occurred during cardiac catheterization, indicating that acid reflux was not a cause of pain, and neither cardiac rate nor rhythm changed during esophageal manipulation [5].

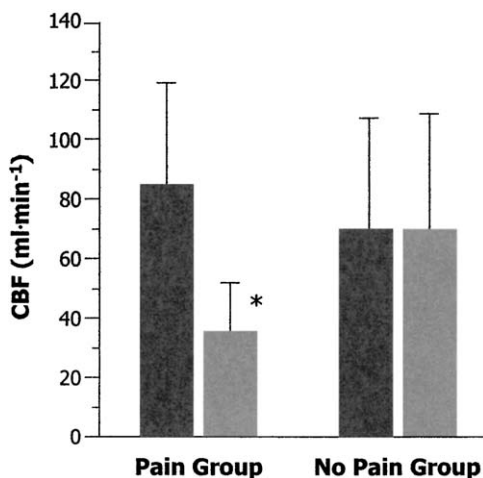


Fig. 2. The effect of acid infusion on coronary blood flow in syndrome X patients with and without chest pain during acid infusion. (Black bars), before infusion; (gray bars), after infusion. (From Chauhan A, Petch MC, Schofield PM. Cardio-oesophageal reflex in humans as a mechanism for “linked angina”. *Eur Heart J* 1996;17:407–13; with permission.)

Although chest pain is not a consequence of angiography, it may occur in patients undergoing angioplasty, presumably due to the transient ischemia induced by the procedure itself. These findings imply that the pain that occurs during ischemia may be, in part, the result of esophageal hypersensitivity.

Cardiac assessments

The pain caused by a cardiac event may occur anywhere from the patient's nose to the navel. When a patient presents with chest pain, the first priority is to assess the probability of a life-threatening condition. These conditions include acute myocardial infarction, unstable angina, aortic dissection, pulmonary embolism, and pericarditis with tamponade.

These conditions can usually be diagnosed quickly by a carefully taken history, thorough physical examination, electrocardiogram, chest radiograph, and blood tests, including cardiac markers (troponin) or cardiac enzymes. The subsequent assessment may point to the need for an echocardiogram or chest computed tomography or magnetic resonance imaging. Life-threatening conditions can usually be detected, and treatment initiated, within an hour or two of the patient's arrival.

Even if an acute cardiac syndrome has been ruled out, it is necessary to determine if pain is cardiac in origin. Chronic, stable cardiac conditions carry an increased risk of myocardial infarction over the long term because cardiovascular disease is progressive. The presence of cardiac ischemia should be determined, and this is relatively easy. It is more difficult, however, to establish whether or not ischemia is the cause of the chest pain. Ischemia and chest pain can coexist without a causal relationship.

Severity of ischemia, left ventricular function, coronary angiographic findings, ventricular arrhythmias, and functional capacity are evaluated. As with more acute cardiac conditions, a history, physical examination, electrocardiogram, chest radiograph, and laboratory test results are valuable in making an accurate diagnosis. The history of chest pain can be categorized as typical angina, atypical angina, or as noncardiac. Typical angina is characterized by retrosternal chest discomfort experienced as pressure or heaviness that lasts several minutes, which is induced by exertion, a large meal, or exposure to cold and is relieved by rest or nitroglycerin. Atypical angina is diagnosed in the presence of any two of those characteristics, whereas noncardiac pain is likely if none or only one of the above is present. The probability of the pain being cardiac in nature increases with age and male gender. [Table 1](#) presents the probability of finding a significant coronary stenosis based on age, gender, and pain history.

Although some patients have a high probability of cardiac origin for their chest pain and others have a low probability, a great number of patients fall into the intermediate area, where no definitive diagnosis for cardiac or noncardiac chest pain can be made. In these patients, provocative tests for

Table 1

Probability of > 70% coronary stenosis based on age, gender, and pain history

Age (yr)	Nonanginal chest pain (%)		Atypical angina (%)		Typical angina (%)	
	Men	Women	Men	Women	Men	Women
35	3–35	1–19	8–59	2–39	30–88	10–78
45	9–47	2–22	21–70	5–43	51–92	20–79
55	23–59	23–59	45–79	10–47	80–95	38–82
65	49–69	49–69	71–86	20–51	93–97	56–84

Each value represents the percentage of patients with coronary artery disease. The first number given in each range (e.g., 3–35) is the percentage for a low-risk, mid-decade patient who does not have diabetes, does not smoke, and does not have hyperlipidemia. The second number in each range is the percentage for a same-age patient who does have diabetes, does smoke, or does have hyperlipidemia.

ischemia can help narrow down the possibilities. Radionuclide tests can detect coronary artery disease by demonstrating unequal distribution of blood flow after exercise or after the administration of a vasodilator. The standard treadmill test can detect the ST-segment changes that are the consequence of ischemia during exercise. A more accurate diagnostic test is stress echocardiography, which detects wall motion abnormalities after exercise or during infusion of dobutamine.

Although a negative test result does not exclude ischemic heart disease as a cause of chest pain, it does indicate an excellent prognosis. A mildly positive test result suggests mild ischemia, although it may be a false positive because these tests have low accuracy in a low-risk population. In either case, the prognosis is good. With a markedly positive test result, there is a high probability of coronary atherosclerosis with significant risk. Further assessment or treatment to reduce risk is indicated (Fig. 3).

Treatment of NCCP

If the pain is determined to be noncardiac in nature, most cardiologists refer a patient to a gastroenterologist or primary care physician for further evaluation. In many cases, the cardiologist may prescribe an H₂-receptor antagonist or a proton pump inhibitor (PPI) because there is a common belief that most NCCP is acid reflux related.

Summary

Evidence indicates that there is a strong cardioesophageal connection in patients who experience esophageal or ischemic problems. Cardiologists and gastroenterologists often find the coexistence of symptoms and functional abnormalities, but determining causation is much more difficult. There is a need for better understanding of the phenomenon of cardiac and NCCP, among cardiologists and gastroenterologists.

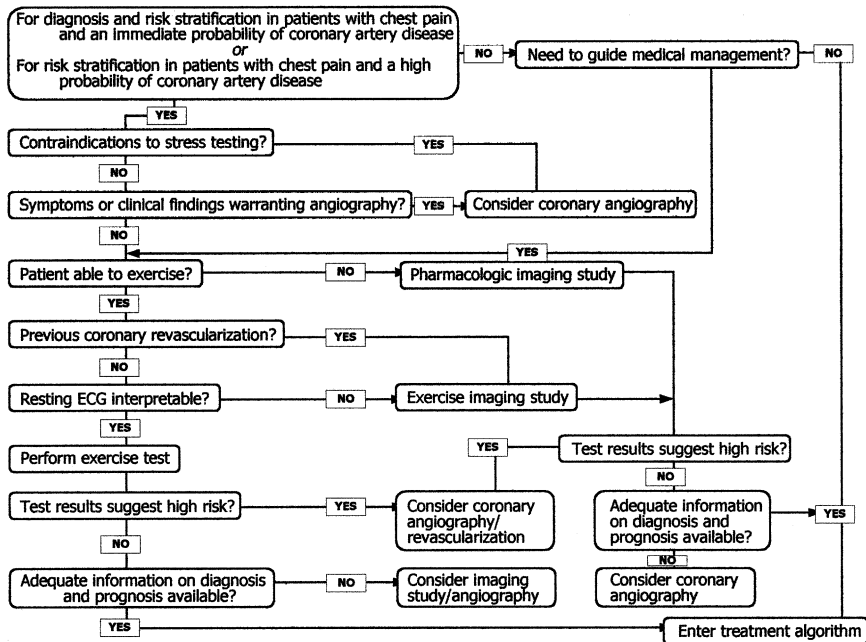


Fig. 3. Algorithm for selection of exercise electrocardiogram, pharmacologic imaging test, exercise imaging test, or coronary angiography for diagnosis for risk stratification.

In evaluating chest pain, the cardiologist assesses the probability that the condition is acute and life threatening; serious and chronic; or noncardiac in nature. If it seems to be cardiac chest pain, appropriate therapy is initiated. In patients in whom there is a strong suspicion of NCCP, a PPI is often prescribed, or the patient is referred to a gastroenterologist or a primary care physician for further evaluation.

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Gastroesophageal reflux disease in noncardiac chest pain

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Noncardiac chest pain (NCCP), or unexplained chest pain, is defined as recurring angina-like or substernal chest pain believed to be unrelated to the heart after a reasonable cardiac evaluation. It affects up to 23% of the general population [1]. The causes of NCCP are diverse and can often overlap [2]. Gastroesophageal reflux disease (GERD) is the most common cause of NCCP. It may be present in up to 60% of the patients with NCCP [3]. Typical reflux symptoms (heartburn or acid regurgitation) have been shown to be significantly and independently associated with the presence of NCCP. In a study by Locke et al [1], NCCP was reported more often in those experiencing frequent heartburn symptoms at least once a week (37%) as compared with those with infrequent GERD (30.7%) and persons reporting no GERD (7.9%) [1]. Eslick et al [4] performed a population-based study to determine the prevalence of NCCP. They discovered that among subjects with NCCP, 53% experienced heartburn, and 58% experienced acid regurgitation.

The prevalence of erosive esophagitis in patients with GERD-related NCCP has been reported to be as low as 10% and as high as 70% [5–9]. The reason for this wide range in percentage can be explained by the different patient populations evaluated. For example, studies conducted at VA medical centers are likely to include more patients with underlying erosive esophagitis than studies conducted in the community.

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Studies have shown that the percentage of NCCP patients with abnormal pH is approximately 50%. Fass et al [10] reported that 41.1% of patients with NCCP had abnormal pH values in a study involving 37 patients. Beedassy et al [11] evaluated 104 patients with NCCP and reported that 48% had an abnormal ambulatory 24-hour esophageal pH monitoring. Of the 104 patients, 52 reported chest pain during their pH study, but only 23 (44%) had an abnormal pH test. Thus, there was no relationship between overall abnormal pH values and chest pain.

Beedassy et al [11] also showed that patients with a positive symptom index (percentage of symptoms that correlates with acid reflux events) were significantly more likely to have an abnormal pH study. Of the 52 patients with chest pain, 10 had a positive symptom index (SI), and 42 had a negative SI. Of those with a positive SI, 80% had abnormal pH study compared with 36% of those with negative SI. However, a recent study by Dekel et al [12] showed that the SI provides little improvement in diagnosing GERD-related NCCP. A total of 94 patients with NCCP were enrolled in the study. Forty-seven (50%) were GERD positive, and 47 (50%) were GERD negative. Only nine patients (19%) in the GERD-positive group and five (11%) in the GERD-negative group had a positive SI. The authors concluded that a positive SI is relatively uncommon in NCCP patients, regardless of whether GERD is present or absent. This is primarily due to lack of chest pain symptoms during the pH test.

In North American studies, most patients with GERD-related NCCP have typical reflux symptoms in addition to their chest pain [13]. In contrast, Chinese patients with GERD-related NCCP rarely present with classic reflux symptoms. A study by Wong et al [14] evaluated patients with NCCP. Only 1 of the 19 patients with abnormal 24-hour esophageal pH monitoring had typical symptoms of GERD (heartburn or acid regurgitation). This may have been due to the difficulty in reporting burning retrosternal discomfort in Chinese patients because there is no direct Chinese translation of the word “heartburn.” Fig. 1 summarizes the prevalence of GERD and GERD-related abnormalities in patients presenting with NCCP.

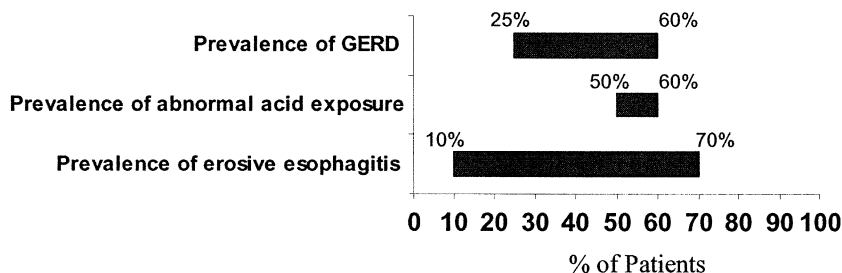


Fig. 1. Prevalence of GERD and GERD-related abnormalities in patients presenting with NCCP.

Pathophysiology

The pathophysiology of GERD-related NCCP remains poorly understood. It is not clear why esophageal exposure to gastric content in some patients causes heartburn and in others causes chest pain. This is compounded by the fact that some patients may experience chest pain at one time and heartburn at other times (Fig. 2).

In a subset of patients with cardiac-related chest pain, the primary cause may be esophageal acid exposure. The esophagus and the heart share a common innervation, and it is possible that esophageal mucosal stimulation may influence the flow in the coronary circulation [15]. Chauhan et al [15] studied patients with syndrome X (negative coronary angiogram but positive stress test) by assessing the effect of acid perfusion in the distal esophagus on coronary blood flow. The investigators demonstrated a significant reduction in coronary blood flow during acid perfusion. The reduction in blood flow was associated with typical angina pain. They suggested that this effect is the result of an esophago-cardiac inhibitory reflex. Rosztoczy et al [16] also found that esophageal acid perfusion decreased coronary blood flow in 45% (19/42) of patients with chest pain. However, the presence of esophago-cardiac reflex was independent of coronary artery disease and microvascular disease. Patients with coronary spasm had significantly higher coronary flow reduction during esophageal acid stimulation.

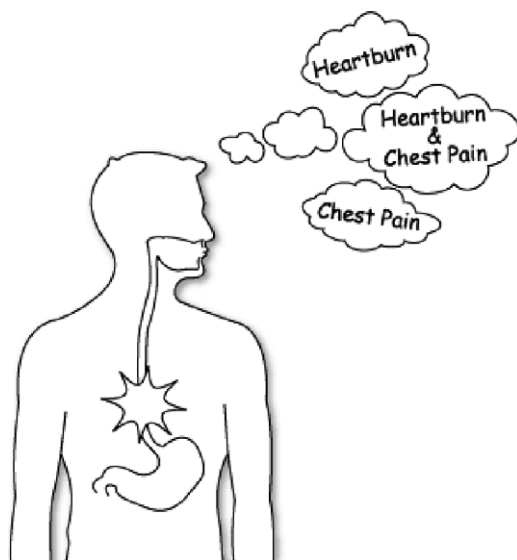


Fig. 2. The diverse presentation of symptoms in the same patient or different patients with NCCP.

Characteristics of the individual reflux episodes (duration and pH level) have been proposed to influence patients' symptoms. Smith et al [17] studied 25 individuals with NCCP to determine the relation between the sensation of pain in GERD and pH of the refluxate. They found that all 25 patients had reproduction of their pain during intraesophageal infusion of solution of pH 1 and 1.5. Reflux events resulting in pain were significantly longer than those without pain and were more often associated with a recently preceding painful episode. Beedassy et al [11] suggested that chest pain related to gastroesophageal reflux is associated with sensitization of the esophageal mucosa by prior acid reflux events.

Different underlying mechanisms have been suggested to result in hypersensitivity in patients with GERD-related NCCP. These include peripheral sensitization of esophageal sensory afferents leading to heightened responses to physiologic and pathologic stimuli and modulation of afferent neural function at the level of the spinal dorsal root or the central nervous system [18]. In one study [19], healthy subjects underwent perfusion of the distal esophagus with normal saline or 0.1 N hydrochloric acid. Perceptual responses to intraluminal esophageal balloon distension, using electronic barostat, were evaluated. As compared with saline, acid perfusion reduced the perception threshold (innocuous sensation) and tended to reduce the pain threshold (aversive sensation). This study demonstrated short-term sensitization of mechanosensitive afferent pathways by transient exposure to acid. The authors suggested that in patients with NCCP, acid reflux induces sensitization of the esophagus, which may subsequently alter the way the esophagus perceives otherwise normal esophageal distensions. Sarkar et al [20] recruited 19 healthy volunteers and seven patients with NCCP. Hydrochloric acid was infused into the distal esophagus over 30 minutes. Sensory responses to electrical stimulation were monitored within the acid-exposed distal esophagus and the non-exposed proximal esophagus before and after infusion. In the healthy subjects, acid infusion into the distal esophagus lowered the pain threshold in the upper esophagus. Patients with NCCP already had a lower resting esophageal pain threshold than healthy subjects. After acid perfusion, their pain threshold in the proximal esophagus fell further and for a longer duration than was the case for the healthy subjects. Additionally, there was a decrease in pain threshold after acid infusion in the anterior chest wall. This study demonstrated the development of secondary allodynia (visceral hypersensitivity to innocuous stimulus in normal tissue that is in proximity to the site of tissue injury) in the proximal esophagus by repeated acid exposure of the distal esophagus. The concurrent visceral and somatic pain hypersensitivity is, most likely, caused by central sensitization (an increase in excitability of spinal cord neurons induced by activation of nociceptive C-fibers in the area of tissue injury). The patients with NCCP demonstrated visceral hypersensitivity and amplified secondary allodynia in the esophagus. It is unclear from the study what mechanism is responsible for the exaggerated secondary allodynia and

what initiates central sensitization in patients with NCCP. Other studies on NCCP [10], using a similar human model of acute tissue irritation by acid infusion, showed no significant effect on pain thresholds.

Several studies have documented altered autonomic function in patients with NCCP. In a recent study, Tougas et al [21] assessed autonomic activity using power spectral analysis of heart rate variability before and during esophageal acidification of patients with NCCP and matched healthy control subjects. Of the patients with NCCP, 68% were considered acid sensitive (ie, they developed angina-like symptoms during esophageal acidification). The acid-sensitive patients had a higher baseline heart rate and lower baseline vagal activity than acid-insensitive patients. During acid infusion, vagal cardiac outflow increased in acid-sensitive but not in acid-insensitive patients. The same investigators have documented an increase in vagal activity in patients with NCCP during other intra-esophageal stimuli (mechanical and electrical). The role that altered autonomic function plays in the pathogenesis of NCCP remains speculative. In most cases in which central and autonomic factors are involved, it is the effect of the former that most likely leads to the occurrence of the latter [22].

A study by Fass et al [10] demonstrated that chest pain and heartburn may be provoked in normal subjects and in GERD patients during esophageal balloon distention of the esophagus. Volume thresholds for heartburn and chest pain in the proximal or distal esophagus were similar; additionally, they did not differ significantly at each esophageal location or between locations. In this study, esophageal balloon distention reproduced typical heartburn symptoms in some patients with documented GERD and chest pain in others. The study demonstrates that a stimulus such as balloon distention may result in different types of esophageal symptoms.

Another explanation as to how GERD may cause chest pain was recently provided by studies using high-frequency, intraluminal ultrasonography. Balaban et al [23] demonstrated a temporal correlation between sustained contractions of the esophageal longitudinal muscle and spontaneous and provoked esophageal chest pain. In a follow-up study, the authors suggested that the duration of the sustained esophageal contraction determines the type of symptom that is perceived by patients. Heartburn was associated with shorter duration contractions, whereas chest pain was associated with contractions of longer duration. These findings, though intriguing, do not fully explain why most acid reflux events that occur in patients with GERD-related NCCP do not trigger any type of symptoms and thus are not perceived.

Clinical presentation

Approximately 70% of patients with GERD-related NCCP have associated reflux symptoms [13]. Patients often present with characteristic symptoms of reflux, including heartburn and acid regurgitation, or report pain provoked by recumbency or swallowing, pain when waking at night,

and relief of pain with proton pump inhibitors (PPIs) [24]. Often the clinical history does not help distinguish GERD-related NCCP from cardiac causes of chest pain. GERD may be triggered by exercise and may cause exertional chest pain that mimics angina even during exercise testing. This point is illustrated by a study of 248 patients with chest pain [25]. Based on medical history, cardiologists determined whether or not patients had cardiac angina. Of the 185 cases thought to be consistent with typical angina, 26% had normal coronary angiograms. Of the 63 patients with “atypical chest pain,” 25% had a positive angiogram. Therefore, all patients who present with chest pain should undergo a comprehensive cardiac evaluation before being referred to a gastroenterologist.

Patients with GERD-related NCCP have a low incidence of GERD-related complications, such as Barrett’s esophagus, esophageal stricture, ulcerations, and adenocarcinoma of the esophagus. Frobert et al [9] performed upper endoscopies on 49 patients with NCCP. Barrett’s esophagus, mucosal erosions, or ulcerations were not seen in any of the patients. In a study by Fass et al [26], of 35 patients with NCCP undergoing upper endoscopy, only one patient was found to have Barrett’s esophagus with a stricture at the gastroesophageal junction. Xia et al [27] reported that among 78 patients with NCCP by upper endoscopy, only two patients had endoscopic evidence of erosive esophagitis. Garcia-Compean et al [28] evaluated patients with only atypical extraesophageal manifestations of GERD, including NCCP. Of the 34 patients diagnosed with GERD by 24-hour esophageal pH monitoring, three (9%) had Barrett’s esophagus. With such a low incidence of finding esophageal mucosal involvement, some authorities suggest that endoscopic screening in GERD-related NCCP patients is a low-yield procedure.

Diagnostic tests

There is no gold standard for diagnosing GERD or GERD-related NCCP. The diagnostic tests that are used to detect GERD-related NCCP include barium swallow, upper endoscopy, ambulatory 24-hour esophageal pH monitoring, and the PPI test. Barium studies and upper endoscopy have little use in the diagnosis of GERD-related NCCP without alarm symptoms. Barium esophagram has a low sensitivity (20%) in diagnosing GERD due to a lack of anatomic changes or the absence of mucosal inflammation in most of these patients [29]. The significance of barium reflux during the procedure as diagnostic of GERD is questionable. Johnston et al [29] found that the proportion of patients with positive pH test did not differ from patients with spontaneous barium reflux (68%) versus no spontaneous barium reflux (65%). Spontaneous barium reflux has also been demonstrated in up to 20% of healthy subjects [2].

Upper endoscopy is an accurate test for diagnosing esophageal mucosal involvement in GERD (erosive esophagitis, stricture, ulcer, and Barrett’s

esophagus). However, it has not been shown to be useful in the initial evaluation of NCCP because only 10% to 25% of patients have endoscopic evidence of esophageal mucosal injury [30].

Ambulatory 24-hour esophageal pH monitoring with symptom correlation is commonly used to evaluate patients with NCCP [31]. Approximately 50% to 60% of NCCP patients have increased esophageal acid exposure and a positive symptom index or a positive symptom index alone. Hewson et al [31] examined 100 consecutive patients with NCCP and detected abnormal esophageal acid exposure in 48 patients (48%). Of the 83 patients with spontaneous chest pain during 24-hour pH testing, 37 patients (46%) had abnormal reflux parameters, and 50 patients (60%) had a positive SI. They concluded that 24-hour esophageal pH monitoring with SI is the single best test for evaluating patients with NCCP. In contrast, Dekel et al [12] demonstrated that positive SI is a relatively uncommon phenomenon in NCCP patients because many patients do not experience chest pain during the pH study. Disadvantages of the 24-hour esophageal pH monitoring are that the study is invasive, costly, inconvenient, and unavailable for many physicians. Reported sensitivity has ranged from 60% to 96%, and specificity has ranged from 85% to 100% [2].

In the future, ambulatory 24-hour esophageal pH monitoring may be replaced with a wireless system (Bravo pH system, Medtronic, Shoreview, Minnesota). This monitoring system is a new USDA class I approved, “catheterless” pH monitoring system. It involves the attachment of a radiotelemetry pH capsule to the mucosal wall of the esophagus (endoscopically or transnasally). It simultaneously measures pH and transmits data to a pager-sized receiver clipped onto the patient’s belt, thereby circumventing the need for a nasally placed catheter, which is uncomfortable for many patients. The Bravo wireless ambulatory pH recording system has been shown to be well tolerated and reliable and provides reproducible results [32]. It is a viable option for patients who are unwilling or unable to undergo conventional ambulatory pH monitoring studies using a transnasally positioned pH probe. The wireless pH system may prove to be helpful in further clarifying the role of GERD in NCCP and in better determining the relationship between symptoms and acid reflux events in these patients.

The ideal therapeutic modality for NCCP would combine its evaluation and treatment in a single step. Consequently, the PPI test has become an attractive, alternative diagnostic test for GERD-related NCCP. The test is simple, noninvasive, and can be used by primary care physicians and specialists. The PPI test uses a short course of high-dose PPI to diagnose GERD in patients with NCCP. The main objective of the PPI test is to achieve a significant improvement in the symptoms of as many patients with GERD-related NCCP as possible within a short period of time [33]. PPIs were selected for this test because of their profound and consistent inhibitory effect on acid secretion and the marked symptom improvement that they provide to GERD patients.

Table 1 summarizes the currently available studies that assessed the diagnostic accuracy of the PPI test in NCCP patients. In two early studies, a single dose of 80 mg omeprazole resulted in variable sensitivity (69% versus 90%) [34,35]. However, Fass et al [10], using omeprazole (40 mg AM and 20 mg PM over 7 days), found a sensitivity of 78.3% and a specificity of 85.7% for diagnosing GERD in patients with NCCP. The positive predictive value of the omeprazole test was 90%, and the negative predictive value was 70.6%. The diagnosis of GERD was established by an upper endoscopy or by 24-hour esophageal pH monitoring. The rabeprazole test, using 20 mg twice daily over a 7-day period, demonstrated 83% sensitivity and 75% specificity in diagnosing GERD-related NCCP. By day 3, all GERD-related NCCP responders had complete or almost complete symptom resolution [36].

Recently, Xia et al [27] showed that treatment with lansoprazole is a useful test in diagnosing endoscopy-negative, GERD-related NCCP. Seventy patients underwent 24-hour esophageal pH monitoring and were randomly assigned to lansoprazole 30 mg daily for 4 weeks or placebo. Symptom scores were reduced significantly in patients treated with lansoprazole compared with placebo. Overall, 53% of patients receiving lansoprazole showed an improvement in chest pain symptoms compared with 35% of those receiving placebo. The sensitivity and specificity of the 4-week test were 92% and 67%, respectively. The positive predictive value was 58%, and the negative predictive value was 94%.

The use of the PPI test is highly dependent on the frequency of chest pain symptoms. If symptoms occur less than once per week, the test may be extended to 2 weeks or longer. When using the PPI test, there was a significant correlation between the esophageal acid exposure by 24-hour esophageal pH monitoring and the change in symptom intensity score after treatment [37]. This suggests that the higher the esophageal acid exposure, the greater the response to the PPI test in patients with GERD-related NCCP.

Table 1
The PPI test in patients with NCCP

Study	n	PPI	Dose	Cutoff symptom improvement (%)	Duration (days)	Sensitivity (%)	Specificity (%)
Young [34]	30	Omeprazole	80 mg/d	75	1	90	80
Squillace [35]	17	Omeprazole	80 mg/d	50	1	69	75
Fass [10]	37	Omeprazole	40 mg AM/ 20 mg PM	50	7	78	88
Fass [50]	56	Lansoprazole	60 mg AM/ 30 mg PM	50	7	78	82
Fass [36]	20	Rabeprazole	20 mg bid	50	7	83	75
Xia [27]	68	Lansoprazole	30 mg/d	50	30	92	67
Pandak [51]	42	Omeprazole	40 mg bid		14	71	82

Studies have also demonstrated that using the PPI test as the first diagnostic tool in patients with NCCP is cost effective. Economic analyses demonstrated that the PPI test saves \$573 per average NCCP patient. It also resulted in an 81% reduction in the number of endoscopies and a 79% reduction in the use of 24-hour esophageal pH monitoring [10]. Ofman et al [38] performed a decision analysis to evaluate the clinical and economic outcomes comparing an initial trial of high-dose omeprazole followed by traditional diagnostic strategies (pH testing, endoscopy, and esophageal manometry) with only traditional diagnostic strategies ordered first. Strategies using the initial PPI test resulted in 84% of patients being asymptomatic at 1 year compared with 74% for the strategies that began with traditional diagnostic testing. The PPI test led to an 11% improvement in diagnostic accuracy and a 43% reduction in the use of invasive diagnostic tests.

The recent introduction of the multi-channel intraluminal impedance will enable us to study about the role of non-acidic reflux in eliciting GERD-related NCCP. Furthermore, this novel technique may be used to identify NCCP patients who failed PPI treatment because of non-acidic reflux [39].

Treatment

Treatment of GERD-related NCCP should involve lifestyle modification and pharmacologic intervention. Elevating the head of the bed at night, reducing fat intake, stopping smoking, and avoiding foods that exacerbate reflux have been shown to decrease reflux symptoms [40]. There are few trials, however, that have assessed the usefulness of acute or maintenance therapy with anti-reflux medications in patients with GERD-related NCCP.

In the literature, there have been small, uncontrolled studies comparing histamine-2 blockers to placebo or omeprazole. The efficacy of histamine-2 blockers has ranged from 54% to 83% [30]. As compared with PPIs, they have demonstrated a limited response. In a small, uncontrolled study by Stahl et al [41], 13 patients with NCCP and GERD were treated with high-dose ranitidine at 150 mg orally qid. Seven patients failed lower doses of ranitidine previously. All patients improved with high doses of ranitidine, although two patients had to have their dose increased to 300 mg orally qid. DeMeester et al [42] followed 23 patients with abnormal esophageal acid exposure and NCCP for 2 to 3 years. Twelve patients were treated medically with antacids and cimetidine, and 11 patients were treated with a surgical anti-reflux procedure. Of the medically treated patients, five (42%) were chest pain free at follow-up. These results are not surprising because histamine-2 receptor antagonists have limited acid suppressive effect due to a relatively short duration of action. A further shortcoming is that tolerance to these drugs generally develops within 2 weeks of repeated administration, resulting in a decline of acid suppression [43]. PPI therapy, on the other hand, produces a more profound and longer duration of acid suppression. In addition, tolerance has not been observed [43].

When omeprazole 20 mg twice daily was administered over a period of 8 weeks to NCCP patients in a double-blind, placebo-controlled trial, the patients who received omeprazole had a significant reduction in the number of days with chest pain and chest pain severity score when compared with patients who received placebo. Although data regarding the efficacy of PPIs in NCCP are available only with omeprazole, it is highly likely that all other PPIs will demonstrate similar efficacy [33]. Patients with GERD-related NCCP should be treated with at least a double dose of PPI until symptoms remit, followed by dose tapering to determine the lowest dose that can control patient's symptoms. As with other extraesophageal manifestations of GERD, NCCP patients may require more than 2 months of therapy for optimal symptom control. Long-term treatment with a PPI has been shown to be highly efficacious [44]. Borzecki et al [45] developed a decision tree to compare empirical treatment for NCCP patients with histamine-2 receptor blockers or standard dose PPI for 8 weeks with initial investigations (upper endoscopy or upper gastrointestinal series). Empiric treatment was more cost effective, with a cost of \$849 per patient versus \$2187 per patient with the initial investigation strategy.

Laparoscopic fundoplication relieves heartburn and acid regurgitation in most patients with GERD, but its effect on chest pain is less clear. DeMeester et al [42] found a temporal correlation in 12 of 23 patients who had acid reflux as a cause of NCCP. Pain resolved in the 12 patients when treated surgically (eight patients) or by acid reducing agents. Patti et al [46] reviewed patients who underwent laparoscopic fundoplication for GERD who complained of chest pain in addition to heartburn and acid regurgitation. Overall, chest pain improved in 85% of the patients after laparoscopic fundoplication. This increased to 96% in patients whose chest pain correlated with GERD most of the time. Farrell et al [47] evaluated the effectiveness of anti-reflux surgery for patients with atypical manifestations of GERD. Chest pain improved in 90% of patients after laparoscopic fundoplication with symptoms resolution in 50% of the patients. Although surgical studies demonstrate a high success rate of anti-reflux surgery in GERD-related NCCP patients, the patient population was highly selected.

Several endoscopic techniques designed to bolster the anti-reflux barrier at the gastroesophageal junction are under investigation [48]. There are four basic types of endoscopic treatments: suturing, radiofrequency, injection, and bulking procedures [49]. The published data report only short-term outcomes of a limited number of patients with usually mild disease. No studies have specifically evaluated patients with GERD-related NCCP. These endoscopic methods are considered experimental and should not be routinely performed. However, their effect on GERD-related NCCP patients should be studied.

An algorithmic approach to the diagnosis and treatment of GERD-related NCCP is presented below (Fig. 3).

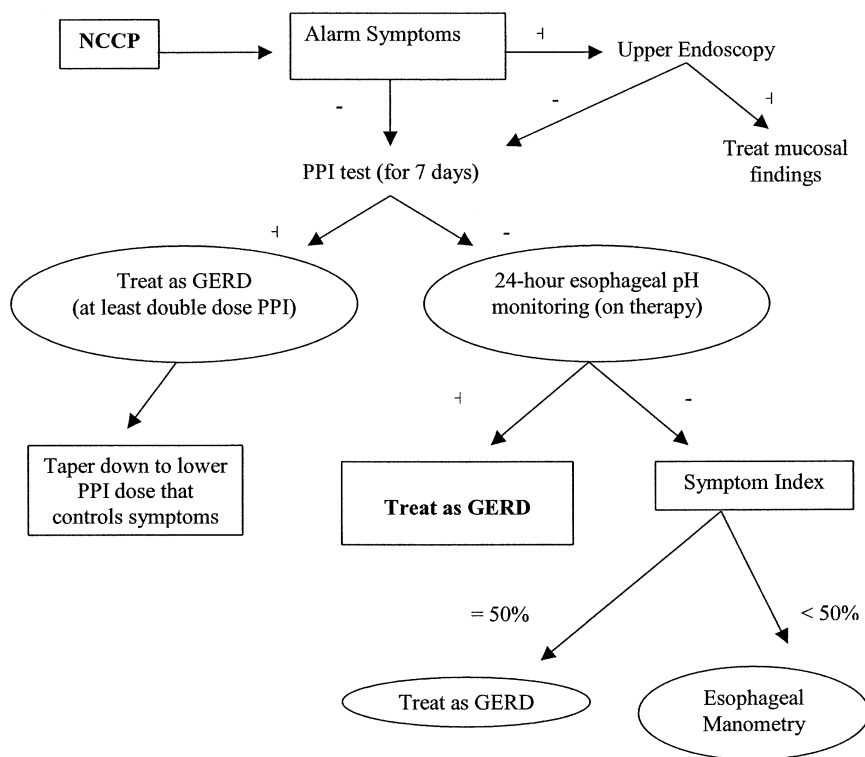


Fig. 3. Diagnosis and treatment flow chart for patients with GERD-related NCCP.

Summary

After a cardiac source has been excluded, the most likely cause of NCCP is GERD. Clinical history often cannot make the diagnosis of GERD-related NCCP. The PPI test is a simple, highly sensitive, and cost-effective tool that should be the first diagnostic test used in evaluating these patients. Patients with GERD-related NCCP require long-term therapy with a PPI, commonly double the standard dose. The introduction of the wireless pH system and the multi-channel intraluminal impedance will help us to further understand the role of GERD in NCCP. Treatment of NCCP has dramatically improved since the introduction of the PPI class of drugs. However, better therapeutic modalities should be sought out to further improve our current treatment of GERD-related NCCP.

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Visceral hypersensitivity in noncardiac chest pain

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Noncardiac chest pain (NCCP) is characterized by episodes of substernal chest pain or discomfort that is not burning in quality. NCCP should be diagnosed only after excluding nonesophageal causes such as cardiac, musculoskeletal, pleuritic, pulmonary, and other disorders. NCCP affects both men and women of all age groups. The exact prevalence of NCCP is not known, but it is a common disorder. For example, up to 30% of the coronary angiograms performed in the United States are normal or have findings that do not explain their symptoms, and many of these patients ultimately are diagnosed with NCCP. The mechanisms of pain currently implicated in NCCP include acid reflux, esophageal dysmotility, psychologic comorbidity, and visceral hypersensitivity. The anatomic site responsible for the development of visceral hypersensitivity in patients with NCCP is not known; however, potential locations include sensory receptors in the esophagus, abnormalities in the extrinsic sensory afferent neurons, and up-regulation of sensory information in the central nervous system (CNS). This article reviews some of the evidence for the potential pathophysiologic mechanisms of visceral hypersensitivity in patients who have NCCP.

Definition of visceral hypersensitivity

Visceral hypersensitivity is a phenomenon in which the conscious perception of visceral sensation is intensified independent of the intensity of the stimulus. Sensations within the esophagus arise from chemoreceptors that recognize acid, mechanoreceptors that recognize distension, and thermoreceptors that recognize temperature.

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To date, most studies on visceral hypersensitivity have focused on the mechanoreceptors in the development of visceral hypersensitivity; however, chemoreceptors, and possibly thermoreceptors, may also be associated with visceral hypersensitivity in some patients.

Evidence for visceral hypersensitivity

Several studies have shown that patients who have NCCP have esophageal and perhaps more generalized visceral hypersensitivity. The most common method of elucidating visceral hypersensitivity in patients with NCCP has been with balloon distention in the esophagus. In 1986, Richter and colleagues [1] performed the seminal study using this technique in patients with NCCP. By progressively inflating a balloon in the distal esophagus at 1 mL intervals (30 mm × 25 mm when inflated at 10 mL), they found that 50% of patients reported pain at balloon volumes of 8 mL or less, while controls began developing chest pain only at volumes of 9 mL or more (Fig. 1). They did not find a difference in the pressure volume curves between the two groups, nor did they find changes in esophageal motility that correlated with the presence of pain. More recently, Rao and colleagues [2] used impedance planimetry to measure the sensory, motor and biomechanical properties in patients with NCCP and healthy controls. They found that NCCP patients had lower pain thresholds to esophageal balloon distention similar to the results of other investigators [1,3,4]. However, unlike previous investigators, they found the esophagus to be stiffer and wider in NCCP patients compared with controls. In a subsequent study, Rao and colleagues found that patients with NCCP continued to

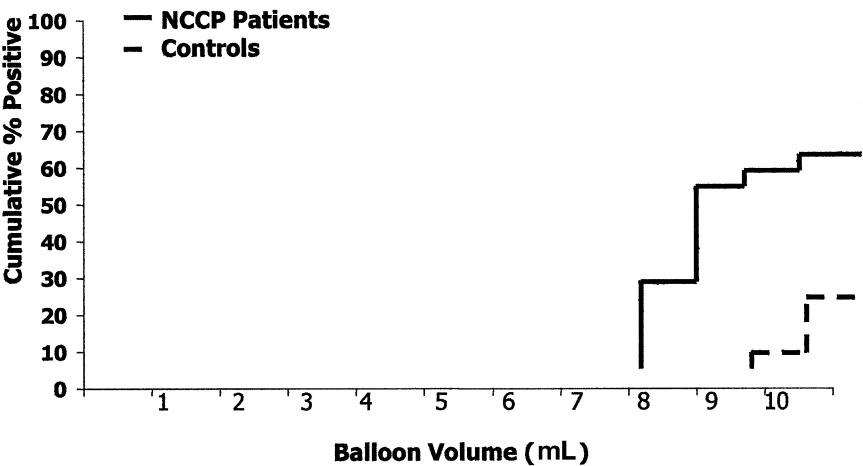


Fig. 1. In a study by Richter and colleagues, patients who have NCCP tended to report pain at lower volumes of balloon distention in the distal esophagus compared with normal controls. (From Richter JE, Barish CF, Castell DO. Abnormal sensory perception in patients with esophageal chest pain. *Gastroenterology* 1986;91:845–52; with permission.)

have lower pain perception thresholds even after inducing relaxation of the esophageal muscle wall with atropine, suggesting that visceral hypersensitivity is the predominant neuromuscular abnormality in these patients [5].

Another study that supports the role of visceral hypersensitivity in patients with NCCP comes from Borjesson and colleagues [6] using transcutaneous electrical nerve stimulation. In this study, they showed that NCCP patients have reduced sensitivity to esophageal balloon distention during simultaneous transcutaneous electrical nerve stimulation compared with healthy controls. Because the somatic afferents stimulated by esophageal balloon distention, these results add further evidence to support the existence of visceral hypersensitivity and suggest that this phenomenon is due to a disorder in the processing of visceral afferent signals.

Role of mechanoreceptors and chemoreceptors in visceral hypersensitivity

Recent evidence by de Caestecker and colleagues [7] suggests that the mechanoreceptors located in the longitudinal muscles of the esophagus are involved in hypersensitivity associated with NCCP. In their study, they found that edrophonium, an anticholinesterase agent, reduced esophageal wall compliance in patients with NCCP and a motility disorder similar to that of control subjects. However, edrophonium resulted in a significant reduction in pain threshold during esophageal balloon distention in patients with NCCP in comparison to the control subjects. From these results, de Caestecker and colleagues suggested that the pain receptor for noxious stretch is likely to be an “in series” mechanoreceptor located in esophageal longitudinal muscle (Fig. 2).

Visceral hypersensitivity can be induced by a variety of repetitive or noxious stimuli through a phenomenon known as sensitization. Mehta and colleagues [8] found that acid infusion in the distal esophagus reduced esophageal balloon distention thresholds in NCCP patients not previously sensitive to balloon distention or acid infusion. Once sensitized, physiologic stimulation of any of these receptors may activate the visceral afferent neurons, thereby causing acute pain. For example, Trimble and colleagues [9] found that patients who were hypersensitive to acid reflux as defined by a positive symptom index with a normal total acid exposure time, also had lower thresholds to esophageal balloon distention. Likewise, Shi and colleagues [10] found that patients who have NCCP and gastroesophageal reflux were hypersensitive to even physiologic amounts of acid reflux. Thus visceral afferents in the esophagus are capable of being sensitized by a variety of stimuli. Once sensitized, acute pain may occur from physiologic stimulation of any of these receptors.

Role of central nervous system in visceral hypersensitivity

The role of the CNS in processing of visceral sensation and the development of visceral hypersensitivity has only recently begun to be

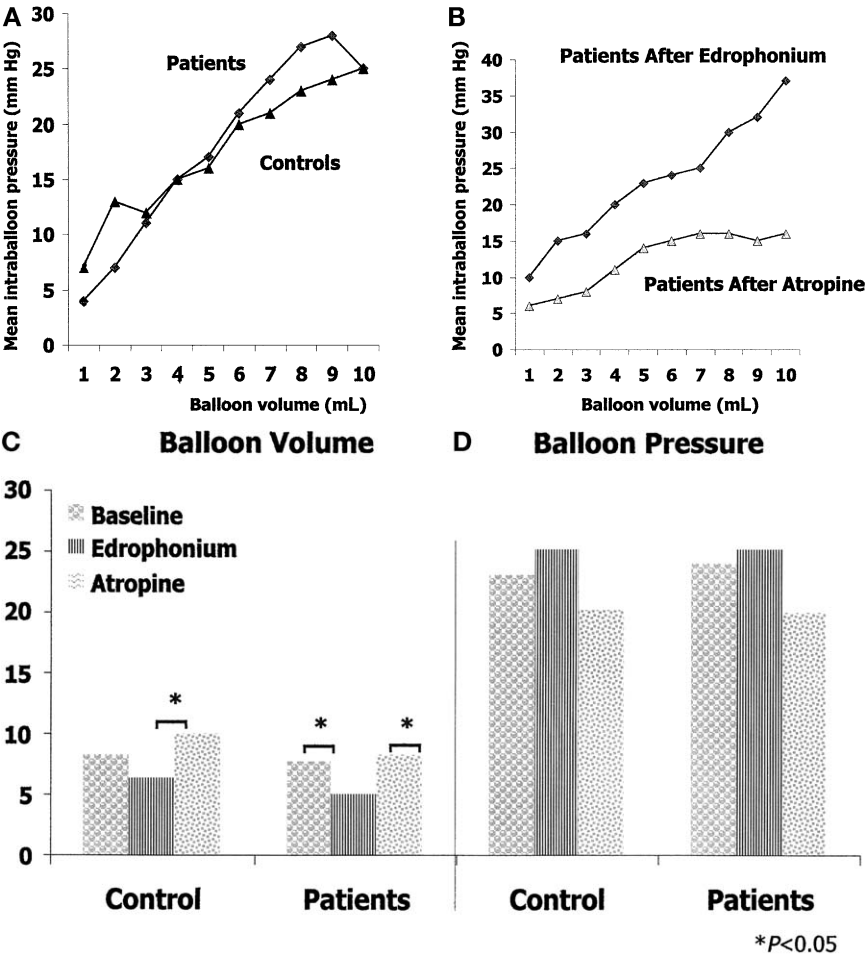


Fig. 2. (A) de Caestecker and colleagues found esophageal wall compliance to be similar in patients with NCCP who had a concomitant esophageal motility disorder and normal controls. (B) The two groups also showed a similar effect of decreased compliance with the anticholinesterase edrophonium and increased compliance after atropine. (C) There were no significant differences between patients and controls of distending volume at perception of discomfort. Edrophonium, however, resulted in a significant reduction in distension threshold for pain in patients who have NCCP. A similar though nonsignificant trend was seen in controls. In both controls and patients, distension volume for pain production after atropine was significantly higher ($P < 0.05$) higher than after edrophonium. (D) No significant difference was present in balloon pressure with atropine or edrophonium in controls or patients who have NCCP. (From de Caestecker JS, Pryde A, Heading RC. Site and mechanism of pain perception with oesophageal balloon distension and intravenous edrophonium in patients with oesophageal chest pain. *Gut* 1992;33:580–6; with permission.)

explored. Aziz and colleagues [11], using positron emission tomography, showed that the insula, primary somatosensory cortex, and operculum are the areas in the brain that are involved with the processing of nonpainful esophageal sensations induced by balloon distention. In contrast, pain sensations from the esophagus induced by balloon distention appear to be processed in the right anterior insular cortex and anterior cingulate gyrus. Smout and colleagues [12] were among the first to suggest that patients with NCCP have abnormalities in the central processing of pain. They found that cerebral-evoked potentials in response to symptomatic esophageal balloon distention had a lower quality score and amplitude compared with normals. The volumes of air required to produce esophageal sensations were lower in patients with NCCP compared with controls. When adjusted for balloon volume, cerebral-evoked potentials were similar between NCCP and controls. This suggests that the mechanoreceptor sensitivity is similar in patients with NCCP and controls and therefore the increased perception to balloon distention is caused by altered processing of the information centrally [12]. Hollerbach and colleagues [13] found similar results with electrical esophageal stimulation. In addition, they also found that electrical esophageal stimulation was associated with decreased sympathetic outflow and increased cardiovagal activity. Together, these studies suggest that patients with NCCP have abnormalities in the central processing of visceral sensations.

Other evidence supporting abnormal central processing of sensory information in patients who have NCCP comes from Sarkar and colleagues [14]. These investigators found that acid perfusion of the lower esophagus lowered the pain threshold of the upper esophagus and an area of the overlying skin in both healthy controls and patients who have NCCP. Patients experienced more significant and prolonged decrease in pain threshold in the upper esophagus after acid perfusion in the distal esophagus. Because somatic and sensory afferents from different areas of the esophagus converge on dorsal horn neurons in the spinal cord [15], these findings suggest an abnormality in the central processing of nociceptive information at or above the level of the dorsal horn neuron.

Finally, other abnormalities of the CNS in patients who have NCCP have also been reported. Tougas and colleagues [16] found that patients with NCCP who experienced angina-like pain during acid infusion of the distal esophagus have decreased resting vagal tone compared with patients with NCCP who were not acid-sensitive. These findings suggest that autonomic dysregulation may be present in at least a subset of patients with NCCP.

Summary

Visceral hypersensitivity is a common cause of NCCP. Mechanoreceptors appear to be important in the pathophysiology of NCCP, although chemoreceptors also appear to play a significant role. The processing of visceral information and possibly the development of central sensitization

may be important in NCCP, although the pathophysiology of NCCP remains poorly understood.

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The psychological aspects of noncardiac chest pain

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Much of the early medical literature covering the psychological aspects of gastroesophageal reflux disease (GERD) and noncardiac chest pain (NCCP) suffers from a lack of scientific rigor. Early studies were done without control groups or standardized measures for gastrointestinal (GI) disorders. Often psychiatric diagnoses were made on the basis of the subjective observations of the investigator as opposed to a diagnosis made using validated psychological screening tools. In the last 10 to 15 years, a large number of validated psychometric instruments have been developed for use in the medical setting. Likewise, psychophysiologic research in medicine has improved by the use of case-control studies. The ability to compare normal control subjects to patients with chest pain of noncardiac origin and to compare the psychological differences between the two groups in a standardized and validated manner is an immense improvement in our ability to investigate the psychological substrates of NCCP. Likewise, improvements in psychiatric nosology, and particularly in the development of standardized psychiatric diagnostic criteria in the form of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV), has allowed for better description of the psychiatric disorders that have been associated with NCCP, such as anxiety disorders (particularly panic disorder), major depressive disorder, and somatoform disorders. Finally, improvements in GI diagnostic technology, such as the development of ambulatory 24-hour esophageal pH monitoring and computerized esophageal motility testing, have created a new level of precision to help identify the physiologic correlates of various psychological states in a precise and accurate manner.

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The study of the relationship between esophageal disorders and psychological disturbance is a broad and somewhat varied literature. We review the literature regarding the presence of GERD in psychiatric patients, the presence of psychiatric disorders in patients with GERD, and the relationship of acute and chronic stress as it relates to NCCP. Finally, we review the relationship between panic disorder, a common substrate of NCCP, and the rationale for the use of antidepressants in NCCP from a physiologic and a psychologic perspective.

The prevalence of gastroesophageal reflux disease in psychiatric patients

The question as to whether psychiatric patients suffer disproportionately from GERD was explored by Avidan et al [1]. They studied 94 psychiatric inpatients and compared them with a control population of 198 nonpsychiatric patients. The presence of a psychiatric diagnosis was associated with an increased risk for heartburn and exercise-induced heartburn. The investigators found an increase of GERD symptoms in patients diagnosed with alcohol dependence, major depression, or bipolar disorder. Patients with other major psychiatric disorders, including schizophrenia, did not complain of GERD more often than control subjects.

The investigators failed to take into account the fact that the psychiatric inpatients were significantly more likely to smoke than control subjects. Smoking is known to contribute to GERD. The authors evaluated the effect of individual psychotropic medications as they related to GERD symptoms. They could not identify any specific drug or class of drugs that the patients were taking for their psychiatric disorders that could be associated with the generation of GERD. They concluded that no particular medication could be identified as a factor in the incidence of GERD. However, in this study all patients were taking multiple medications, including tricyclic antidepressants, benzodiazepines, or phenothiazine, all of which have the effect of lowering basal lower esophageal sphincter (LES) pressure. Finally, the diagnosis of GERD was based on patient interviews and was not verified by objective criteria, such as ambulatory 24-hour esophageal pH monitoring or the presence of erosive esophagitis as documented by endoscopy. Because no objective physiologic testing was accomplished, it is impossible to say whether the psychiatric patients had physiologic reflux [1]. The authors concluded that GERD was more common in psychiatric patients than in nonpsychiatric control subjects and that this greater prevalence possibly reflected a reduced threshold for the perception of symptoms. However, the failure of the authors to address the issues of cigarette smoking and the effects of multiple psychotropic medications being taken by the psychiatric patient group and their effect on esophageal reflux put into question the validity of their conclusions.

The prevalence of psychiatric disorders in patients with gastroesophageal reflux disease

Psychological factors are implicated in a number of GI illnesses, but their role in GERD has not been fully defined. To answer this question, Baker et al [2] performed psychological assessments in 51 subjects with classic symptoms of GERD. In their study, 39 of the 51 subjects had endoscopic evidence of erosive esophagitis. These subjects were compared with 43 asymptomatic control subjects. A battery of psychologic assessments was administered to all subjects, and the investigators found that patients with GERD were more likely to be anxious or depressed or to have phobias and somatoform symptoms. Secondary analysis revealed that a subset of the reflux patients (30%) accounted for differences on psychological test scores between the two groups. The investigators concluded that although most GERD sufferers have a psychological profile similar to those without GERD, a subset of GERD patients experience significant psychological distress [2]. Despite methodologic problems in the selection of subjects for this study, it provides evidence that in some patients with GERD there may be a strong psychiatric component to the perception and expression of their disease.

Care seeking may be another marker for psychological dysfunction in GERD patients. All of the patients assessed in the Baker study [2] were care seekers. There is literature demonstrating that in patients with irritable bowel syndrome (IBS), there are psychological differences between those who seek care versus those who do not [3]. The application of this concept to GERD is uncertain. However, the issue of care seeking in patients with GERD and its relationship to psychological variables was examined in 138 patients presenting for de novo treatment of GERD at a gastroenterology clinic. These patients were compared with 39 heartburn sufferers who had never sought medical care for their reflux symptoms and with 40 healthy individuals with no symptoms of GERD. These patients were assessed psychologically using standardized psychometric instruments. Individuals with GERD seeking treatment were more likely to experience phobias, obsessions, and somatization than healthy individuals or non-health care seeking GERD sufferers. Care seekers also had less social support than non-care seekers or healthy normal subjects [4]. Although not definitive, this study suggests that patients with GERD who seek care may be a self-selected, more psychosocially impaired group.

The issue of acute as opposed to chronic psychosocial stress as a correlate to GERD perception and expression was studied by Bradley et al [5]. They examined the effects of acute stress on 17 subjects with symptomatic, endoscopically proven GERD. Esophageal manometry testing was performed on entry to and exit from the study. These patients were given the Millon Behavioral Health Index (MBHI), which was designed to assess personality traits, interpersonal style, the impact of stress, motivation for

change, and compliance with care in medical settings. Tests provide specific predictions for patients with GI disorders and other medical conditions. It does not assess personality traits per se but rather “susceptibility” to stress in the presence of certain illness states [5]. In this study, indwelling pH probes measured acid reflux during experimentally induced stressful tasks. This allowed the investigators to measure real-time reflux of acid into the esophagus in a response to acute stress. Patients were given stressful tasks and neutral tasks. In addition to subjective measures of GERD symptoms and feelings of anxiety, objective measures of autonomic function, including blood pressure, and heart rate were taken during the experimental profile.

Subjects who scored high in GI susceptibility on the MBHI were more likely to report GERD symptoms during stressful tasks but experienced no change in levels of acid reflux as measured by the indwelling pH probe. Those with low scores on GI susceptibility on the MBHI were significantly less likely to report GERD symptoms and to experience no changes in pH. There were no changes in levels of acid reflux into the esophagus. The investigators concluded that acute stress did not seem to precipitate reflux [6].

Noncardiac chest pain and psychological distress

Epidemiologic studies can help us better understand the issue of psychological stress and NCCP. In a large British study of NCCP, more than 5300 adolescents with an average age 15 years were assessed for a variety of physical symptoms, for their current psychologic state, and the health of their parents. These subjects were followed for an average of 15 years, after which they were reevaluated at the age of 36 years. Subjects reporting chest pain at the reevaluation were monitored for an additional 7 years to determine the outcome of their chest pain. Approximately 17% of subjects reported NCCP at age 36 years, and 1% reported exertional chest pain. A significant relationship was found between psychiatric disorders and the presence of persistent chest pain (odds ratio [OR] 3.55). The risk for psychiatric comorbidity increased substantially in patients with exertional chest pain (OR 29.08). A high level of psychological distress also seemed to be associated with the presence of persistent chest pain. Analysis of the data revealed two other variables associated with chest pain: parental illness and fatigue during childhood [7].

The relationship between noncardiac chest pain and panic disorder

The establishment of a precise definition of panic disorder has contributed immensely to research in NCCP. Chest pain is a common symptom in people having panic attacks [8]. Several well constructed studies that investigated the prevalence of panic disorder among those with NCCP have found that between 15% and 60% of patients with NCCP have panic

disorder [9–12]. The epidemiologic profile for NCCP with panic disorder tends to be a younger woman (< 30 years of age) with chest pain and no family history of early onset heart disease [11]. Although this profile is not pathognomonic, it should increase the index of suspicion for panic disorder as a cause of chest pain in patients who meet the demographic profile.

Although the pathophysiologic mechanisms behind the association of NCCP and panic disorder are not known, some intriguing possibilities have come to light recently. Hyperventilation can cause esophageal spasm and panic attacks, but the implications of this interaction are not understood. Stollman and Rogers [13] performed an observational study of 46 consecutive patients with NCCP and normal coronary angiograms. Esophageal motility was recorded after voluntary hyperventilation at 40 breaths per minute for 3 minutes. Hyperventilation induced diffuse esophageal spasm in 4% of patients and nonspecific motility disorders in 22%. Fifteen percent of patients experienced chest pain. The esophageal abnormalities reversed when the patient stopped hyperventilating. Other studies have shown that panic attacks can be provoked in patients prone to them by lowering pH through hyperventilation [14]. In susceptible patients, hyperventilation can precipitate a panic attack.

How does this relate to chest pain? Hyperventilation can possibly be used as a diagnostic tool. If it produces changes in esophageal motility or causes chest pain, then panic disorder may be involved in generating the patient's NCCP.

The rationale for the use of antidepressants in noncardiac chest pain

The use of antidepressants in NCCP finds support in the high incidence of psychiatric comorbidities found in patients with functional GI disorders in general and with NCCP in particular. This is true of chest pain and panic disorder. Additionally, the rich innervation of the gut via the enteric nervous system and the overlap of these pathways with those coming from the heart, trachea, and bronchi provide numerous opportunities to intervene neuropharmacologically to decrease the sensitivity (ie, neurotransmission) of afferent signals from the esophagus to the brain. The rich innervation of the esophagus and its connections to the other organs in the chest provide numerous opportunities to intervene pharmacologically to influence the activity of these receptors. This may make antidepressants, and in particular the tricyclics, useful in this setting. These agents already have an established role in the treatment of extraintestinal chronic pain syndromes and in the treatment of other functional GI disorders [3].

Imipramine and trazodone have been explored as possible treatments for NCCP. Trazodone is relatively free of anticholinergic side effects and therefore is less likely to induce GERD through a lowered LES pressure. Trazodone was used by Clouse [15] to treat 29 patients with esophageal

symptoms (including chest pain) and esophageal contraction abnormalities in a 6-week, double-blind, placebo-controlled trial. The 15 patients who received active medication (trazodone 50–150 mg/day) reported a significantly greater global improvement in their symptoms than those receiving placebo. Although esophageal motility changes, as measured by manometry, did not correlate with clinical response, chest pain was remarkably reduced.

There was a high degree of psychiatric comorbidity in the Clouse study that cannot be discounted [15]. In the active treatment group, 40% of patients had depression, whereas only 21% in the placebo group did. Other psychiatric diagnoses were better balanced between the two groups. The most commonly reported disorder was generalized anxiety disorder, which was found in 46% of all patients, in 47% of the active group, and in 43% of the placebo group [15].

In a later study, Cannon et al investigated the use of imipramine in 60 patients with NCCP and normal coronary angiograms. Twenty patients were given clonidine at a dose of 0.1 mg twice daily, 20 were given imipramine 50 mg nightly plus a morning placebo, and 20 were given placebo twice daily in this double-blind, 3-week trial. At baseline, 41% of these patients had abnormal motility studies, and 63% had a psychiatric disorder. Replication of pain with ventricular stimulation was recorded in 87% of subjects, but increased myocardial oxygen consumption could not be documented. Clonidine was given to determine if there was an adrenergic component to the subject's NCCP.

Imipramine produced significant reduction in chest pain complaints and levels of distress. Neither clonidine nor placebo had any effect in reducing subject's chest pain scores [16]. As in the Clouse study [15], the improvements were not related to any changes in esophageal motility, cardiac function, or psychological scores. Given these results, it seems reasonable to conclude that despite the high level of psychiatric comorbidity, it was not treatment of depression or other psychiatric disorders that caused the subjects to improve clinically. Imipramine seemed to have a visceral analgesic effect at the dose used in the study.

Summary

There is some evidence to support a psychosocial link to GERD, although it is a weak one. The little research that has been done in this area is, in general, poor and inconclusive. Better designed studies must be done. The elements that seem to offer the best possibilities for research in GERD are the psychological variables involved in care seeking and the variations between care seekers and non-care seekers. In addition, research on psychosocial predictors of response to proton pump inhibitors, prokinetic agents, and antidepressants and other pain-modulating drugs need to be better understood.

The psychosocial link to NCCP is stronger with regard to panic disorder, but much research needs to be done. Despite the paucity of well done, rigorously controlled studies in NCCP patients, that there is a high prevalence of psychiatric disturbance in this group. Parental health and childhood trauma are intriguing areas for further research, particularly in light of the connection between abuse and IBS and other functional GI disorders.

Finally, panic disorder has been established as an important comorbidity of NCCP. It also merits more research, particularly into the pathophysiology that may link these two disorders.

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Brain processing of esophageal sensation in health and disease

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In the last 10 to 15 years, commonly used neurophysiologic and neuroimaging techniques have been adapted for use in the human gastrointestinal (GI) tract, rapidly expanding the discipline of neurogastroenterology [1]. Although work in this area has increased our understanding of normal GI neurophysiology, clinicians have been critical of the failure of this research to translate and improve the diagnosis and treatment of functional GI disorders (FGD). However, when compared with somatic pain research, human visceral pain research is in its infancy. Before specific hypotheses can be generated and tested, a solid foundation based on a comprehensive understanding of normal visceral pain processing and the implications of these findings to disease states has to be constructed. We have not reached this point; thus, clinical research in this area remains fraught with uncertainty.

We provide an overview of the current literature pertaining to transmission and subsequent processing of esophageal sensation and pain within the central nervous system (CNS). In addition, we provide a brief critique of recent neuroimaging studies in health and FGD and describe how simple neurophysiologic techniques may be used to differentiate between specific mechanisms of visceral hypersensitivity in noncardiac chest pain (NCCP).

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The pain experience

The experience of pain has two distinct dimensions: sensation and affect [2]. The sensory dimension of pain allows localization of a painful event to the offending body region and evaluation of its intensity. This is the sensory–discriminatory aspect of pain processing. The affective dimension of pain is more complex and comprises several components that combine to produce the emotion of pain.

First, there is the unique unpleasantness associated with pain that is characterized by the use of words, such as “burning” and “aching,” that are used only when describing noxious sensory events. An additional component of pain unpleasantness is the short-term fear and anxiety that it induces during and in the immediate aftermath of the painful event. Secondary pain affect is the other constituent of the affective dimension of pain. This deals with emotional feelings regarding the long-term implications of pain, such as a desire to escape its presence and the associated suffering as pain persists. These components comprise the affective–cognitive–motivational aspects of pain processing [2].

Clinically, pain can be subclassified into superficial, neuropathic, and deep. Superficial pain arises from cutaneous structures; neuropathic pain results from damage to nervous tissue; and deep pain results from structures such as joints, muscle, bone, and the viscera [3]. Deep pain constitutes the majority of pain treated by clinicians and is characterized by poor localization, tonic increases in muscle tone, and a propensity to evoke strong autonomic responses, such as changes in heart rate and blood pressure [3].

In contrast to deep pain from bilateral structures such as limbs, pain arising from one visceral region is not easily differentiated from that occurring in another. Additionally, visceral pain is often referred to superficial regions, causing somatic hyperalgesia. These unique qualities and characteristics of visceral pain allow it to be separated clinically and experimentally from other types of deep pain [4,5]. The pain experience is complex, with many of its characteristics common to each pain modality. However, subtle differences in the neuroanatomic organization of the ascending pathways and the subcortical and cortical structures involved in the transmission and interpretation of pain account for our ability to differentiate between pain subtypes. The following section describes the neural structures implicated in the conduction and interpretation of esophageal pain.

Extrinsic esophageal innervation

The esophagus has a dual extrinsic innervation that projects from the CNS. This is provided by the vagus nerve and from spinal visceral afferents housed in the cardiac and splanchnic nerves [6]. The vagus nerve (10th cranial nerve) has an afferent to efferent ratio of 9:1, with 70% to 90% of

fibers within the nerve trunk being unmyelinated neurons and the rest being thinly myelinated A δ -fibers [7–9]. The majority of esophageal vagal afferent neurons have cell bodies in the nodose ganglia, lying just below the jugular foramen; however, a minority lies more proximally within the jugular ganglia [10].

Vagal afferent fibers from the nodose ganglia terminate within the brain stem in the medial division of the nucleus of solitary tract, where there is also rostrocaudal viscerotropic organization within distinct subnuclei [11]. Second-order neurones project to and influence a variety of neurones in the hypothalamus and brainstem, including the vagal motor nuclei, the rostral areas of the ventrolateral medulla, and the parabrachial nuclei. The cortical projections from the brainstem include the orbitofrontal, infralimbic anterior cingulate, and insula cortex, the latter having reciprocal connections with the secondary somatosensory cortex. Recent work by Ito et al [12] has demonstrated vagal projections to lateral primary somatosensory cortex in rats.

Vagal afferent receptors

Vagal afferents have receptive fields in the mucosal and muscle layers of the esophagus [6]. Mucosal afferents can be classified as mechanoreceptors, chemoreceptors, or thermoreceptors. Polymodal mechanoreceptors that respond to chemical stimuli have also been identified [13]. Most mucosal afferents are unmyelinated C fibers, which are described as “in parallel” because they demonstrate afferent discharge to a mechanical stimulus (ie, stretch) but not to muscle contraction (ie, peristalsis). They are rapidly adapting because afferent discharge occurs abruptly at the onset of stimulation and ceases quickly after [6]. Muscle afferent vagal fibers are slowly adapting mechanoreceptors that respond to passive distension and to active muscle contraction and contain unmyelinated and myelinated fibers [6,14].

Sengupta et al [6,14] have shown that vagal afferents have a low threshold of activation to mechanical stimulation and are saturated at levels of distension that are within the physiologic range. They are therefore thought to mediate non-noxious sensations such as nausea and satiety. However, a role for vagal afferents in the modulation of nociception has recently been established. Vagal afferents acting via the brain stem exert an inhibitory and excitatory influence on spinal nociceptive transmission [15,16]. This may help to explain why some patients experience extreme sensory dysfunction after vagotomy [17].

Spinal visceral afferents

Spinal visceral afferents constitute 5% to 10% of all fibers in the thoracic and lumbar dorsal nerve roots. Most visceral afferents pass via pre- and

para-vertebral ganglia en route to the spinal cord and present collaterals to the prevertebral ganglia [9,18,19].

Spinal afferents have their cell bodies in the dorsal root ganglia (DRG), which are located within the cervical, thoracic, and upper lumbar spine. Two types of cell bodies have been identified within the DRG. The majority are small to medium cell bodies, which suggests that the majority of axons of visceral afferents are unmyelinated C-fibers, whereas approximately 13% are larger cell bodies, suggesting that a small proportion of visceral afferents have axons that are thinly myelinated A δ fibers [6].

GI spinal afferents run within different visceral nerves that enter the sympathetic trunk and pass through the white ramus to join the spinal nerve before entering the DRG. The esophagus is innervated craniocaudally by afferents from 22 or 23 paired DRG located between the first cervical to the second lumbar segments and are housed in the cardiac (superior, middle, and inferior) and splanchnic (thoracic, greater, and lesser) nerves [18,20,21]. Two main areas of peak innervation have been demonstrated in animal studies in the upper cervical (C2–C6) and thoracic (T2–T4 and T8–T12) spinal segments [6,18,19].

Visceral afferent information is transmitted proximally along the spinal cord via a number of tracts, of which the spinothalamic tract and the dorsal columns are the most important [6]. These project to the thalamus and onto cortical structures including SI, SII, insula, and anterior cingulate.

Spinal visceral afferent receptors

Despite the majority of afferents in the mucosa being vagal, some mucosal spinal afferents have been identified. These are mainly chemoreceptors, responsive to changes in pH, osmolality, and various nutrients (eg, glucose). It is thought that these afferents are involved in the regulation of gut reflexes such as motility and secretion. Mucosal spinal afferents that are responsive to thermal stimuli have also been identified [6,13,22].

Two types of spinal muscle afferents have been identified, and both show a monotonic, linear increase in response to distending pressures up to 120 mm Hg, well within the noxious range [6,23]. The first are in series and respond to low and high thresholds of stimulation. These are called wide dynamic range mechanoreceptors and have stimulus response functions that cover the physiologic and nociceptive ranges of stimulation. These are considered to play a role in regulatory functions of the esophagus in normal physiologic conditions. The second type of spinal muscle afferents are in parallel and are high-threshold mechanoreceptors that respond only to stimulation intensities above 50 mm Hg, which is classified as in the noxious range. These afferents are thought to be important in the transmission of nociception [6,23].

In summary, vagal afferents seem to be involved in the mediation of physiologic processes, which mostly occur below our level of perception.

Spinal afferents are also involved in these regulatory processes but additionally encode noxious stimuli because they respond to non-nociceptive and nociceptive stimuli. The vagus may also have an important role in the modulation of nociceptive transmission.

Ascending tracts and thalamic nuclei

The extrinsic innervation of the esophagus is diffuse and complex. The considerable divergence of esophageal afferents across many spinal segments is coupled with subsequent convergence with visceral afferents from other GI regions and viscerosomatic afferents within the spinal cord [18,19]. It has been shown that approximately 75% of spinal somatic afferents also respond to visceral stimulation [24].

Visceral afferent transmission predominantly ascends in the spinothalamic tract (STT) and postsynaptic dorsal column pathways [25] terminating in the ventro-posterior lateral (VPL) nucleus of the thalamus [26–28]. Eighty-five percent of VPL neurons respond to visceral and cutaneous stimuli, although the visceral input is not viscerotropically organized [29]. The properties and projections of VPL neurons strongly suggest a role in the sensory-discriminatory aspects of pain processing [24]. Evidence for a role of the VPL nucleus in visceral and referred pain comes from a study in which, after stimulation of the VPL nucleus, symptoms of chest pain were reproduced in a patient with angina pectoris without concurrent changes in cardiovascular function [30]. This is not to say that visceral afferents do not project to other thalamic nuclei; VPL seem to play the most significant role in relaying nociceptive information to the higher brain regions that form the visceral-cortical pain matrix.

The cerebral cortex

Despite abundant nociceptive projections from thalamic nuclei to many regions of the cerebral cortex, its role in pain processing remained in doubt for many years [31,32]. However, animal studies and, more recently, functional brain imaging studies in humans have revealed that the cerebral cortex plays an important role in the sensory–discriminatory and affective components of pain. The following section summarizes the role of the four main cortical regions that have consistently been shown to participate in pain processing.

The primary somatosensory cortex

Lesions of the primary sensory cortex (SI) in humans have revealed contradictory evidence for its role in pain perception. These studies have shown that lesions may cause hypoalgesia, hyperalgesia, or have no effect at

all [33,34]. The number and localization of nociceptive neurons within SI may partly explain these conflicting results. SI is predominantly involved in processing non-noxious, somatosensory information, such as pressure and warmth, from the body, giving us vital information about our external environment and allowing modulation of motor function. Consequently, nociceptive neurons are greatly outnumbered by neurons that respond to tactile stimulation. In addition, nociceptive neurons project to distinct regions of SI, at the borders between the cytoarchitectonic areas 3b-1, and 3b to 1, and 1 to 2 respectively [35]. Therefore, it is highly probable that the location of the lesions in the above-mentioned studies may be important in determining their affect on pain perception.

Animal studies have revealed abundant projections of nociceptive neurons to SI from the VPL nuclei in the thalamus. These neurons are somatotropically arranged and have restricted receptive fields, and activity within these neurons is correlated with the duration and intensity of a noxious stimulus [36]. These data suggest that nociceptive neurons in SI encode the sensory discriminatory aspects of pain processing.

Secondary somatosensory cortex

The secondary somatosensory cortex (SII) lies in the parietal operculum in the upper bank of the sylvian fissure [37]. Processing of pain within SI and SII is in parallel, as opposed to the serial processing of tactile information between these two areas [38]. SII receives nociceptive projections from the VPI thalamic nuclei that have mostly large, bilateral receptive fields. Projections from SII enter the temporal lobe limbic structures via the insula.

SII is thought to be important in helping us to recognize the nature of a painful stimulus. Evidence to support this comes from lesion studies that have shown that damage to SII impairs the ability to identify the nature of noxious stimuli so that, although the stimulus is still unpleasant, subjects cannot differentiate between, for example, mechanical or heat pain [36].

The insula

The insula has a complex role in pain processing that has not been adequately defined. It has two distinct regions: (1) the granular posterior insular, which is thought to process tactile, auditory, and visual somatosensory function and (2) the dysgranular anterior insula, which is involved in olfactory, gustatory, and viscer-autonomic functions [39]. Although the majority of pain studies have shown nociceptive inputs to the anterior insula, the presence of nociceptive inputs to the posterior insula have also been described.

Whereas the insula receives projections from SII, recent studies have shown that it also receives direct projections from nociceptors within the ventromedial posterior nucleus in the medial thalamus. Insula nociceptive neurons have large receptive fields, respond to different stimulus modalities,

and are strongly activated by visceral stimuli. Although the insula does not play an important role in sensory discrimination, lesion studies have shown that damage to the insula reduces pain affect and other appropriate pain reactions. It is therefore thought that the insula integrates information from direct thalamic projections with that received from SII and relays this to limbic structures to modulate autonomic reactions and pain-related memory/learning processes [36]. Recent evidence from studies of the insula cortex using intracortical electrodes in patients with temporal lobe epilepsy have shown that the posterior/mid-insula region is part of a somesthetic network involved in processing painful and nonpainful somatic sensations [40–42]. In contrast, stimulation of the anterior insula in the same subjects elicited viscerosensitive and visceromotor responses, indicating that the anterior insula is part of the visceral network [40–42].

The cingulate cortex

The cingulate cortex is an extensive area of the limbic system that overlies the corpus collasum and comprises two distinct regions: the anterior and posterior portions. The anterior cingulate cortex (ACC) has been most commonly implicated in pain processing [43,44]. The ACC receives direct projections from the medial thalamic nuclei. These nociceptive neurons do not display somatotopic organization and have large, bilateral receptive fields. Lesion studies in patients after cingulotomy have shown that although pain was still perceived, it was less distressing and there was less motivation to avoid the painful stimulus. Consequently, the ACC has a role in the affective-motivational aspects of pain processing [45]. This is not to rule out a role for the PCC in pain processing. Data from EEG recordings have suggested that painful cutaneous laser stimulation activates a cortical source within the posterior cingulate, which is activated later than somatosensory areas [46,47].

Other cortical regions

The experience of pain encompasses many different facets of human consciousness. Studies of pain have revealed activation of many other cortical regions in addition to those described above. These areas include dorsolateral prefrontal, posterior parietal, and primary motor and supplementary motor cortices. Activation has been seen in the cerebellum and caudate nucleus [24,45,48]. Evidence to help us understand the role of these regions in pain processing remains sparse, and further study is needed to ascertain their functional significance.

Electrophysiologic assessment of esophageal afferents in health

The complexities of esophageal innervation have been known for many years, yet it is only in the last 10 years that we have attempted to objectively

characterize the neurophysiologic basis of esophageal sensation in humans [1]. Commonly used neurophysiologic techniques have been adapted, allowing us to noninvasively investigate the integrity and characteristics of GI afferent pathways. Our knowledge in this area is slowly expanding.

Neurophysiologists have used evoked potentials (EP) to study somato-sensory, visual, auditory, and pain pathways for half a century. This technique involves the brief presentation of a sensory stimulus, which is time- and phase locked to the recording of the electroencephalogram (EEG) via surface electrodes placed on the scalp. The event-related signal is small in amplitude but occurs at the same moment in time after each stimulus, whereas the large amplitude background EEG is occurs randomly. To extract the desired signal, repeated stimuli are given, and the subsequent brain activity is averaged. This reduces the unwanted EEG while enhancing the event-related EP [49].

Frieling et al [50] recorded EP responses to esophageal stimulation, suggesting that the esophageal-evoked response (EEP) was predominantly mediated via vagal afferent pathways. However, further studies revealed that as stimulation intensity and sensory perception increased toward pain, there was an associated reduction in the latency and increase in amplitude of the EEP components (Fig. 1A) [51,52]. This phenomenon is common across all evoked potential modalities and reflects the recruitment of an increasing number of afferents. The stimulus–response characteristics of EEP therefore implicate spinal afferents in the mediation of this response because vagal afferents saturate at stimulation levels well below the noxious range [23].

The ability to record objective neurophysiologic measures that correspond directly to subjective pain ratings overcomes many of the limitations of previous studies of visceral hypersensitivity [53]. These have relied on descriptive methods of reporting visceral sensation, and, although care is taken to eliminate subjective factors from introducing response bias, no truly objective measures of visceral sensation have been available. EEP therefore is destined to become an important tool in the clinical investigation of visceral pain mechanisms.

A comparison of EEP elicited by electrical and mechanical stimulation showed that both responses were mediated by thinly myelinated A δ -fibers, that both produced responses of identical morphology, and that the latency difference between the first mechanical and electrical EEP component of ~50 milliseconds was due to the physical delay encountered during balloon inflation (not due to the activation of different fiber types) (Fig. 1B) [52]. This is not to say that unmyelinated C-fibers are not activated by esophageal stimulation; they do not contribute to the early response complex recorded with EEP [52].

The amplitude of mechanically evoked EEP was smaller than that seen in electrical stimulation. The amplitude of the EEP increases with increased afferent recruitment. These amplitude differences could therefore be explained by the fact that mechanical stimulation is specific to mechanosensitive

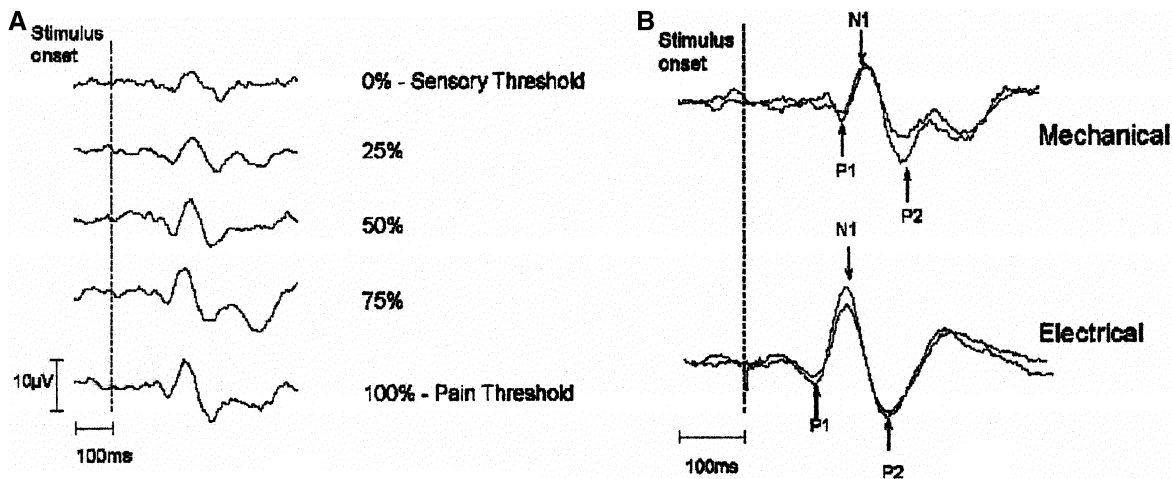


Fig. 1. (A) Stimulus–response characteristics of the EEP in response to mechanical stimulation. As the stimulation intensity increases from sensory threshold through to pain, there is an associated decrease in the latency of the EEP components and an increase in their amplitude. This allows us to use EEP as an objective measure of esophageal sensation. (B) A comparison of EEP recorded in response to mechanical and electrical stimulation. The morphology of both EEP responses is similar; however, electrical EEPs have shorter latency and larger amplitude responses. EEP recorded on a second occasion have been overlaid to demonstrate the reproducibility of the technique. (*Adapted from* Hobson AR, Sarkar S, Furlong PL, Thompson DG, Aziz Q. A cortical evoked potential study of afferents mediating human esophageal sensation. *Am J Physiol Gastrointest Liver Physiol* 2000;279:G139–47; with permission.)

afferent receptors, whereas electrical stimulation activated all afferents regardless of modality, leading to greater afferent recruitment [52].

Visceral EPs are similar in nature to somatic pain EP responses elicited by thermal cutaneous laser stimulation. Like esophageal stimulation, laser stimulation selectively activates nociceptive afferents—namely, thinly myelinated A δ and unmyelinated C-fibers. The resultant laser EP response shares several other characteristics with EEP in that it habituates over time, is maximally recorded at the vertex, and changes in the latency of components can occur with alteration of the level of vigilance/attention afforded to the stimulus [52,54]. These similarities become important when considering the physiologic basis and functional relevance of the EEP, which is discussed in subsequent sections.

Functional neuroimaging of the esophageal-cortical pain matrix

The scalp-recorded EEP represents a summation of cortical activity related to specific stages in the cortical processing of esophageal sensation and pain. Pain is a result of a complex interaction of many brain regions. This has been demonstrated for somatic pain using metabolic neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), which have revealed pain-related activity within a network of cortical and subcortical structures termed the “pain matrix” [45]. PET and fMRI rely on the principle that increased neuronal activity within the brain is associated with increased metabolism and regional cerebral blood flow. Comparison of images recorded during resting and active periods reveals regions of increased cortical activity, and these measures have been used to increase understanding of the functional properties of the brain [55,56].

There have been seven studies of esophageal sensation and pain using PET or fMRI in health [57–63] and none in NCCP. A recent meta-analysis of these studies revealed that the esophagus is represented in all of the major cortical pain regions (ie, SI, SII, insula, and cingulate in addition to prefrontal cortex and motor cortex) [64]. Activation of subcortical regions, such as the thalamus and periaqueductal gray, has also been demonstrated with PET [57]; however, only one fMRI study has shown convincing subcortical activation [63]. These studies show relatively good concordance, giving us confidence that they are an accurate representation of esophageal cortical processing.

The major differences between esophageal and somatic pain processing have been examined in several studies. The most recent of these studies, performed by Strigo et al [63], compared cortical activity generated by distension of the esophagus and thermal stimulation of the anterior chest wall. Both stimuli were matched psychophysical for intensity; however, esophageal stimulation was perceived to be more unpleasant than cutaneous

stimulation, and the major differences in cortical representation occurred in SI, insula, and pre-frontal cortex.

In the study by Strigo et al, esophageal and chest wall stimulation activated SI in the region associated with the homonuclear representation of the trunk; however, esophageal stimulation alone activated the more lateral aspects of SI (often referred to as the gustatory region of SI). The authors concluded that this diffuse representation of the esophagus in SI was consistent with the fact that visceral pain can be referred to the skin but not vice versa [63].

This study also revealed greater activation of the anterior portion of the insula (AI) to chest wall stimulation when compared with esophageal distension. Previous studies have shown bilateral activation of the AI to be the most consistent finding across all esophageal neuroimaging studies, and this area plays an important role in the emotional modulation of esophageal sensory processing [62]. However, AI is also strongly activated by thermal stimulation [65], and the differences seen here may merely reflect the fact that a higher number of somatic thermo-sensitive neurons are present in this region when compared with visceral specific neurons. Both stimuli produced bilateral activation of the posterior insula, which is known to process somesthetic sensation, providing further evidence for the convergence of visceral and somatic pain processing.

Although PET and fMRI have revealed many salient features of pain processing, they do not have sufficient temporal resolution to map cortical activity because it changes on a millisecond-by-millisecond basis. This is important because different components of pain processing occur in different temporal time windows [46]. Therefore, identifying the sequence of activation of cortical structures within the pain matrix would not only give us important information regarding the central conduction of the esophageal pain pathways but also would allow us to dissociate the functional relevance of specific cortical regions in the temporally distinct stages of pain processing. In addition, PET and fMRI rely on group pooling of data, which is unlikely to be useful clinically unless studying a homogenous patient population, which is not the case in NCCP. The following section describes a neuroimaging technique that may overcome some of these limitations.

Recording esophageal–cortical neuromagnetic activity

Studies have used magnetoencephalography (MEG) to record esophageal cortical neuronal activity [66–68]. MEG detects the minute magnetic fields generated by groups of active cortical neurons using highly sensitive sensors known as SQUIDS (super conducting quantum interference device). Unlike the electrical signal recorded with EP, which is distorted by all of the structures that lie between the cortical source and the recording electrode, the magnetic field generated by an active group of cortical neurons passes

through these structures unattenuated [69]. The major advantage of using MEG is that it has comparable spatial resolution to PET and fMRI in addition to millisecond temporal resolution; therefore, pain-related cortical activity can be imaged dynamically as it changes in real time.

Esophageal MEG studies have shown that activity in SI and SII/insula [66–68] occurs approximately 70 to 190 milliseconds after stimulation; however, due to limitations in previous MEG analysis techniques, further information regarding other cortical structures was not reported. Preliminary findings using a new method of analyzing the brain's neuro-magnetic signals, synthetic aperture magnetometry (SAM), may allow us to construct a more detailed model of esophageal-cortical pain processing. In brief, SAM improves the signal-to-noise ratio of MEG recording, allowing signals to be detected throughout the cortex including deeper structures such as the ACC, which were previously thought to be invisible to MEG sensors [69,70]. A related MEG analysis technique (dynamic imaging of coherent sources) has recently shown that the ACC plays an important role in processing “second pain” after painful cutaneous thermal stimulation [71].

SAM allows us to place “virtual” electrodes into regions of interest throughout the cortex and estimates the cortical neuronal activity in response to esophageal stimulation. Using a similar protocol to that used for EEP, we can detect the evoked magnetic field response from each virtual electrode position [72]. Fig. 2 shows the evoked field response recorded from virtual electrodes placed in lateral SI and perigenual ACC after painful and nonpainful esophageal stimulation. These data reveal that the earliest activity occurs in regions that process sensory discriminatory aspects of esophageal sensation (SI/SII), whereas secondary processing occurs in the ACC approximately 60 milliseconds after activation of SI/SII. Because the signal detected with MEG is the magnetic component of the electrical field recorded with EEP, it can be used to temporally correlate activity occurring within specific cortical regions with the scalp recorded EEP. This allows us to say that the earliest EEP component (P1), which occurs approximately 80 to 110 milliseconds after esophageal stimulation, is likely to reflect activation of cortical regions involved in processing pain sensation, whereas later components (N1, P2) are an amalgamation of cortical activity within regions that process pain sensation and affect. These later components represent secondary processing of esophageal sensation/pain.

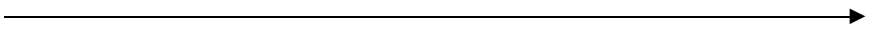
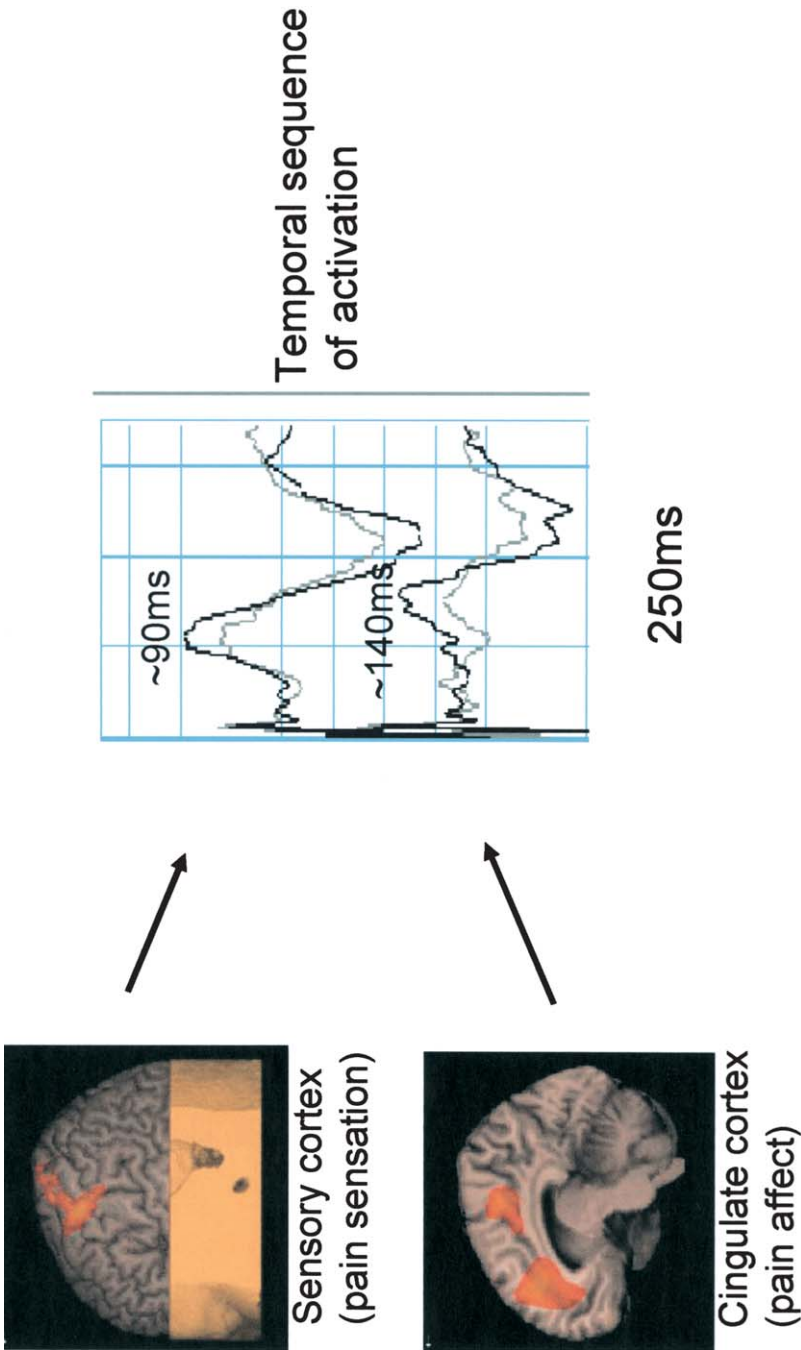


Fig. 2. Evoked field response recorded with MEG/SAM after painful and nonpainful electrical stimulation of the esophagus. The top trace is recorded from a virtual electrode positioned in the lateral portion of the primary somatosensory cortex; the peak latency of this response is 90 milliseconds. This corresponds to the P1 component of the EEP and is consistent with this region's role in the sensory discriminatory aspects of pain processing. The lower trace is recorded from a virtual electrode positioned in the perigenual cingulate cortex; the peak latency of this response is 140 milliseconds. This later response is consistent with this regions involvement in affection/cognitive processing of esophageal pain.



Constructing a model of the esophageal pain matrix

Combining information from the animal and human studies described above, we can construct a hypothetical model of afferent transmission and CNS processing of esophageal sensation, revealing that somatic and visceral pain processing are similar. Esophageal nociceptive signals are transmitted to the STT and PSDC pathway [73] where this relatively small afferent input converges with viscerosomatic afferents [74] and is conveyed primarily to the ventro-posterior lateral nucleus of the thalamus and onto cortical structures. Divergence of the esophageal primary afferents results in the visceral signal entering the spinal cord at several dermatomal levels (C2–T12) [18], explaining the diffuse nature of the sensation evoked by esophageal stimulation across the chest wall. In addition, rather than projecting specifically to contralateral SI, as would be seen when noxious stimulation is applied to a limb, esophageal representation is diffuse, encompassing bilateral activation of SI in the trunk and intra-abdominal regions.

As seen in somatic pain [75], activity occurs bilaterally in SII and posterior insula, which is followed by activation of limbic structures. Early activity occurring in SI, SII, and posterior insula most likely relates to information relayed directly via projections from the thalamus; however, it is not clear whether the later activity seen in limbic regions relates to direct projection of information from other thalamic nuclei or to secondary processing via intracortical pathways.

Using this model we can relate esophageal pain processing to other sensory systems. A study that has compared the sequential processing of tactile information within the somatosensory cortex with parallel processing of somatic pain suggested that these differences represent an evolutionary development that dictates that our response to pain involve avoidance of harmful stimuli rather than a requirement for sophisticated sensory capacities [38]. Because visceral pain usually occurs as a response to something we have ingested rather than something we have touched, visceral pain processing can be thought of as an even less sophisticated system. Consequently, nociceptive visceral afferents are few in number but converge within the spinal cord to “piggyback” visceral nociceptive information onto the ascending pathways of the somatic pain matrix and project to associated cortical structures, thus registering the occurrence of a painful visceral event.

This is not to say that visceral afferents do not project directly to cortical structures independently of somatic afferents; there is ample evidence from animal studies that this is the case [39]. However, in comparison to afferent transmission via viscerosomatic afferents, this component is likely to be small and most likely has a role in the autonomic reactions to pain rather than pain consciousness per se. This may also help to explain the stronger representation of visceral pain within the limbic system [76].

Neurophysiologic profiling of noncardiac chest pain

Although the functional brain imaging techniques described above offer an important insight into the neuroanatomy and function of the cortical structures within the pain matrix, their use as clinically diagnostic techniques in the study of pain remains limited. In contrast, the use of electrophysiologic recording techniques has proved valuable in identifying the contribution of CNS lesions in the generation of somatic pain syndromes [77,78].

Several GI research groups have used these techniques for use in the GI tract with the aim of explaining chronic pain symptoms in patients with FGD. The resultant studies have shown reduced [79–81] and enhanced [82–84] evoked responses in NCCP and IBS patients, and a cohesive picture regarding CNS abnormalities in FGD has yet to be developed. The use of suboptimal recording parameters and the lack of a clear hypothesis regarding the abnormalities under investigation have contributed to the disappointing results, and, despite their initial promise, these techniques have had no impact on the management of FGD.

The search for an organic cause of symptoms in FGD has yet to yield a successful biomedical explanation that can be used to develop successful treatment strategies. Patients are diagnosed on the basis of symptomatic criterion (the Rome II criteria), which aims to provide a framework by which clinicians can understand, categorize, and treat FGD symptoms [85]. A prerequisite for many studies of FGD is that patients enrolled in a study must conform to the Rome II criteria; however, this approach creates a difficult situation for clinical researchers.

Grouping together patients under a formal definition assumes a degree of homogeneity within the described population. Although it is widely accepted that visceral hypersensitivity plays an important role in the etiology of NCCP [86], it is not possible to subdivide patients on the basis of specific mechanisms, meaning that patients in whom sensitized visceral afferents may be the predominant cause for their symptoms are grouped together with patients in whom psychologic factors may be the predominant mechanism. Subsequently clinical trials in FGD describe hugely varying efficacy of treatments [87], and functional brain imaging studies of FGD patients that rely on grouping data have reported contradictory results [88,89].

We have previously developed the optimal stimulation and recording parameters needed to produce highly reproducible esophageal evoked responses [90,91]. Using these parameters, we can provide objective measures of esophageal sensation and demonstrate changes in the sensitivity of the esophageal afferent pathway due to experimentally induced central sensitization [92]. This work provides a solid foundation on which patient studies can be developed because the robustness of the technique has been demonstrated. In the following section we describe a case report of two

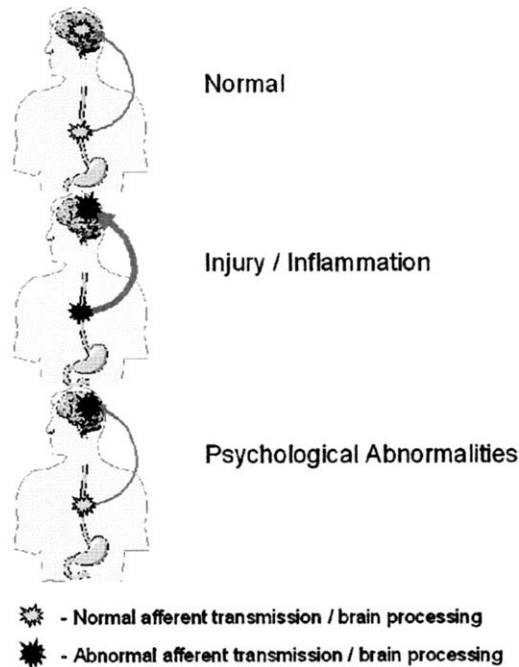


Fig. 3. Two proposed hypotheses relating to the mechanisms of esophageal hypersensitivity in NCCP.

NCCP patients and demonstrate how we can use EEP to neurophysiologically profile patients and objectively differentiate between the mechanisms of visceral hypersensitivity.

Hypersensitivity versus hypervigilance

We propose a simple hypothetical model to explain visceral hypersensitivity in patients with unexplained GI pain. This states that in most patients, injury/inflammation is the principle initiator of central sensitization (CS), which can persist long term, and if there is continuing occult injury then it may lead to chronic pain. It is also possible that CS may be amplified in the presence of cognitive bias (hypervigilance) toward visceral sensation. However, in some patients with visceral hypersensitivity, hypervigilance alone may be the predominant factor. From MEG studies, the early EEP response, which relates to the P1 component, reflects activation of primary and secondary somatosensory areas and posterior insula (regions that process pain sensation), whereas subsequent components (N1, P2) most likely reflect a cumulative and temporally overlapping activation of sensory and cognitive areas (regions that process pain sensation and pain affect).

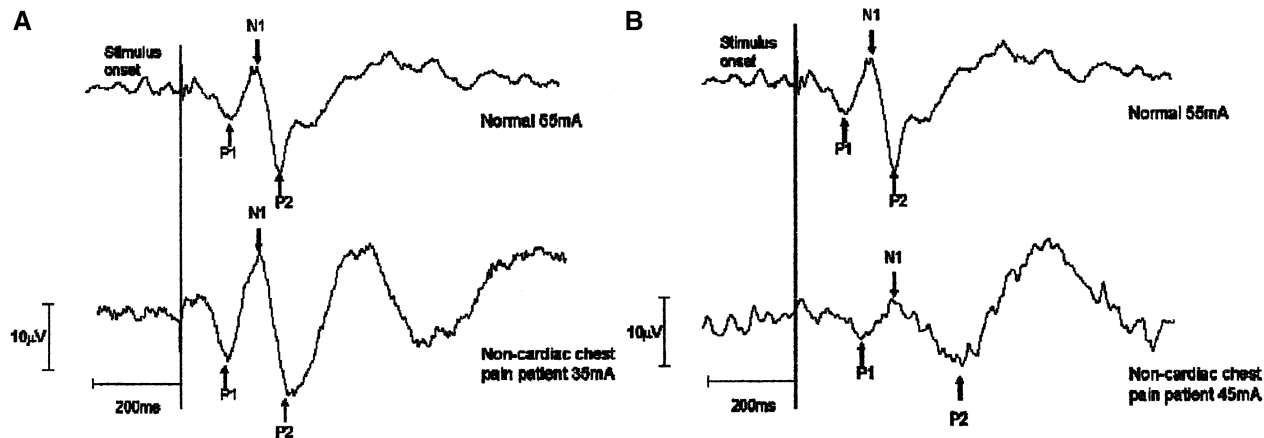


Fig. 4. (A) A normal EEP (*top*) and an EEP in our first NCCP patient. This patient demonstrated esophageal hypersensitivity that was associated with enhanced early and late EEP components. We believe this demonstrates objective neurophysiologic evidence that this patient has sensitized esophageal afferents. (B) A normal EEP (*top*) and an EEP in the second NCCP patient. This patient demonstrated esophageal hypersensitivity that was associated with reduced amplitude and delayed latency of the first three EEP components. However, there was enhancement of the late (500 milliseconds) EEP component, which is likely associated with secondary pain processing. We believe this demonstrates objective neurophysiologic evidence that this patient does not have sensitized esophageal afferents and is hypervigilant of esophageal sensations.

Using this information, we propose that NCCP patients can be subdivided on the basis of their neurophysiologic responses.

The first group of NCCP patients that have sensitization of visceral afferents should demonstrate reduced EEP latency responses and show enhanced cortical processing of visceral sensation in the sensory discriminative (P1) and the cognitive/emotional processing (N1, P2) areas because of the larger signal arriving at the cortex compared with healthy volunteers for a given stimulation intensity (Fig. 3, middle panel). The second group of NCCP patients with hypervigilance has normal or delayed EEP latency in comparison to healthy subjects and demonstrates normal or reduced activation of the sensory discriminative cortical areas (P1) because they over-report the intensity of stimulation but have increased activation in the cognitive/emotional areas relating to the later components of the EEP response (Fig. 3, bottom panel).

In this case study, two female patients presented with symptoms of anginal-like chest pain in the absence of any cardiac abnormality (as tested by exercise ECG and coronary angiography). Both had a previous trial of proton pump inhibitors, which did not alleviate symptoms, and there was no evidence of motor abnormalities or gastroesophageal reflux on physiologic testing. Esophageal balloon distension and electrical stimulation revealed evidence of esophageal hypersensitivity using the method of ascending limits technique. An electrical stimulation intensity, which was 75% of the difference between the subjects sensory and pain thresholds, was used to elicit EEP.

Fig. 4 shows the EEP responses in both patients and demonstrates that these seemingly identical patients have drastically different neurophysiologic profiles. Patient A demonstrates visceral hypersensitivity to esophageal stimulation in addition to short-latency, large-amplitude EEP responses. We believe that this profile is consistent with our first proposed subgroup on NCCP (those with sensitization of visceral afferents). However, patient B, although demonstrating visceral hypersensitivity, has long latency early EEP components. This indicates that the afferent signal arriving at the cortex is not exaggerated, yet the late responses, which reflect affective processing, are enhanced when compared with normal. We believe that this profile is consistent with our second proposed subgroup of NCCP (those that are hypervigilant of visceral sensations).

Summary

This case study demonstrates that patients with NCCP can be subclassified on the basis of sensory responsiveness and neurophysiologic profiles. This approach identifies specific abnormalities within the CNS processing of esophageal sensation in individual patients, allowing us to objectively differentiate those with sensitized esophageal afferents from those that are hypervigilant to esophageal sensations. The importance of

this approach is to underline that NCCP comprises a heterogeneous group of patients, and only when we have defined the phenotype of this condition and identified groups of patients with specific CNS abnormalities will it be possible to perform clinical studies aimed at answering specific hypotheses. The development of a comprehensive pathophysiologic model that identifies the specific causes of symptoms in patients with esophageal hypersensitivity will allow the future management strategies of these patients to be targeted more specifically and efficiently. This will have great benefits to patients' well-being and health care use.

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Current and future treatment of chest pain of presumed esophageal origin

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Management of functional esophageal chest pain is largely empirical. Because gastroesophageal reflux disease (GERD) is the most common cause of esophageal chest pain and because symptoms are at least partially provoked by acid reflux events in many patients (or esophageal reflux could be a coincidental disorder rather than the cause of pain), anti-reflux therapy plays an important role in the diagnosis and treatment of patients with noncardiac chest pain (NCCP), but the pathogenetic mechanism remains unclear. Increased pain perception or visceral hyperalgesia has been observed in these patients; therefore, drugs that interfere with pain perception may be indicated. This mechanism could also explain the beneficial effect of low-dose antidepressants, serving as visceral analgesics; furthermore, the efficacy of psychopharmacologic agents and psychological or behavioral approaches has been established for several functional gastrointestinal (GI) disorders. Esophageal motility disorders are thought to play an important role in the genesis of NCCP, but therapeutic trials aimed at decreasing esophageal motility pressure have produced inconsistent results, raising the possibility that alterations in pain perception may also be the cause in these patients. Therefore, in patients with non-GERD-related esophageal chest pain, including those with motility abnormalities, pain modulators remain the cornerstone of therapy. We review the available therapies for patients with non-GERD-related esophageal chest pain and future developments for the treatment of NCCP.

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Anticholinergics and muscle relaxants

Anticholinergic drugs, such as atropine, L-hyoscyamine, and pirenzepine, induce a decrease in amplitude of esophageal peristalsis and in lower esophageal sphincter pressure, making them potentially useful for the treatment of hypercontractile esophageal disorders [1]. Cimetropium bromide [2] has been proposed as a treatment for patients with associated with esophageal dysmotility NCCP, but there are no published clinical trials examining the value of anticholinergic agents in the symptomatic management of patients with NCCP. However, in a study with atropine, Rao et al [3] reported a relaxation of the smooth muscle within the esophageal wall together with an actual decrease in the thresholds for discomfort and pain in patients with NCCP. These findings suggest that hyperalgesia rather than motor disfunction seems to be the predominant mechanism of functional chest pain of esophageal origin and that muscle relaxation by itself may not improve visceral pain.

Peppermint oil, a carminative, has been shown to inhibit smooth muscle contractions through an effect on calcium channels. In an open-label study of eight patients with diffuse esophageal spasm (DES), peppermint oil completely eliminated the simultaneous esophageal contractions in all patients. Two of the patients who were symptomatic with chest pain at the time of the study reported resolution of their symptoms after treatment [4]. Peppermint oil is thought to increase heartburn that does not seem to result from an increased acid reflux [5]; therefore, it is not advised in subjects with GERD-related NCCP.

Nitroglycerin and long-acting nitrate agents have been shown to provide symptomatic improvement in patients with DES [6,7] but have a poor effect on esophageal pressures [8]. No controlled studies of patients with esophageal pain treated with these agents have been reported.

Calcium channel blocking agents, including diltiazem and nifedipine, have been suggested for treating patients with spastic motility disorders. Richter et al [9] found that nifedipine had a dramatic dose-response effect by decreasing the amplitude of distal esophageal contractions in patients with nutcracker esophagus. Oral diltiazem in high doses (150 mg) (ie, the dosage shown to decrease the amplitude and duration of peristaltic contractions in these patients [9]) also decreased the amplitude and duration of peristaltic contractions in these patients [10]. In a double-blind, placebo-controlled trial, oral nifedipine (10–30 mg tid) decreased the amplitude of esophageal contractions but was no better than placebo in relieving chest pain in 20 patients with nutcracker esophagus after 6 weeks of treatment [11]. Similar results were found in eight patients with diffuse esophageal spasm [12]. Diltiazem (60–90 mg qid) was compared with placebo in a double-blind crossover trial in 14 patients with nutcracker esophagus who complained of chest pain or dysphagia [13]. Active diltiazem therapy significantly decreased distal esophageal pressures and mean chest pain scores when compared with

placebo. The conflicting results of these studies suggest that a reduction in the amplitude of esophageal contractions may not improve chest pain.

Botulinum toxin

Botulinum toxin A (Botox, Allergan Pharmaceuticals, Irvine, California) binds to presynaptic cholinergic nerves and inhibits the release of acetylcholine [14]. Because a portion of the lower esophageal sphincter (LES) tone is cholinergic, Botox decreases basal LES pressures. A number of studies have shown that injecting botulinum toxin into the LES of patients with achalasia improves dysphagia, regurgitation, and chest pain [15–46]. In a preliminary, open-label pilot study, Miller et al [25] treated 15 patients with chronic symptomatic chest pain, dysphagia, or regurgitation caused by non-achalasia, nongastroesophageal reflux-induced spastic esophageal motility disorders. After endoscopic injection of 80 U of Botox at the level of the gastroesophageal junction, the chest pain score decreased significantly at 7, 30, 60, and 90 days after treatment. Seventy-three percent of patients after 1 month and approximately 50% of patients after 6 months had good or excellent response (50% to 75% and > 75% decrease in total symptom score, respectively). Half of the patients required subsequent treatment with repeated Botox, pneumatic dilation, and bougienage session. Forty-three percent of the patients treated with a second Botox injection showed a good response. Botox injection resulted in good or excellent response in 71% of the patients. In this study, patients were not selected with chest pain as their only symptom; rather, patients had a wide variety of esophageal symptoms, including dysphagia, regurgitation, and chest pain. Recently, the same group of investigators [26] included 29 patients with chest pain as the major complaint secondary to nonreflux, nonachalasia spastic esophageal motor disorders in another open-label study using Botox injection into the gastroesophageal junction. The overall response rate was similar to the previous study. Seventy-two percent of the patients responded with at least 50% reduction in chest pain. The mean duration of the response for chest pain was 7.3 ± 4.1 months (range 1–18 months). Women responded significantly better than men (95% versus 5%). The response according to the type of esophageal motility disorder was not found to be significant. Half of the patients who responded to the first injection required a second administration of Botox. Although these two studies have encouraging results, randomized controlled trials comparing Botox injections with other therapeutic modalities need to be performed.

Psychotropic medications

According to Clouse [27], the rationale for using psychotropic medications in esophageal chest pain is based on (1) the high prevalence

of psychiatric disorders reported in patient groups with esophageal symptoms and minor motor dysfunction; (2) the recognized psychophysiologic effects on esophageal motor activity; (3) the potential benefits that nerve-modulating drugs may have on the pathogenesis of the syndromes (independent of psychiatric factors); and (4) observations from treatment trials for chronic pain syndromes, including irritable bowel syndrome. Independent of psychiatric factors, when adequate acid suppression therapy fails, symptom relief may be obtained with low-dose antidepressants (Table 1). In a 6-week, double-blind, placebo-controlled trial of trazodone (100–150 mg/day), a significantly global improvement with less residual distress over esophageal symptoms (chest pain, dysphagia for solids or liquids, heartburn, regurgitation) was seen compared with placebo in patients with esophageal contraction abnormalities [28]. In this study, no differences were found in changes of measured manometric parameters. The symptomatic improvement was independent of changes in anxiety or depression, but a reduction in the somatization scale of the SCL-90R was considerably greater in responders than in nonresponders even after excluding items of the SCL-90R related to esophageal symptoms. A reduction in the somatization scale can be interpreted as showing that the best correlate with a reduction in esophageal symptoms in responders to trazodone, from a psychological standpoint, is a generalized reduction in somatic symptom reporting [28]. Trazodone has anxiolytic and antidepressant properties, the latter presumed to be related to its interference with transmitter uptake in central serotonergic neurons [29].

Trazodone seems to be less effective than tricyclic antidepressants (TCAs) in the management of chest pain. In 60 patients with normal coronary angiograms (22% had ischemia appearing on electrocardiogram during

Table 1
Psychotropic medications in noncardiac chest pain of presumed esophageal origin

Study	Treatment	n	Design	Results
Clouse et al (1987) [50]	Trazodone	29	Double-blind, placebo-controlled	Global improvement (chest pain, dysphagia, heartburn, regurgitation)
Cannon et al (1994) [52]	Imipramine	60	Controlled placebo or clonidine	Improvement in the number of chest pain episodes
Prakash and Clouse (1999) [53]	Amitriptyline	6	Open label	Symptom reduction or remission in 81% of patients
	Nortriptyline	6	Follow-up 2.7 yr	
	Imipramine	3		
	Desipramine	2		
Varia et al (2000) [54]	Setraline	30	Double-blind, placebo-controlled	Reduction in daily pain score
Beitman et al (1989) [57]	Alprazolam	15	Open label	Reduction in panic frequency and chest pain episodes
Wulsin et al (1999) [58]	Clonazepam	27	Double-blind, placebo-controlled	50% reduction in Hamilton Anxiety-total score

exercise, 41% had abnormal esophageal motility, 63% had one or more psychiatric disorders, and 87% reproduced their chest pain by right ventricular electrical stimulation or intracoronary infusion of adenosine), imipramine, a TCA, significantly reduced the number of episodes of chest pain compared with clonidine or placebo. This response was neither dependent on the results of cardiac, esophageal, or psychiatric testing at baseline nor on the change in psychiatric profile during the course of the study, which improved in all three study groups [30]. Follow-up information over a median of 2.7 years (range 0.8–8.6 years) obtained from 21 outpatients treated with TCAs after incomplete response to anti-reflux therapy showed an initial symptom reduction or remission in 81% of the subjects [31]. Of these, 41% were successfully treated continuously over an average of 2.6 years, 29% eventually discontinued successful treatment after more than 6 months with sustained benefits, and 29% discontinued because of side effects. TCAs used by the responders were amitriptyline, nortriptyline, imipramine, and desipramine; the dosage used to reach this response was 20 to 75 mg/day (median 50 mg/day), a dose that was reached within 2 months. Early change to a second TCA was required in 18% to reduce side effects. Seventy-one percent of initial responders to TCAs chose to remain on concomitant antisecretory medications, yet less than 15% selected anti-reflux treatment as the best therapy received.

There is little experience with selective serotonin reuptake inhibitors (SSRIs). In a recent study, sertraline showed a significant reduction in daily chest pain compared with placebo, suggesting the need for further studies on the efficacy and tolerability of SSRIs in the management of NCCP [32].

These studies suggest that antidepressants have a long-term benefit in the management of functional esophageal chest pain. A dosage increase to a target dose of 50 mg/day is appropriate when using TCAs, and occasional drug change is required to improve adherence. Patients breaking through an initial response usually improved again with a slight dosage increase [33]. Their benefit is not restricted to painful symptoms, and a mechanism that extends beyond reduction of visceral hypersensitivity may be present. Whether tricyclic antidepressants could modulate the effects of other intraluminal stimuli, such as acid, remains unknown. A recent meta-analysis of antidepressants for functional GI symptoms that included five studies for functional esophageal symptoms, including chest pain, showed that antidepressants have a significant treatment benefit across the studied disorders. Their effect was not restricted solely to pain reduction: Measures of global improvement or syndromatic regression also were favorably affected [34].

Functional chest pain is associated with depression and anxiety, which may exacerbate pain episodes and lead patients to use health care resources. The anxious patient fears myocardial infarction despite reassurance and negative cardiologic evaluation. Pharmacotherapy for anxiety or panic disorder may play an important role in these patients [33]. In an 8-week,

open-label trial, alprazolam was given at a starting dose of 0.5 m/day, which was adjusted to the most effective one. Of the 15 patients with panic disorders and chest pain with no evidence of coronary artery disease, 75% reported a 50% or greater reduction in their panic frequency and a marginally significant drop in episodes of chest pain with a mean dose of 4.3 ± 2.2 mg/day [35]. Clonazepam, in a flexible dose range of 1 to 4 mg/day, showed in a 6-week, placebo-controlled, double-blind study a superiority over placebo in achieving 50% reduction in the Hamilton Anxiety total score in chest pain patients with panic disorder [36].

Cognitive-behavioral therapy

Studies have shown that patients with NCCP are more likely to have hypochondriasis, anxiety, and panic disorders compared with the general population and that patients with chest pain and normal coronary angiograms are more likely to have panic disorders, major depression, and anxiety compared with patients with positive coronary disease [37,38]. Psychological treatment in the form of reassurance has been the mainstay of the management of NCCP, and in the vast majority this treatment is sufficient. Patients who trusted their medical diagnoses have shown a better outcome than those who did not trust or understand them, which was associated with lower resource use of health care resources, particularly the emergency room [39]. However, reassurance is insufficient in patients in whom anxiety has become established as a separate problem [40]. Depression and anxiety (state and trait) are maintained for at least 1 year after cardiac catheterization despite benign coronary state and ample reassurance [38]. Data have also revealed that after 1 year, 86% of the patients with normal coronary arteries still complain of chest pain and 71% report that the pain is similar or worse than at the time of cardiac catheterization [38]. Anxiety and depression found in these patients may not be purely reactive but may also operate as causal and maintaining factors [41]. Panic disorder and hypochondriasis can be treated successfully with cognitive-behavioral therapy, based on the theory that preoccupation with and misinterpretation of physical symptoms, such as impending heart attack, play a central role in these patients and can give rise to anxiety [42,43]. The success of cognitive therapy in the treatment of panic disorders has led to effective treatment of anxiety accompanying NCCP [40]. In one study, 31 patients with NCCP and negative medical investigation were randomized to cognitive-behavioral therapy (teaching them how to anticipate and control symptoms and modify of inappropriate health beliefs) or assessment only. Both groups had significant reductions in chest pain, limitations and disruption in daily life, autonomic symptoms, distress, and psychological morbidity [44]. Using a systematic approach that emphasizes cognitive intervention, such as examining and modifying beliefs about the cause of chest pain, 50% and 48%

of the patients were pain free at 6 and 12 months, respectively, in comparison to only 6% and 13% of the patients allocated to usual care [45]. Another study randomized patients to group psychological treatment that included education, relaxation, breathing training, graded exposure to avoided activities because of pain and light exercise, and challenging automatic thoughts about heart disease. The control group was assigned to a waiting period before reassessment for entering a treatment [41]. Treatment was associated with a significantly greater reduction in chest pain frequency and pain-free days per week and improvement in anxiety and depression scores, disability, and exercise tolerance; these results were maintained at 6-month follow-up. The authors concluded that further work is required to establish which elements of the treatment package are the most effective and the mechanism by which they operate [41].

Surgery for motility disorders

Long esophageal myotomy has been suggested as treatment in patients with intractable chest pain caused by esophageal motor abnormalities, mainly DES and nutcracker esophagus. The procedure has caused a marked reduction in the amplitude contractions in the distal four fifths of the esophageal body [46]. Accordingly, abnormal contractions occurring in bursts may further decrease blood supply and cause chest pain in a relatively ischemic organ. In a study with total thoracic esophagomyotomy, including the LES, coupled with a short and complete fundoplication, an improvement rate of 88% over a 5-year follow-up period was reported [47]. In another study that included 42 patients, the majority with DES and the remainder with a variety of associated motor disorders demonstrated a recurrence or persistence of pain postoperatively in five patients over a 5-year, 8-month follow-up period [48]. Finally, Cuschieri [49] reported complete or substantial relief of chest pain in 18 patients and no relief in five others using a thoroscopic long myotomy performed from the left side. However, longitudinal myotomy is rarely, if ever, indicated in patients with NCCP and esophageal dysmotility.

The future

Visceral hyperalgesia has emerged as an important cause of chest pain, and different underlying mechanisms have been suggested. These include peripheral sensitization of esophageal sensory afferents leading to heightened responses to physiologic or pathologic stimuli, altered modulation of afferent neural function at the level of the spinal dorsal root, or altered central processing. Mediators have been proposed, such as opioids and serotonin (which act on receptors in peripheral terminals of visceral afferent

nerves), substance P, neurokinins, calcitonin-gene related peptide (CGRP), or excitatory amino acids (eg, glutamate) (which act through ion channels and receptors such as N-methyl-D-aspartate [NMDA] on dorsal horn neurons within the spinal cord or through the release of serotonin, catecholamines, dopamine, acetylcholine, or adenosine, acting on supraspinal targets in the brainstem, within the limbic system, in the prefrontal cortex, or in the descending modulation pathways) [50]. Research into the underlying mechanisms that result in the development of NCCP may lead to novel therapeutic modalities. Theophylline, an adenosine receptor antagonist, has been tested by Rao et al [51] in 16 patients found to have hypersensitive esophagus to balloon distension. These patients had negative coronary angiography or stress thallium study, normal upper endoscopy and esophageal manometry, and a normal 24-hour pH study or no improvement in chest pain with a double dose of omeprazole or pantoprazole. An infusion of theophylline significantly increased the thresholds for distension-induced pain in 12 out of 16 patients and increased the cross-sectional area of the esophagus. In patients with improvement of chest pain or normalization of sensory thresholds after the infusion, oral theophylline was prescribed for 3 months. Oral theophylline completely abolished chest pain in one patient and caused a > 50% reduction in pain frequency and intensity in six patients [51]. The same group of researchers found, in a double-blind, placebo-controlled, cross-over study that evaluated 19 patients, that theophylline SR 200 mg PO bid significantly decreased the number of pain episodes and the intensity of pain and increased the number of pain-free days. Adverse events were nausea, insomnia, tremor, and lightheadedness [52]. These results warrant further studies using adenosine antagonists for the treatment of functional esophageal chest pain.

Visceral hyperalgesia is present in functional disorders such as functional dyspepsia and irritable bowel syndrome (IBS); it is therefore possible that drugs capable of producing a beneficial effect in these disorders might also be effective in NCCP. The short introduction of alosetron, a 5-hydroxytryptamine (5-HT) type 3 antagonist, for the treatment of diarrhea-predominant IBS female patients and the beneficial effects of this compound on sensory and pain perception in IBS raised the hope for a therapeutic potential in patients with NCCP [53]. Cilansetron, a similar 5-HT₃ antagonist that is being studied for IBS [54], may also be beneficial in the treatment of functional esophageal chest pain. The role of tegaserod, a partial 5-HT type 4 agonist, in modulating pain originated from the GI tract is less clear. In a prospective, randomized, double-blind, placebo-controlled multicenter study in patients with GERD, tegaserod 1 mg/day and 4 mg/day caused a > 50% decrease in acid exposure in the postprandial period. However, the 1 mg/day treatment group was the only one to achieve a statistically significant reduction in the percentage total time pH < 4 [55]. The effect of tegaserod in reducing esophageal acid exposure together with

the possible benefit on visceral pain makes the drug a potential medication in the treatment of chest pain of presumed esophageal origin.

Octreotide, a synthetic, long-acting analog of somatostatin, has been shown to increase colonic visceral perception thresholds in IBS patients without modifying muscle tone [56]. It has recently been shown that octreotide significantly impaired the ability to perceive the stimulus induced by esophageal balloon distension in healthy subjects [57]. In a preliminary placebo-controlled trial, octreotide significantly decreased pain perception in response to intraesophageal balloon distension in patients with NCCP [58].

Fedotozine, a peripherally acting kappa opioid agonist, has been shown to improve abdominal pain intensity and to reduce perception of intra-colonic balloon distension in IBS patients without inducing changes in colonic compliance [59]. In the future, fedotozine may prove to be effective in NCCP.

Antispasmodics exerting their effects on central pain perception may be another possibility. Also, antagonists for the NK-1, NMDA, and CGRP receptors that have been evaluated in animal models of somatic and visceral pain [60–62] may prove effective in NCCP. However, in a recent study in healthy volunteers, dextromethorphan, an NMDA receptor antagonist, increased the perception of nonpainful sensations during gastric distension without altering the perception of pain [63]. Studies with more specific NMDA receptor antagonist are warranted. Finally, modulators of the central corticotropin-releasing factor receptor that is related to amplification of viscerosensory information [64] may provide effective therapies for the treatment of chest pain of presumed esophageal origin.

Summary

Patients with chest pain of presumed esophageal origin should be reassured and should undergo an esophageal manometry study. In patients with spastic esophageal disorders, a trial with calcium channel blockers or low-dose antidepressants used as visceral analgesics is the best approach. In patients with non-GERD-related, nonspastic esophageal motility disorder, low-dose antidepressants seem reasonable. Anxiolytics are useful in patients with panic disorders, and psychological interventions (eg, cognitive-behavioral therapy) are also valuable, mainly in patients in whom reassurance is not sufficient to avoid the misinterpretation of their symptoms. In the future, visceral sensitivity modifying agents such as serotonergic agonists or antagonists may become the cornerstone of therapy in patients with chest pain of presumed esophageal origin. Combinations of different approaches, such as proton pump inhibitors and psychotropic or antinociceptive agents, should also be evaluated in clinical trials.

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Treatment of spastic esophageal motility disorders

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Esophageal motility testing in patients with noncardiac chest pain (NCCP) or dysphagia commonly reveals a spectrum of abnormal patterns. These motility abnormalities include diffuse esophageal spasm (DES), nutcracker esophagus (NE), nonspecific esophageal motility disorders (NEDM), hypertensive-lower esophageal sphincter (H-LES), and achalasia. To provide a critical frame of reference that may serve as a tool to clinicians and investigators, Spechler and Castell [1] and Kahrilas [2] have suggested grouping the esophageal motility disorders according to the contraction characteristics of the esophagus or presumed pathophysiologic basis (ie, inhibition or excitation of the esophagus) (Box 1 and Table 1). We examined the outcome of therapeutic trials for the management of patients with abnormal esophageal motility except for achalasia.

Problems with therapeutic trials in patients with spastic motility

Despite the frequently noted prevalence of these disorders, their cause, pathophysiology, and importance remains to be determined [3]. The structural basis of the abnormal esophageal motility patterns has been difficult to study because most of these patients do not require surgery or rarely, if ever, come to autopsy. It is unclear whether the manometric abnormalities in patients with NCCP have physiologic consequences. During manometry, patients noted to have simultaneous contractions consistent with DES or the high-amplitude peristalsis observed in NE are rarely symptomatic. Various therapeutic trials aimed at improving the abnormal motility patterns have shown that, despite significant amelioration of the abnormal motility, there is a lack of symptomatic improvement

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Box 1. Classification of esophageal motility abnormalities

Inadequate lower esophageal sphincter (LES) relaxation

- Classic achalasia
- Atypical disorders of LES relaxation
- Uncoordinated body contraction
- Diffuse esophageal spasm

Hypercontraction

- Nutcracker esophagus
- Isolated hypertensive LES

Hypocontraction

- Ineffective esophageal body motility
- Universal lack of peristalsis: classic achalasia

Modified from Spechler SJ, Castell DO. Classification of oesophageal motility abnormalities. *Gut* 2001;49:145–51; with permission.

[4]. Rao et al [5], using esophageal impedance planimetry and balloon distension studies, found that a disturbed esophageal sensory processing is more likely to correlate with symptoms than abnormal esophageal motility. These findings support the theory that esophageal dysmotility may represent a marker or an epiphenomenon associated with patient’s symptoms rather than the cause [6]. Several investigations have underscored the importance of visceral sensitivity in patients with NCCP. These studies suggest that the enhanced visceral sensitivity noted in patients with NCCP may be responsible for the pain and that treatment aimed at modifying pain perception may be more valuable than therapeutic efforts directed at improving esophageal motility [7]. Thus, the results of therapeutic trials in this field must be viewed in the context of our insufficient understanding of the significance and pathologic basis of esophageal motility disturbances.

Table 1
Classification of esophageal motility disorders based on inhibition or excitation

Disordered inhibition	Excessive inhibition	Inadequate excitation
Achalasia and pseudo-achalasia	Nutcracker esophagus	Nonspecific esophageal motility disorder
Diffuse esophageal spasm ^a	Diffuse esophageal spasm Vigorous achalasia Hypertensive lower esophageal sphincter syndrome	

^a This disorder can result from disordered or excessive inhibition.

Modified from Kahrilas PJ. Esophageal motility disorders: current concepts of pathogenesis and treatment. *Can J Gastroenterol* 2000;14:221–31; with permission.

Pharmacologic treatment

Traditionally, pharmacologic options for painful motility disorders have been directed at reducing or improving the abnormal esophageal pressures or uncoordinated motility. The pharmacologic agents used for this purpose include nitrates, calcium antagonists (such as nifedipine or diltiazem), and anticholinergic compounds [8]. Long-term outcome studies are unavailable, and most of the basis for therapy in this area remains anecdotal [9]. In addition to the agents mentioned previously, we evaluate recent trials that have expanded the potential therapeutic options for the treatment of spastic motility disorders, other than achalasia, with the use of compounds such as nitric oxide donors, botulinum toxin, and psychotropic agents.

Nitrates

Nitrates are potent relaxants of gastrointestinal (GI) smooth muscle through the stimulation of cyclic guanosine monophosphate-dependent (cGMP)-dependent pathway [10]. In 1973, Orlando and Bozyski [11] showed that nitrates effectively reduced manometric findings and symptoms in a 21-year-old student suffering from DES. Since that seminal observation, several trials have addressed the efficacy of nitrates in the treatment of DES. Table 2 summarizes the published data. The experience with these agents is limited to fewer than 50 patients. No placebo-controlled trials have been completed (studies were all open label). However, all authors describe symptomatic improvement after primarily short-term studies, and, in some trials, long-term use. These uncontrolled clinical observations suggest that nitrates induce prompt chest pain relief in selected patients with DES. Gastroesophageal reflux disease (GERD) must be excluded because prior trials of nitrates in patients with DES and coexisting GERD have shown an unpredictable response for patients with GERD [12]. Side effects, such as headaches and decrease in systemic blood pressure, may limit the use of these agents.

Nitric oxide antagonists

Nitric oxide (NO) is a major inhibitory neurotransmitter in the GI tract [13]. In the smooth circular muscle of the human esophagus, it acts as an

Table 2
Nitrates and esophageal motility

Author	Year	n	Trial	Outcome
Orlando [11]	1973	1	Open	+
Swamy [12]	1977	12	Open	+
Parker [98]	1981	1	Open	+
Mellow [99]	1982	5	Open	+
Millaire [100]	1989	22	Open	+
Konturek [18]	1995	5	Open	+ (IV inf)

inhibitory nonadrenergic, noncholinergic neurotransmitter regulating the latency period and latency gradient and the contraction amplitude of esophageal peristalsis [14]. In vivo studies in humans have shown that by removing NO or inhibiting its production with N-monomethyl-L-arginine, the simultaneous contractions characteristic of diffuse esophageal spasm can be induced [15,16]. Therefore, pharmacologic agents that result in the augmentation of NO may improve the clinical and manometric patterns of patients with hypercontractile responses.

Glyceryl trinitrate (GTN) is a donor of NO, and L-arginine is a basic, semi-essential amino acid that acts as a substrate for the synthesis of NO [17]. Konturek et al [18] showed in an acute study of five patients with DES that GTN (100–200 µg/kg/hr IV) caused a dose-dependent elongation of peristalsis and duration of esophageal contractions accompanied by a significant improvement in symptoms. At the doses used, L-arginine (300 mg/kg/hr IV) had no effect on esophageal parameters of symptoms. These observations seem to support the role of endogenous NO in the pathogenesis of spastic dysmotility.

NO is generated in vivo from L-arginine. Luiking et al [19] evaluated the effects of long-term oral administration (8 days) of L-arginine (30 g/day) or glycine (placebo, 13 g/day; isosmolar) on esophageal motility parameters in 10 healthy control subjects. They noted a prolongation in transient LES relaxation and an increase in late postprandial LES pressure but no effects on esophageal motility. Bortolotti et al [20] examined the effects of L-arginine IV and after oral administration (30 mL of a 10% L-arginine solution tid versus placebo) in eight patients with spastic esophageal motility (DES, n = 3; NE, n = 5). The study was a double-blind, crossover trial with each phase (placebo or drug) lasting 6 weeks. The “acute” IV infusion did not induce any significant changes on esophageal peristalsis of LES parameters. However, the oral administration resulted in a significant reduction of chest pain episodes. No side effects were noted. The results of this small trial require further confirmation.

NO is involved in multiple biologic actions, and its effects are not confined to the GI tract. NO mediates vascular smooth muscle cell relaxation [21]. This beneficial effect on the myocardium circulation has led investigators to study this agent in patients with chest pain who have coronary endothelial dysfunction or microvascular angina. Some of these patients with endothelial dysfunction resemble the clinical profile of patients with spastic motility disorders. They suffer from recurrent chest pain and have normal epicardial coronary vessels. In addition, many of them have abnormal esophageal motility [22]. Studies in the cardiology literature examined the effects of oral L-arginine in patients with chest pain and abnormal coronary endothelial function. Although the esophageal motility of these patients was not investigated, the authors found that after a randomized, single-blind study with L-arginine (3 g tid), there was a symptomatic improvement in chest pain when compared with placebo

[23]. These studies suggest that further trials of L-arginine are warranted in patients with spastic motility disorders.

Sildenafil (Viagra, Pfizer Labs, New York, New York) blocks phosphodiesterase type 5, which degrades NO-stimulated 3'-5' cGMP. This action results in accumulation of NO-stimulated cGMP, which in turn has an inhibitory effect on smooth muscle cells. In a recent study of 6 healthy volunteers and 11 patients with a variety of spastic motility disorders (NE, n = 4; DES, n = 1; HLES, n = 3; achalasia, n = 3), sildenafil significantly reduced LES pressure vector volume and distal esophageal amplitude in healthy control subjects. Manometric improvement was also observed in 9 of 11 patients with hypercontractile esophageal motility; however, only four of these patients reported symptomatic improvement, and two of these four discontinued drug therapy due to side effects [24]. Larger, placebo-controlled trials are needed to determine whether this compound or other related agents maybe of benefit to patients with hypercontractile disorders.

Anticholinergic agents

Cholinergic (muscarinic) innervation plays an important role in esophageal peristalsis and LES activity [25]. Acetylcholine is the natural ligand for the muscarinic receptor; however, the receptor was so named because it is selectively activated by muscarine [26]. Five muscarinic acetylcholine receptors, encoded by five distinctive genes, have been identified (M1 through M5) [27]. Recent research in human esophageal smooth muscle cells has shown that these muscarinic receptors respond to acetylcholine with a rise in calcium from intracellular stores and has provided a culture model for the study of esophageal contractility [28]. Yet, there remains a paucity of information as to the specific relationship of these receptors to the control of esophageal peristalsis or their role in patients with spastic motility. However, cholinergic dysfunction, such as defects in muscarinic innervation or altered muscarinic sensory regulation, may play a role in the pathogenesis of esophageal motility disorders. A number of studies have evaluated the effects of anticholinergic agents on esophageal motility, and they are reviewed in the subsequent section.

Atropine and the active form of atropine (L-hyoscyamine) have been studied primarily in healthy control subjects. These compounds reduce the amplitude of distal peristalsis and the incidence of normal peristalsis [29–31]. Atropine has also been shown to attenuate esophageal balloon-induced chest pain in healthy volunteers [32]. This finding suggests that the cholinergic sensory system may be involved in the genesis of esophageal pain.

Pirenzepine is a slightly selective M1-antagonist introduced for the treatment of peptic ulcer disease because of its ability to inhibit gastric acid secretion. This agent has variable effects on esophageal motility. At low doses (25–50 mg), it does not seem to have an appreciable effect on esophageal motility [33]. At high doses, in healthy volunteers, it reduced the LES

pressure and esophageal contraction amplitude and increased propagation velocity [34].

The cholinergic antagonist propantheline bromide (oral doses of 30 mg) decreases peristaltic contraction and LES pressure and increases the velocity of the propagation in the esophagus of healthy volunteers [35]. The effects of this compound in patients with chest pain have not been evaluated.

Bassotti et al [36] studied the effects of cimetropium bromide in patients with NE. During an acute infusion study using a single-blind design, eight patients with NE and similar control subjects received cimetropium bromide (10 mg IV). There was a significant reduction of distal esophageal amplitude and LES pressures. It is unknown whether this agent has beneficial effects on clinical symptoms or during long-term clinical trials.

In summary, the pharmacologic actions of several anticholinergic agents suggest that these are appealing compounds for the treatment of esophageal motility disorders. However, there are no clinical trials supporting the use of muscarinic blocking agents for the treatment of patients with painful esophageal motility. Furthermore, systemic side effects, such as dry mouth and tachycardia, may limit their use. The role of new muscarinic receptor antagonist with specific selectivity remains to be evaluated.

Botulinum toxin

Although systemic side effects may preclude the use of oral anticholinergic agents, the recognition that injection of botulinum toxin (Botox, Allergan Pharmaceuticals, Irvine, California), a potent local anticholinergic agent, may benefit, albeit temporarily, patients with achalasia [37] has fueled the interest in this compound for the treatment of non-achalasia, spastic dysmotility.

Botox binds irreversibly to cholinergic nerve terminals, reducing LES pressures in animal model and humans [38]. In 1996, Miller et al [39] treated 15 patients with spastic motility disorders (DES, NEMD, and lower esophageal dysfunction) unresponsive to previous medical therapy with intraesophageal injection of Botox (80 U). They obtained a favorable response in up to 67% of the patients, although a second injection was required to sustain remission. Recently, the same investigators amplified their observations after an open-label trial of Botox in 29 patients with spastic motility disorders other than achalasia [40]. They found that 72% of the patients experienced symptomatic improvement. The mean duration of response was 6.2 ± 4.8 (SD) months; six of nine responders required a third dose to maintain remission. No information was provided regarding the effects of Botox on esophageal manometry. Storr et al [41] treated nine patients with DES with Botox (100 U at multiple sites in the distal esophagus, 1- to 1.5-cm intervals) with favorable outcomes. After 6 months, eight patients remained improved, but a repeat injection was required in four of these subjects to maintain remission. Several preliminary reports in abstract form or letter to the editor have also indicated a beneficial response with

Botox in a variety of patients with spastic disorders [42–44]. Table 3 summarizes the published experience with Botox. Placebo-controlled trials are needed to confirm these observations.

Calcium blockers

Calcium plays an important role in esophageal muscle contraction [45]. In animal studies, interference with calcium entry at the cellular level leads to decreased LES pressure and esophageal contractions [46,47]. There are several calcium-blocking agents available. The experience with these compounds for the treatment of esophageal dysmotility is mostly limited to the first generation of calcium blockers, most studies are open label, and there is insufficient information regarding long-term efficacy.

Nifedipine

Nifedipine has been shown to decrease the frequency and amplitude of nonperistaltic esophageal contraction in healthy subjects [48]. Clinical experience in the treatment of esophageal motility remains limited. Table 4 provides a summary of therapeutic trials in patients with DES.

Richter et al [4] completed the only controlled trial of nifedipine in patients with NE. Twenty patients received oral nifedipine (10–30 mg tid) or placebo during a 14-week crossover study. Despite a statistically significant improvement in esophageal amplitude, no symptomatic benefits were observed.

Diltiazem

In healthy control subjects, diltiazem (90, 120, or 150 mg orally) had no effect on distal esophageal contractions [49]. Clinical improvement has been described in two clinical studies in patients with NE but not in a small study of patients with DES (Table 5) [49–51].

Verapamil

Verapamil decreases LES pressures and the amplitude of esophageal peristalsis in animal studies [52,53], but results in humans have not been consistent [54]. No studies have been done with this agent in patients with spastic esophageal motility disorders.

Table 3
Summary trials: treatment of spastic disorders with Botox

Author	Year	n	Publication type
Miller [39]	1996	15	Full paper
Cassidy [43]	1996	10	Abstract
Nebendahl [42]	1999	9	Abstract
Storr [41]	2001	9	Full paper
Miller [40]	2002	29	Full paper

Table 4
Nifedipine trials in diffuse esophageal spasm

Author	Year	Study design	n	Dose	Outcome
Blackwell et al [48]	1981	Open label	6	20 mg tid	3/6 improved
Alban Davies et al [101]	1982	Double-blind, placebo	10	10–40 mg tid	Short term improvement
Nasrallah et al [102]	1982	Open-label	1	10 mg tid	Improved
Nasrallah et al [103]	1985	Open-label	4	10 mg tid	Improved
Thomas et al [104]	1986	Open-label	6	10–20 mg tid	Improvement of dysphagia
Banciu et al [105]	1990	Open-label	18 ^a	10–20 mg	Acute “improvement of radiologic appearance”

^a Patients defined radiologically.

Psychotropic medications

Tricyclic antidepressants

Psychiatric illness has been reported in as many as 84% of cases of patients with chest pain and esophageal dysmotility [55]. Investigators have found a higher prevalence of psychiatric diagnoses among patients with NEMD when compared with patients having achalasia or normal manometry. The most common psychiatric diagnoses identified among these patients include anxiety disorders, depression, somatization, and perceived vulnerability to serious heart disease and panic disorders [55–58].

Antidepressants such as the tricyclic compounds imipramine, desipramine, clomipramine, amytryptiline, and trazodone improve chronic pain of somatic and visceral origin. In healthy volunteers, imipramine decreases pain thresholds to experimental somatic pain [59]. At low doses, antidepressants have had beneficial effects in the treatment of diverse types of chronic pain syndromes [60]. The mechanism of action of these compounds is not known. It is likely that the analgesic effect of these agents is not dependent on the mood-altering virtues of these pharmacologic agents.

A controlled trial of trazodone in symptomatic patients with NEMD was completed by Clouse et al [7]. Patients treated with 100 to 150 mg/day of trazodone noted a significant improvement after 6 weeks of treatment

Table 5
Diltiazem trials

Author	Year	Study design	n	Dose	Outcome
Richter et al [49]	1990	Open-label, 8-weeks	10 (NE)	90 mg tid	Improved
Cattau et al [50]	1991	Double-blind, placebo-controlled, 8-week	14 (NE)	60–90 mg tid	Improved
Drenth et al [51]	1990	Double-blind, cross-over, 10 week	8 (DES)	60 mg tid	No significant improvement

Abbreviations: DES, diffuse esophageal spasm; NE, nutcracker esophagus.

compared with placebo-treated patients. Manometric parameters did not change despite symptom improvement. Trazodone should be used with caution in male patients because of its potential to induce priapism. Recently, Prakash and Clouse [61] reported a retrospective analysis of 21 patients treated with a variety of tricyclic antidepressants after incomplete response to anti-reflux therapy. They found that 75% of patients with chest pain continued to find effective symptomatic relief during long-term use of up to 3 years.

Imipramine at 50 mg nightly has been found effective for the treatment of patients with NCCP regardless of the esophageal motility findings. During a double-blind, placebo-controlled trial of 60 patients with chest pain, Cannon et al [62] found that imipramine produced a significant reduction in chest pain. The response to imipramine was not dependent on the results of cardiac, esophageal, or psychiatric testing. However, repeat assessment of cardiac sensitivity while on treatment showed significant improvement only in the imipramine group. This observation suggests that the improvement induced by imipramine is likely caused by a visceral analgesic effect. Recent studies by Peghini et al [63] in healthy subjects support the notion that the effects of imipramine are mediated via a visceral analgesic effect.

An uncontrolled study from Japan found that a combination of psychotherapy and trazodone (50 mg) orally or clomipramine (25 mg IV daily) for a month produced clinical and radiologic improvement in nine patients with DES [64]. There is limited information available about the therapeutic efficacy of other tricyclic compounds.

Selective serotonin reuptake inhibitors

The results of the previously described trials with imipramine and trazodone raise the possibility that other psychotropic agents may be effective for the treatment of patients suffering from recurrent chest pain. This is important because the traditionally available agents imipramine and trazodone can produce undesirable effects, such as anticholinergic reactions, antiarrhythmic activity, and sedating effects, which limit their use. Furthermore, trazodone can induce priapism. Imipramine has numerous actions, including anticholinergic, antihistamine activity, serotonin reuptake blockade and norepinephrine blockade. It is unclear which of these properties conveys the therapeutic benefit, although Cannon [65] has suggested that the serotonin pathway may be important.

Based on this hypothesis, Varia et al [66] evaluated the effects of sertraline (Zoloft, Pfizer Labs, New York, New York) in patients with unexplained NCCP. After a single-site, single-blinded, placebo-controlled trial, 30 subjects with NCCP were recruited. Cardiac disease was excluded by coronary angiography in nine subjects and by stress test in the remaining

subjects. Five subjects did not complete the study due to noncompliance or scheduling problems, and no further data were collected from them. The subjects were randomized to receive sertraline or identical-appearing placebo for 8 weeks. Doses started at 50 mg and were adjusted to a maximum of 200 mg. Dosage was adjusted by the investigator on the basis of each subject clinical response. Subjects rated pain responses on a visual analog scale (0 = no pain, 10 = extreme pain). In addition, the Beck Depression Inventory and SF36 Health Survey Manual were scored at baseline and final visits. Intention-to-treat analysis was used to examine these subjects' outcomes. Subjects receiving sertraline obtained significantly more reduction in pain scores than those randomized to placebo. No differences in response were observed between subjects with negative angiogram or those with a negative stress test alone. The SF36 subscale response rate was better for the placebo group (suggesting a favorable emotional outcome but not chest pain improvement). No data were provided regarding esophageal testing. Unique side effects occurred in a number of the patients (27%), including delayed ejaculation, decreased libido, and restlessness. The findings of this study support the conclusions of other investigators regarding the favorable effects of selective serotonin reuptake inhibitors (SSRIs) for the treatment of unexplained physical symptoms and syndromes [67,68].

Carminatives

Carminatives are natural foodstuffs that are thought to improve symptoms of bloating and gas by facilitating eructation and the passage of flatus. In a small trial by Pimentel et al [69], two of eight patients with DES noted symptomatic improvement in chest pain. In addition, peppermint oil eliminated the simultaneous contractions and decreased high contraction pressures without obvious side effects. This was an uncontrolled study without a placebo arm. The mechanism of action of this agent remains undetermined [70].

Enhanced visceral pain perception

The studies described above have shown a discordant outcome between the changes in esophageal motility and therapeutic outcome and thus have raised the possibility that mechanisms other than disturbed motility may contribute to the patients' symptoms. Several investigators have observed an increased pain perception (nociception or visceral hyperalgesia) in patients with chest pain after a variety of stimuli [71–75]. Schapiro et al [71] reproduced chest pain by intra-atrial boluses of normal saline in 10 of 11 patients with NCCP. None of seven patients with coronary atherosclerosis and none of the nine patients with mitral valve prolapse experienced chest pain.

The enhanced visceral hyperalgesia is not confined to the heart. Esophageal balloon distension reproduced the typical chest pain in 18 (60%) patients with NCCP but in only 6 (20%) healthy volunteers [56]. Patients also experienced chest pain at lower volumes of esophageal distension (8 mL or less), whereas none of the control subjects reported pain at this volume of balloon distension. The provocation of chest pain after esophageal balloon distension is a reproducible phenomenon during same-day or subsequent-day studies [76]. It is also not influenced by age or body weight and is more common in female subjects [77]. In addition, a persistent visceral hyperalgesia has been noted in long-term studies (1 year) [78]. Visceral hyperalgesia has also been described in patients with microvascular angina [22] and in patients suffering from “functional GI disorders” such as non-ulcer dyspepsia, irritable bowel syndrome (IBS), and sphincter of Oddi dysfunction type III [22,79–81]. These findings suggest that visceral hyperalgesia may be a biologic or surrogate marker in patients with functional disorders of the GI tract, including patients with NCCP [80].

Pharmacologic treatment for visceral perception

The finding of visceral hyperalgesia in patients with NCCP has shifted therapeutic efforts to seek agents that can blunt visceral sensation. Because visceral hyperalgesia is an abnormality shared by patients with other functional GI disorders, it is possible that drugs capable of producing a beneficial effect for patients with IBS might offer the same salutatory effects for those with NCCP.

Somatostatin analog: octreotide

Octreotide (OCTR) is a synthetic analog of somatostatin. This drug has been shown to decrease sensation induced by rectal balloon distension in normal subjects and in healthy control subjects [82–84]. Johnston et al [85] have recently shown that OCTR significantly impaired the ability to perceive the stimulus induced by esophageal balloon distension in healthy subjects. During a preliminary placebo-controlled study, we have shown that OCTR produced a significant decrease in pain perception after intraesophageal balloon distension in patients with NCCP [86]. A controlled trial is needed to determine whether the effects of this agent will be extended on a long-term basis. However, cost limitations and the lack of an oral formulation may render this agent less attractive for the management of patients with chronic recurrent chest pain.

5-HT₃ antagonists

Alosetron is a potent and selective 5-HT₃ antagonist. A French study has shown that alosetron (0.25 mg bd and 4 mg bd) increases sensory and pain

perception for intracolonic balloon distension in patients with IBS [87]. The beneficial effects of this compound on sensory and pain perception in patients with IBS raise the possibility that this drug may also be effective for selected patients with NCCP. Major side effects, such as ischemic colitis, have resulted in withdrawal of this agent from the market. The role of other related compounds recently approved by the FDA for the treatment of IBS, such as tegaserod, remains to be explored.

Fedotozine

The kappa opioid agonist fedotozine alters the function of digestive nerve afferent pathways in various animal models [88]. Recent studies in 14 patients with IBS subjected to a double-blind, crossover trial of fedotozine compared with saline (placebo) showed that fedotozine is capable of improving perception to intracolonic balloon distension in patients with IBS. The effects of the drug occurred without inducing changes in colon compliance [89]. These findings suggest that this compound could have a beneficial effect in patients with NCCP.

Nonpharmacologic therapy: hot water swallows, cognitive therapy, reassurance

Cold liquid intake may precipitate dysphagia and chest pain in patients with spastic motility disorders. Triadafilopulos et al [90] reported the effects hot water swallows in patients suffering from a variety of spastic motility disorders (DES, NE, NEMD, H-LES, achalasia, scleroderma, and dermatomyositis). They found a clinical improvement in 28 (48%) patients. Although this was not a controlled study, this report argues that simple measures such as dietary changes may have role in the management of patients with spastic dysmotility.

Limited trials have suggested that cognitive behavioral therapy can be useful for a group of patients with NCCP [91]. Unfortunately, suitable trained therapists are scarce, and patients tend to resist referral to psychologists or psychiatrists. There is also insufficient information regarding the effect of psychotherapy on esophageal motility contractions. Finally, there is supportive evidence to suggest that many patients improve after being reassured that their chest pain is esophageal, not cardiac, in origin [3].

Gastroesophageal reflux disease and spastic dysmotility

Several studies have reported the frequent coexistence of GERD in patients with spastic dysmotility. Between 22% and 66% of patients with chest pain may have coexisting GERD [92–95]. We have shown that treatment of patients with NE and coexisting GERD (documented by 24-hour ambulatory pH test) results in symptomatic improvement despite lack of resolution of the esophageal motility abnormalities [96]. Calcium-channel

blockers, nitrates, and anticholinergic agents may decrease the LES pressures and thus increase reflux, which may explain the failure of these drugs to provide symptomatic improvement in some patients with spastic dysmotility. Thus, in the evaluation and management of patients with spastic dysmotility, treatment of the coexisting GERD seems more important than therapy aimed at reducing the motility abnormalities. Indeed, two recent larger placebo controlled trials by Achem et al [93] and Fass et al [97] in patients with NCCP and GERD have underscored the importance of acid suppression in patients with NCCP, regardless of the esophageal motility findings.

Summary

Treatment of spastic motility disorders continues to be challenging. Therapeutic options remain limited due in part to our lack of understanding of the pathophysiology and significance of these disorders. Furthermore, most of therapeutic trials to date are hampered by the poorly designed nature of the study, including the small size of the trials and the lack of placebo arm. Most of the available information suggests that there seems to be an important dissociation between symptoms (chest pain/dysphagia) and esophageal dysmotility. Drug treatment aimed at visceral sensitivity seems more effective in relieving symptoms than spasmolytic medications. Recent trials with Botox, nitric oxide derivatives, and SSRIs offer promising results. Rigorous study design that includes large placebo-controlled trials is needed in this area.

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Noncardiac chest pain: an Asian view

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Noncardiac chest pain (NCCP), or chest pain of esophageal origin, affects approximately one quarter of the population during their lifetime [1,2]. Although NCCP is a benign condition, the associated morbidity resulting from limited activity, inability to work, and health care use is enormous [3–5]. Despite the significant burden, the prevalence, natural history, and medical-seeking behavior of NCCP remain poorly defined because of a lack of population-based studies, particularly in the Asian population. Furthermore, the best modality of treatment for patients with NCCP remains to be determined.

Epidemiology in Asia

Locke et al [5], in a community-based survey of 1551 subjects in Olmsted County, Minnesota, reported a population prevalence of 23% for NCCP. Three other population-based studies, performed in the United Kingdom and Australia and in a Mexican American population, used the Rose Angina questionnaire and reported a prevalence of 24% to 33% for NCCP [6–8]. Recently, a telephone-based telephone survey of 2209 Hong Kong Chinese estimated an annual prevalence of 19.5% for NCCP (defined as chest pain not including heartburn and with no history of ischemic disease) [9]. Thus, NCCP is a common condition in Asia.

Typical reflux symptoms, such as heartburn, appear less in the Asian population when compared with the western population. This may be related to the fact that there is no direct translation of the word “heartburn”

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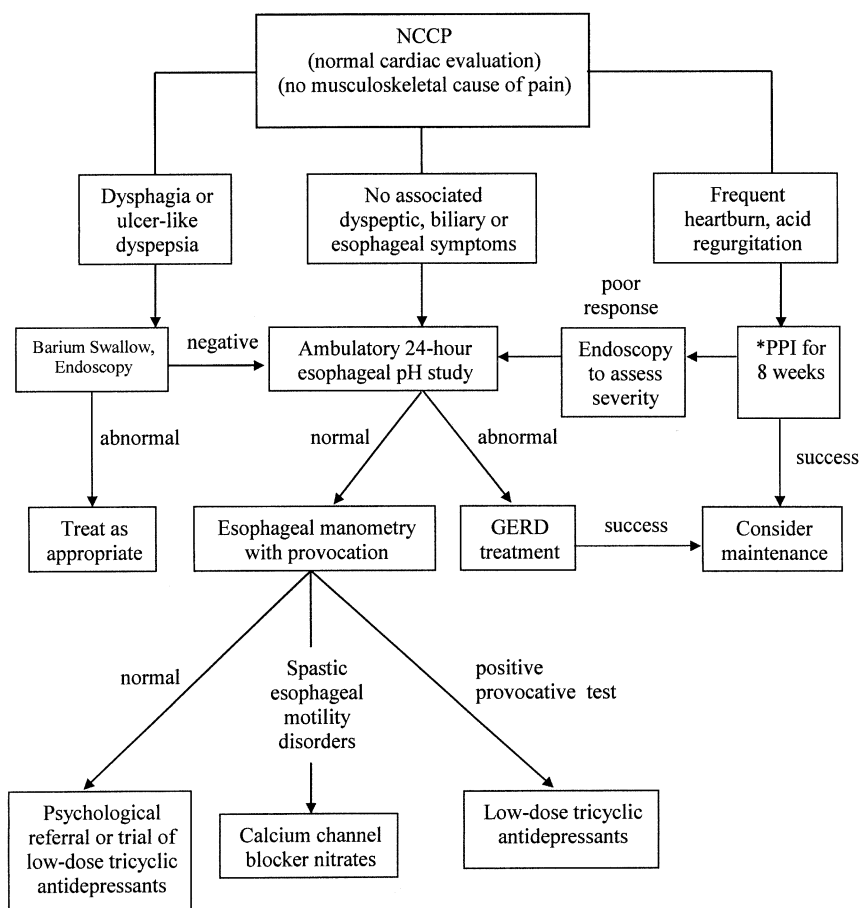
in most Asian languages [10]. In the population survey mentioned previously, the five most common gastroesophageal reflux disease (GERD)-related symptoms were acid regurgitation (87%), feeling of acidity in stomach (45%), angina-like chest pain (35%), heartburn (30%), and dyspepsia (29%). Dysphagia is present in 6.5% of the study subjects [9]. Furthermore, subjects with NCCP symptoms over the past year had a significantly higher anxiety and depression scores, required more days off work, and had their social life affected by the chest pain when compared with subjects without chest pain.

Patients with NCCP have a high proportion of psychiatric disorders, including anxiety, somatization, depression, and panic disorder [11]. Furthermore, psychiatric, esophageal, and cardiac disorders may overlap [12]. Previous experimental studies have shown that patients with NCCP are more sensitive than those with coronary artery disease to cardiovascular and noncardiovascular pain stimuli [13–17]. Body awareness is also greater [18,19]. Thus, in patients with NCCP, psychological rather than physiologic responses to stress may contribute to the perception of chest pain. In the authors' unit, patients with NCCP had a higher tendency to monitor danger cues in their bodily conditions and the environment, use problem-focused coping, display a coping pattern with a poorer strategy-situation fit, and receive less emotional support from others as compared with control subjects (healthy volunteers and a pain control group of patients with rheumatism). These findings suggest that monitoring perceptual style and inflexible coping style are risk factors that enhance one's vulnerability to NCCP. Emotional support may be a resource factor that reduces one's susceptibility to NCCP [20].

Investigations

After a normal coronary angiogram, esophageal evaluation is commonly pursued. The diagnostic tests available include upper endoscopy, 24-hour esophageal pH monitoring, esophageal manometry, and provocative testing, which attempts to elicit typical chest pain symptoms. The single best test in the evaluation of NCCP is 24-hour esophageal pH monitoring combined with symptom analysis (Fig. 1) [21,22].

Approximately 50% to 60% of patients with NCCP in the western population have increased esophageal acid exposure or positive symptom index [21,22]. Data on the use of pH testing in Asian patients with NCCP have been relatively scant until recently. Ke et al [23] studied 52 patients with NCCP and found a high prevalence of GERD in patients with NCCP using a combination of tests. Lau et al [24] studied 521 Chinese patients with chest pain and identified 108 patients (20.7%) whose pain was not related to cardiac causes. Using ambulatory 24-hour pH monitoring and baseline esophageal manometry, 28.7%, 19.4%, and 5.6% of these patients were



*PPI – proton pump inhibitor

Fig. 1. A suggested algorithm for the management of patients with NNCP.

found to have abnormal reflux parameters, abnormal manometric findings, or both, respectively [24]. Similarly, Ho et al [25] studied 80 consecutive patients with recurrent chest pain and performed upper endoscopy, esophageal manometry, acid perfusion test, and prolonged ambulatory pH and pressure monitoring. Endoscopic esophagitis, positive acid perfusion tests, pathologic reflux, and positive chest pain-reflux correlation were detected in 8.8%, 15.7%, 23.0%, and 48.0% patients, respectively. The overall prevalence of GERD was 32%, and esophageal motility disorder was relatively uncommon. Yu et al studied a cohort of 34 patients with NCCP but no reflux symptoms by 24-hour esophageal manometry and pH-metry [26]. Only 50% of these patients had experience chest pain during the monitoring, and the majority of chest pain episodes (57%) did not have any association

with motility or pH abnormalities. The authors concluded that ambulatory esophageal manometry and pH-metry is a useful tool for the evaluation of NCCP, although the yield is low in patients without reflux symptoms. Recently, Wong et al [27] studied 78 Chinese patients with NCCP and found that upper gastrointestinal pathology was present in 10% of patients. The remaining 70 patients received acid perfusion test, esophageal manometry, and ambulatory 24-hour esophageal pH monitoring. Symptoms and quality of life were assessed by the 36-item Short Form Health Survey (SF-36). Significant acid reflux symptoms were present in only 7% of patients. Abnormal 24-hour esophageal pH, indicating gastroesophageal reflux, was present in 29% of patients. The percentage of simultaneous contractions was higher and the percentage peristalsis was lower in patients with NCCP when compared with normal subjects by ambulatory 24-hour esophageal pH monitoring. Patients with NCCP had a lower SF-36 score when compared with control subjects [27]. Hu et al [28] found that acid perfusion in healthy volunteers reduced the perception threshold and tended to reduce the pain threshold to intraluminal esophageal balloon distension. A similar mechanism may operate in patients with NCCP in whom acid reflux sensitizes the esophagus and alters the perception of normal esophageal distensions. Thus, it has been suggested that NCCP patients with GERD may be hypersensitive to even physiologic amounts of acid reflux (ie, visceral hyperalgesia). We believe that visceral hyperalgesia plays an important role in the etiology of NCCP in the Asian population because abnormal pathologic reflux was demonstrated in only around 20% to 30% of patients [25,27].

Esophageal abnormality has been identified in 25% to 30% of patients with NCCP in the western population, using the combination of esophageal manometry and provocative testing [29]. The commonly used provocative tests include the Bernstein test (to reproduce symptoms by infusing acid into the distal esophagus), the Tensilon test (to reproduce symptoms by inducing forceful contractions of the esophagus by intravenous edrophonium), and the balloon distension test. However, the diagnostic yield of these tests in Asian populations is much lower [25,27,28]. Some investigators believe that an esophageal motility disorder may only be an epiphenomenon rather than the cause of the pain itself [30]. This is reflected by the American Gastroenterological Association guidelines on esophageal manometry, which recommended that it should not be used as the initial test for the evaluation of patients with NCCP [31].

Treatment

Acid suppression and the omeprazole test

Because GERD is the most common esophageal abnormality, acid suppression is the most common treatment [32–37]. Two randomized,

double-blind, placebo-controlled studies on the use of omeprazole versus placebo for the treatment of NCCP have been published. In the first study, 36 patients were randomized to receive omeprazole 20 mg bid or placebo for 8 weeks. A significantly higher overall symptomatic improvement was seen in the omeprazole group (81% versus 6%) [32]. The second study was a placebo-controlled, randomized, crossover study of 1-week omeprazole use in 37 patients with NCCP (at least three times per week and over 3 months duration) [33]. After initial symptom evaluation, endoscopy, and 24-hour pH testing, high-dose omeprazole 60 mg/day (omeprazole 40 mg AM and 20 mg PM) or placebo was given for 1 week. The results of this study showed that 62.2% (23/37) of patients had evidence of reflux disease: seven had abnormal esophageal acid exposure by pH testing only, eight had erosive esophagitis only, and eight had both. Compared with the combination of upper endoscopy and 24-hour pH testing for reflux, a positive omeprazole test had a sensitivity of 78.3% and a specificity of 85.7% [33]. Economic analysis showed that the omeprazole test approach is a cost-saving one for the evaluation of patients with NCCP. Subsequently, the diagnostic efficacy of other proton pump inhibitors in NCCP has been demonstrated by lansoprazole and rabeprazole [38,39].

Recently, our group studied the effect of lansoprazole 30 mg once daily versus placebo in 68 Chinese NCCP patients with normal upper endoscopy [40]. The chest pain symptom score was reduced significantly in both groups ($P < 0.001$). In the lansoprazole group, more patients with than without abnormal reflux showed symptom improvement (92% versus 33%, $P = 0.001$), giving a diagnostic sensitivity of 92% and a specificity of 67%. In the placebo group, the rates of symptom improvement were similar between those with and without abnormal reflux (33% versus 35%, $P = \text{NS}$). This study suggested that the proton pump inhibitor (PPI) test is equally useful for the diagnosis of NCCP in the Asian population.

Patients who fail to respond to a trial of reflux therapy should be evaluated by 24-hour ambulatory pH study. The use of dual esophageal and gastric pH electrodes while continuing therapy has also been suggested [2], which allows for the assessment of acid control and symptom correlation.

Antidepressants

In patients with non-GERD, related NCCP, low-dose tricyclic antidepressants and, more recently, selective serotonin reuptake inhibitors have been effective [12,41–43]. The effect of antidepressants is likely mediated through a visceral analgesic action that acts against visceral hyperalgesia in patients with NCCP. Asian data on the use of antidepressants for the treatment of NCCP are lacking, and properly designed randomized controlled trials are required.

Health care use of noncardiac chest pain in Asians

Few studies have assessed the factors associated with health care use in NCCP. In an Australian population study [8], no particular factor was found to be associated with health seeking behavior. Because GERD is the most common cause of NCCP, we may extrapolate the data from studies in GERD patients. In our population study, the frequency of heartburn, female gender, a higher depression score, and social life being affected were independent factors associated with health seeking behavior in subjects with GERD [9]. It has been shown that in heartburn sufferers psychological factors strongly correlated with health seeking behavior [44]. Among subjects with heartburn, health seekers had more severe heartburn symptoms, more psychological distress (phobia, obsession, and somatization), were more likely to view an event as a hassle, and had less social support [44]. We found that GERD subjects with a higher depression score are more likely to seek medical care [9]. Depressed subjects are more likely to be aware of and to report their symptoms and are less tolerant of the symptoms [45]. Thus, they may be more likely to seek help. Similar findings were found in the study of health seeking behavior in patients with dyspepsia and patients with irritable bowel syndrome [46]. We believe that psychological morbidity may play an important role in health seeking behavior. Co-existing depression and anxiety may act as a catalyst for a patient to seek medical care, rather than being the cause of symptoms.

Summary

NCCP is a common condition in Asia. The diagnostic approach of NCCP in Asians is similar to the Western population. GERD is the most common etiology. PPI therapy is an attractive alternative to other invasive diagnostic tests for NCCP and is equally effective for the Asian population.

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Preface

Pharmacological principles governing the use of proton pump inhibitors: tailoring therapy to improve GERD outcomes



M. Michael Wolfe, MD
Guest Editor

The recognition that H^+ , K^+ ATPase constituted the final step of acid secretion led to the development of a class of drugs, the proton pump inhibitors (PPIs), that are targeted toward this enzyme. At present, five different PPIs are available for use throughout the world, all of which share a common structural motif—a substituted pyridylmethylsulfinyl benzimidazole—but vary in terms of their substitutions. They also share common inhibitory mechanisms and are all weak protonatable pyridines with a pK_a of approximately 4 to 5, which causes them to accumulate selectively in the acid space of the secreting parietal cell. Within that space or on the surface of the enzyme, they undergo an acid-catalyzed conversion to a reactive species, the thiophilic sulfenamide or sulfenic acid, which are permanent cations.

In addition, although PPIs are capable of inhibiting gastric acid secretion over an extended period, all possess a very short plasma half-life. Because of their unique pharmacology, PPIs are most effective when the parietal cell is stimulated to secrete acid in response to a meal; consequently, when administered orally these drugs should be taken before or with a meal (preferably breakfast) and should not be used in conjunction with H_2 -receptor antagonists, prostaglandins, somatostatin analogs, or other antisecretory agents. In contrast, when used intravenously in individuals who are not eating, PPIs most effectively inhibit secretion when administered by continuous infusion.

When used properly, PPIs are without question the most potent inhibitors of gastric acid secretion available and thus have become the mainstay of therapy for several acid-related disorders.

Of all the acid-related disorders afflicting humans, gastroesophageal reflux disease (GERD) is certainly the most prevalent. Heartburn, its cardinal symptom, is experienced by the vast majority of adults at some point during their lifetime. Epidemiologic data indicate that approximately 40% of the United States population experiences heartburn at least once a month, while 14% have weekly symptoms and 7% to 10% have heartburn every day. Although most individuals report heartburn as their only symptom, 10% to 20% of those with GERD will develop serious complications of chronic reflux, including erosive esophagitis, peptic esophageal strictures, metaplasia (Barrett's esophagus), and adenocarcinoma of the esophagus. In addition to these serious esophageal complications, over the past decade increasing attention has been focused on the extraesophageal manifestations of GERD, such as tracheopulmonary involvement and noncardiac chest pain.

The majority of heartburn sufferers treat themselves by avoiding certain foods and using antacids. The recent availability of over-the-counter H₂-receptor antagonists, either as single agents or in combination with antacids, has enhanced further the options for self-medication. Nevertheless, many patients do not obtain significant relief from these measures and thus find it necessary to seek medical advice. Currently, several safe and effective treatments for GERD are available that not only relieve symptoms but also heal esophageal inflammation.

Antacids have been employed since the time of the ancient Greeks, who used compounds containing calcium carbonate to treat various digestive maladies. These drugs are now used exclusively to treat mild episodic heartburn and are rarely prescribed. When used by individuals for the treatment of heartburn, they offer the advantage of prompt but often unsustained relief. H₂-receptor antagonists are used extensively for GERD, both in over-the-counter and prescription formulations. Early studies of the efficacy of these drugs were disappointing, primarily because they were performed using doses commonly employed to treat peptic ulcer disease. These agents are effective in providing symptomatic relief in individuals with intermittent mild to moderate episodes of heartburn. They are best taken for the prevention of heartburn; however, when combined with an antacid, they provide both prompt and sustained symptom relief.

Numerous studies have documented the efficacy of PPIs in controlling GERD symptoms and healing esophagitis. Comparative trials of PPIs and H₂-antagonists show a clear advantage with the former agents, and PPIs are also effective in patients with GERD unresponsive to high-dose H₂-blocker therapy. In general, standard doses of PPIs (omeprazole/esomeprazole 20 or 40 mg, lansoprazole 30 mg, rabeprazole 20 mg, or pantoprazole 40 mg, all administered before breakfast) will relieve symptoms and heal esophagitis in

approximately 80% to 90% of cases. A large meta-analysis clearly demonstrated the superiority of PPIs over H₂-receptor antagonists in both relieving symptoms and in healing esophagitis.

Beginning with the development of the H₂-receptor antagonists and, more recently, the proton pump inhibitors, the treatment of GERD has been revolutionized. Hundreds of millions of individuals who previously received inadequate therapy have benefited significantly by these remarkably effective and safe agents.

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Living with chronic heartburn: insights into its debilitating effects

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Over the past 15 years, physicians have become gradually aware that heartburn is not simply the occasional symptom of over-indulgence but more often the cardinal symptom of an underlying disease called gastroesophageal reflux disease (GERD). Findings about heartburn, its prevalence, and sequelae need to be put into a rational context so that the magnitude of the problem can be appreciated. This article presents an overview of one's evolving understanding of heartburn and its impact on patients.

The prevalence of heartburn

By the early 1990s, several pieces of information suggested that heartburn is much more common than physicians previously thought. A 1988 study by The Gallup Organization showed that 44% of Americans had monthly heartburn, 20% had weekly heartburn, and 7% had daily heartburn (Fig. 1) [1]. A more carefully performed, controlled study conducted in Olmstead County, Minnesota, found that 17.8% (95% confidence interval [CI], 15.8–19.9) of the population had weekly heartburn. This prevalence rate was slightly lower than that of the Gallup poll. However, an additional 2% of the population had weekly heartburn or regurgitation (19.8%, 95% CI, 17.7–21.9)—bringing the number closer to 20%, which is consistent with that found in the Gallup poll [2]. Thus, 1 in 5 Americans suffers from heartburn on a regular basis.

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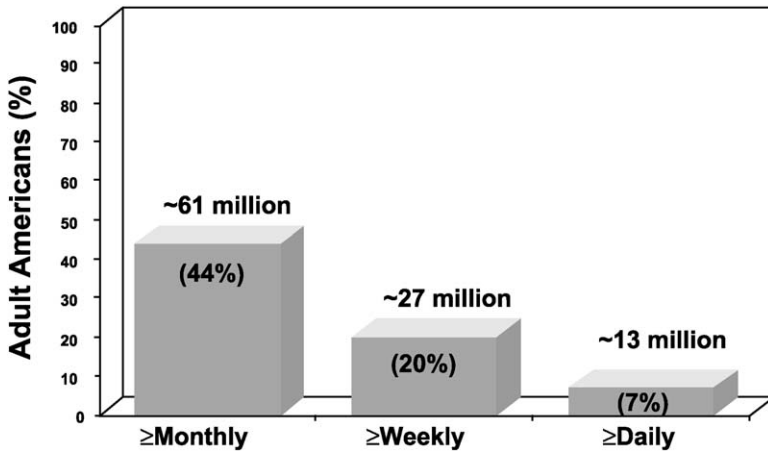


Fig. 1. Heartburn prevalence in American adults. (From The Gallup Organization. A Survey on Heartburn Across America. Princeton (NJ): The Gallup Organization; 1988.)

In May of 2000, the American Gastroenterological Association commissioned another study by The Gallup Organization that concentrated on the subgroup of people experiencing weekly or more frequent heartburn. One thousand people completed the telephone survey. To everybody's surprise, 79% of those surveyed had nocturnal heartburn. Sixty-five percent of those with weekly heartburn had heartburn both day and night. This finding of such a high prevalence of nighttime symptoms was of particular surprise to the gastroenterology community. The duration of symptoms was also surprisingly long; in fact, only about 15% of patients had experienced symptoms for less than 1 year, but 85% had symptoms persisting for 1 to 10 years or more (Fig. 2) [3].

Many of the respondents were taking active steps to control the condition. Seventy-two percent of the respondents were using medications. Among those taking medications, 38% were taking a prescription medication, 47% an over the counter (OTC) medication, and 15% were taking both types of medication. When those who experienced both day and nighttime symptoms were asked which affected them most, 50% voted that nighttime symptoms were the most troublesome. An almost equal number of 45% voted for daytime symptoms and 5% were not sure. The study also provided much information about how heartburn affected people's lives, as is discussed later in this article.

The impact of heartburn

Quality of life

Greater than 60% of the respondents to the 2000 Gallup poll on heartburn had sleep disturbance, which impacted on their work and their quality of life

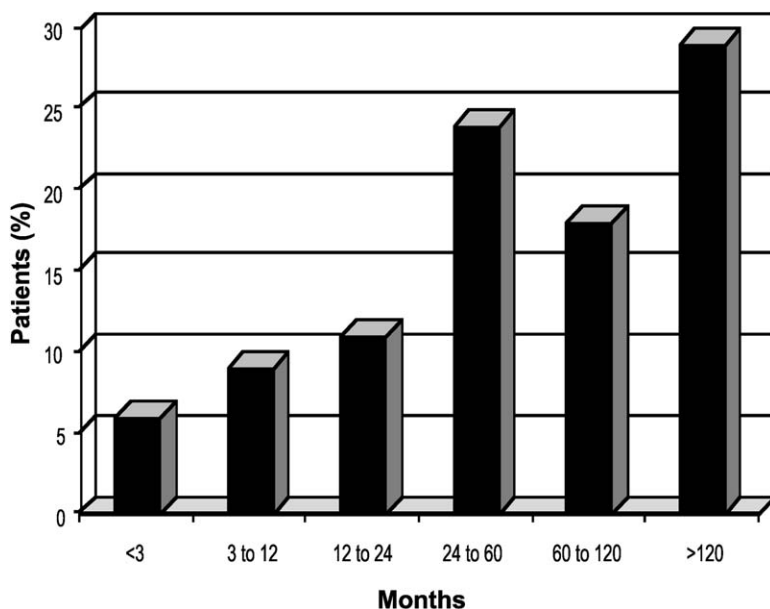


Fig. 2. The duration of reflux symptoms for patients from <3 months to >120 months. (From American Gastroenterological Association. *Understanding Heartburn in America*. Princeton (NJ): The Gallup Organization; 2000.)

(QoL) the next day. Somewhere between 35% and 50% of the patients had moderate or severe symptoms, the remainder had less severe symptoms. Specific QoL measures were affected. The respondents indicated that heartburn affected their ability to eat what they wanted, to eat when they wanted, their ability to get a good night's sleep, and to sleep when they wanted (Fig. 3).

Impact of disease severity

When the frequency of nighttime heartburn was measured, about a third of the patients reported frequent heartburn (Fig. 4). Again, about a third of the patients had heartburn less than once a week and about a third had heartburn once to twice per week. When one looks at severity, only about 30% had very mild or mild disease and about two-thirds of the sample had moderate, fairly severe, or severe symptoms. Looking at the use of drugs in those who had nighttime heartburn once a week or more, 71% had tried an OTC medication, over 41% had tried a prescription medication, and about 39% kept an OTC medication at the bedside. This included several people who were on prescription proton pump inhibitors (PPIs). So even though the survey respondents were taking potent drugs (at the time of the survey omeprazole and lansoprazole were the only PPIs available in the United States), they were not relying on these drugs to be effective throughout the night.

The respondents were asked whether heartburn was keeping them awake or waking them up. About equal numbers complained of each of these

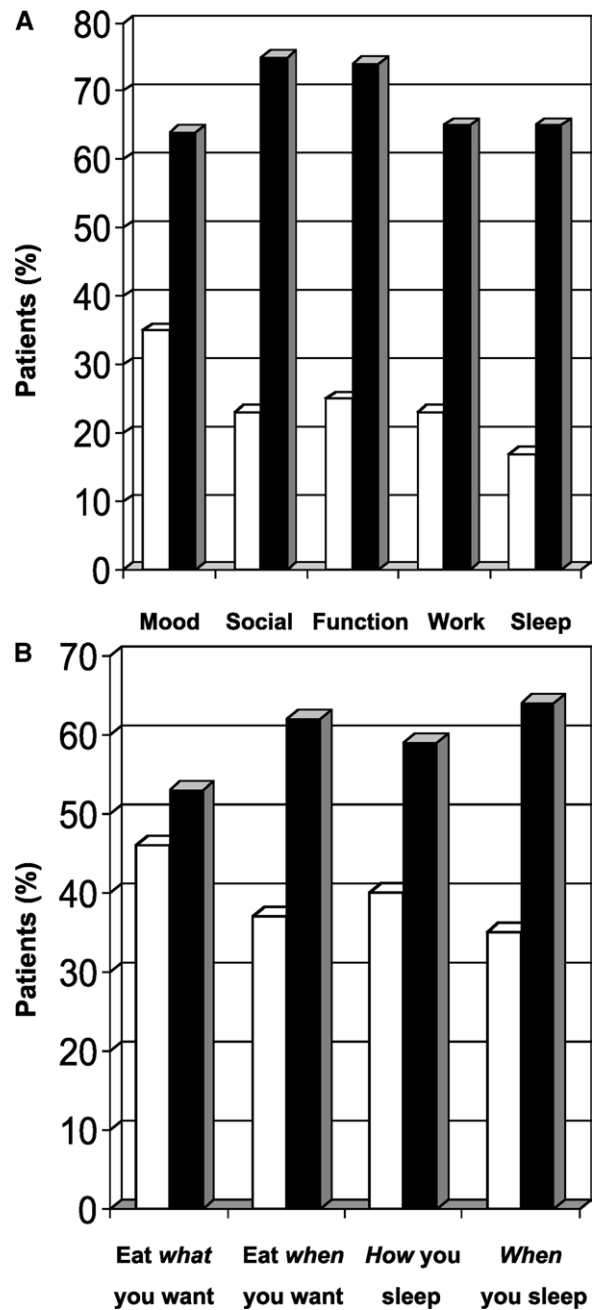


Fig. 3. Heartburn affects various aspects of a patient's life, such as (A) mood and general well-being and (B) the ability to eat or drink what he or she wants and the ability to sleep. (From American Gastroenterological Association. Understanding Heartburn in America. Princeton (NJ): The Gallup Organization; 2000.)

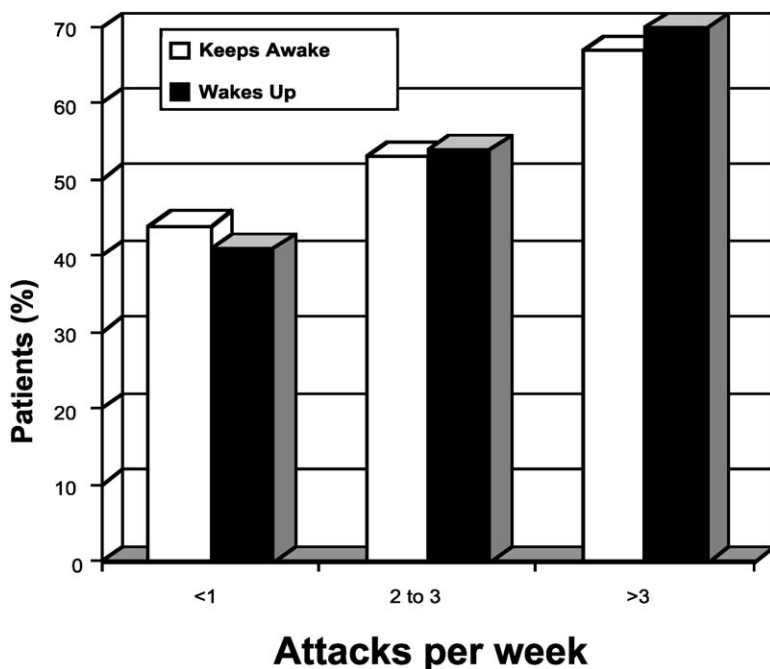


Fig. 4. The effects of heartburn on sleep in relation to frequency of attack measured in surveyed group. (From American Gastroenterological Association. *Understanding Heartburn in America*. Princeton (NJ): The Gallup Organization; 2000.)

problems, unrelated to the frequency of the attack. When the respondents were surveyed about symptoms that accompanied heartburn in the preceding 30 days, 62% complained of some gas, mainly upper abdominal gas. About 55% had a burning sensation in the chest; 52% a burning sensation in the throat; 50% reflux of gastric contents into the mouth; and smaller numbers had belching, cough, dysphonia, hoarseness, nasal sinus or breathing problems, chest pain, or dental erosions. These results seem to confirm again what gastroenterologists have come to realize, namely, that for many patients the extraesophageal manifestations of the disease are significantly troublesome and often the major complaint [4]. Most of these symptoms are relieved by adequate PPI therapy. In contrast, gas and nausea do not generally respond to acid suppressive therapy.

Pathophysiologic consequences of heartburn

What is the relationship between heartburn and inflammation? In surveys looking at patients undergoing endoscopy for symptomatic GERD, about half have esophagitis, about half have no esophagitis, and about 12% have Barrett's esophagus [5]. Physicians used to think that there was a progression of disease between these groups, but with long-term follow-up studies now

in Italy, the United States, and several other countries, transitions are uncommon and it seems very likely that many people remain in their initial category for as long as 10 years of follow-up. Thus, the grade of their disease usually either remains unchanged or relapses with a lesser degree of severity, or is cured; only a minority show progression to a more severe grade of disease [6–12].

The potential for disease progression to a more serious or complicated stage, although small, has been much emphasized of late. In a recent study, heartburn was identified as a risk factor for the development of adenocarcinoma of the esophagus [13]. Is this association between heartburn and carcinoma a cause for alarm? A study by Lagergren et al [13] found that the relative risk for adenocarcinoma was high in patients with heartburn (odds ratio 7.7; 95% CI, 5.3–11.4). However, the absolute risk of developing adenocarcinoma of the esophagus is low. Only about 7000 cases a year of adenocarcinoma of the esophagus occur in the United States, although reports suggest that the rate may be increasing [14].

If there are 280 million Americans in the United States, then an estimated annual risk for adenocarcinoma of the esophagus is 1 in 40,000. Depending on the frequency of symptoms, heartburn patients are at greater risk. For example, a patient with monthly heartburn might have a 1 in 10,000 risk for developing the cancer, a patient with weekly heartburn a 1 in 4500 risk, and those with daily heartburn a 1 in 2000 risk. However, in patients who have diagnosed Barrett's esophagus, the risk for adenocarcinoma is 30 to 60 times greater than that in the general population. Therefore, patients with Barrett's esophagus probably have a risk of about 1 in a 1000 per year (or perhaps a cumulative life-time risk as great as 1 in 200) of developing esophageal adenocarcinoma. However, if the data from Cameron et al [15] are correct as to the high prevalence of Barrett's esophagus in patients at autopsy (regardless of cause of death), this estimate of risk in patients with Barrett's esophagus is grossly exaggerated.

The bigger picture: GERD

If heartburn is the most common symptom of GERD, what is this condition? Defining GERD is important, because many people experience reflux that might not constitute a pathologic process. Recently a group of experts convened in Genval, Belgium and were given the charge of defining GERD. According to this group, the term GERD should be used for individuals exposed to the risk of physical complications of reflux or in whom reflux causes significant impairment of health related well-being or QoL after adequate reassurance of the benign nature of their symptoms [16]. The last clause was added because some recent studies conducted to examine the impact of PPI therapy on QoL scores showed that these changed immediately after the initial endoscopy without initiation of therapy [17,18]. However, the improvement in QoL that accompanied reassuring the patient

as to the absence of cancer was rapidly dissipated, and by 6 weeks patient scores were at their original values.

In a study by Winters Jr. et al [5], findings in 97 patients subjected to endoscopy showed 45.3% of reflux patients had esophagitis, 42.3% had no esophagitis, and 12.4% had Barrett's esophagus, with or without esophagitis. Only about half of all endoscoped patients presenting with reflux symptoms have demonstrable mucosal abnormalities (ie, esophagitis or Barrett's esophagus).

Can another form of the disease be present? The Genval Workshop also tried to define NERD, non-erosive reflux disease (or non-erosive esophageal disease), which is heartburn not accompanied by any abnormal findings at endoscopy, a pattern commonly seen in clinical practice and not necessarily always mild [16]. The Genval Workshop decided that the term "non-erosive esophageal disease" should be reserved for individuals who satisfy the definition of GERD but who do not have either Barrett's esophagus or definite mucosal breaks, erosions, or ulcers at endoscopy.

So we have GERD and NERD and where does that leave us with QoL? Studies Of Psychological General Well-Being (PGBW) scores (an index that has been well-validated in numerous diseases) in GERD patients, show that only psychiatric patients have poorer QoL, as indicated by lower scores. Among the common conditions listed here, duodenal ulcer, angina pectoris, and heart failure, all have less impairment of PGBW scores than patients with GERD, although one tends to think of these as more significant diseases in many cases [19,20].

A systematic breakdown of the various parameters that comprise QoL reveals that all measurements are below normal in patients suffering from GERD. The general health perceptions, physical and social function, mental health, and vitality scores of these individuals all rate significantly lower than normal [20]. Even more conspicuous is the increased perception of bodily pain and the extent to which this physical problem is deemed to interfere with the usual daily activities of those suffering from heartburn.

One must point out that symptom severity predicts neither the severity of disease nor the presence or absence of erosive lesions [21,22]. Furthermore, symptom severity does not predict response to therapy [23]. Symptom relief and mucosal healing are closely related to the dose and potency of the acid-suppressing medication and the duration of therapy [24,25]. While most studies examine the results of 8 weeks of therapy, in the author's practice, patients are often treated for 12 to 16 weeks. Symptom relief, however, does not ensure that lesions have healed, and in some patients lesions may still be present or progressing despite symptom relief.

Summary

Heartburn is a common, often disabling condition. Twenty percent of adults exhibit symptoms at least once weekly. Few obtain complete

satisfactory relief of their symptoms without the simultaneous implementation of significant lifestyle modifications and appropriate pharmacologic intervention. Poor sleep and chronic symptoms impair the QoL in 25% to 30% of such cases. Nocturnal symptoms are more troublesome, more difficult to treat, and are often manifested by extraesophageal symptoms. Several patients, however, unknown to their physicians continue to experience heartburn, despite lifestyle changes and taking prescription drugs. Adequate acid suppression is currently essential to effective management of the condition.

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The role of acid suppression in the management and prevention of gastrointestinal hemorrhage associated with gastroduodenal ulcers

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Acute peptic ulcer bleeding and the development of stress ulcers are two conditions that can affect the management of patients in the intensive care unit (ICU). Recently, new options have become available for providing acid suppression to these patients. This article discusses the emerging literature on optimizing acid suppression as part of an overall management strategy in critically ill patients.

Peptic ulcer bleeding

Prevalence

In the United States, 150,000 hospitalizations per year are related to evaluation and treatment of bleeding ulcers [1]. The mortality rate for bleeding ulcers is about 6% to 7% [2]. Peptic ulcers are the most common source of acute upper gastrointestinal (UGI) hemorrhage, causing approximately 45% to 50% of cases [1,3]. Unfortunately, despite medical advances, the mortality rate of UGI bleeding has remained constant at 10% [3]. A leading explanation for this phenomenon is a change in the patient population. Through innovations in medical technology and the availability of transfusions, patients who would have hemorrhaged to death 40 years ago now survive the ordeal. Old age and multiple comorbidities, however,

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increase the risk of succumbing to complications associated with UGI bleeding [4]. Therefore, as the population ages, elderly patients with multiple comorbidities constitute a greater percentage of the population with UGI bleeding and, thus, may increase mortality rates [5].

At the Prince of Wales Hospital in Shatin, Hong Kong, China, UGI bleeding is one of the most common diagnoses for hospital admission, with 1000 patients with peptic ulcer disease seen each year. In addition, 5% of emergency admissions have peptic ulcer bleeds. Eighty percent of the patients will stop bleeding spontaneously, and 5% will die [6]. Most patients die of recurrent bleeding, a factor that increases mortality tenfold [7]. These results suggest the importance of optimizing the management of UGI bleeding to prevent morbidity and mortality.

Risk assessment

Endoscopic therapy is generally effective for managing acute UGI bleeding, but patients may rebleed after the procedure. Patients at risk for rebleeding after UGI hemorrhage include those who have ulcers characterized by active spurting, visible protuberant vessels, or adherent clots (Fig. 1) [7]. Because of the predictive value of these stigmata of recent hemorrhage, proper identification upon endoscopy is important. To improve the likelihood of accurate diagnosis, classification systems (eg, Forrest's system) for nonvariceal UGI bleeding have been proposed. Typical endoscopic features described in Forrest's classification are useful to assess the risk of

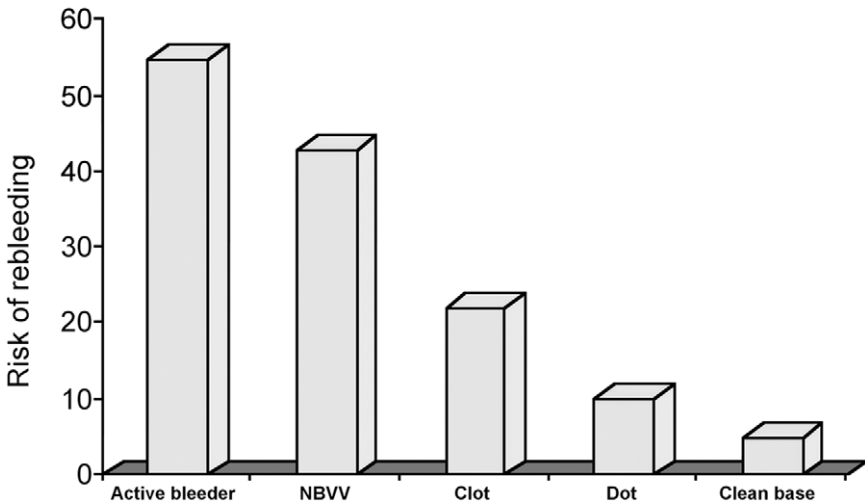


Fig. 1. The correlation between the risk of recurrent bleeding and the endoscopic appearance of an ulcer. NBVV, nonbleeding visible vessel. (Data from Laine L, Peterson WL. Bleeding peptic ulcer. *N Engl J Med* 1994;331:717–27.)

recurrent bleeding [1]. A triage system has been proposed to determine the most appropriate timing for performing an endoscopy on a patient with UGI bleeding.

Several scoring systems using clinical or endoscopic characteristics have been proposed in recent years to predict the likelihood of a poor outcome following peptic bleeds. Saeed et al [8] developed the Baylor bleeding score, which incorporates objective data to identify patients likely to rebleed within 72 hours after successful endoscopic hemostasis of ulcer hemorrhage. The study group determined that untreated endoscopic stigmata remain predictors of rebleeding, but effective treatment of the lesions eliminates the excess risk. Clinical criteria, mainly the number and severity of concomitant illnesses, then become the primary determinants of rebleeding [8]. Rockall et al [4] validated a risk scoring system in patients with acute UGI bleeding. The score, which is based on age, presence of shock, comorbidity, diagnosis, and endoscopic stigmata or recent hemorrhage, also seeks to identify patients with high risk of further bleeding or death. According to Rockall et al [9], the intended plan for low-risk patients is early endoscopy and discharge, thereby shortening hospital stays and increasing economic savings.

Although endoscopic intervention is an established technique for treating major peptic ulcer hemorrhage (often stopping active bleeding) and reducing the risk of rebleeding, 15% to 20% of these endoscopically treated ulcers will still rebleed [10]. Therefore, additional therapeutic options are needed [11]. Acid suppression therapy is one option that has been examined to manage acute ulcer bleeding and to prevent ulcer rebleeding.

Endoscopic treatments

The two main endoscopic approaches for treating peptic ulcer bleeds are injection with adrenalin and thermocoagulation (eg, heat probe). Approximately 10 years ago, a study was performed to compare the two treatment modalities in 132 patients with bleeding ulcers. Although epinephrine injection provided significantly greater control of bleeding initially in 96% of the patients compared with 83% with heat probe ($P < 0.05$), outcomes as measured by subsequent transfusion requirement (4.5 units versus 3.8 units), emergency surgery (20% versus 22%), hospital stay (8 days versus 7 days), and mortality (2 deaths versus 4 deaths) were comparable between the two groups [12]. Yet, endoscopic injection is technically easier to perform, making it a more appealing procedure compared with the heat probe.

To maximize the probability of a positive outcome, most patients are treated with a combination of injection and heat probe. One study determined that the frequency of rebleeding in patients treated with combination therapy was 3.7% compared with 9.0% in patients treated with injection alone [6]. Epinephrine injection also was studied in combination with human thrombin injection. The investigators found that 4.5% of 70 patients

receiving combination therapy rebled, compared with 20% of the same number of patients injected with epinephrine alone [13].

Although individual or combination endoscopic therapy is effective, endoscopy has limitations. In a study conducted nearly 15 years ago, Johnston et al [14] evaluated five endoscopic thermal devices and observed various negative consequences depending on the technique. Monopolar electrocoagulation and neodymium: yttrium-aluminum-garnet laser, for example, caused erosion of tissue and vessels. All endoscopic treatment modalities effectively coagulated vessels with small diameters; however, the endoscopic thermal devices performed poorly on large-diameter vessels (> 2 mm).

Acid suppressive therapies for UGI bleeding

An understanding of the differences between hemostasis in the UGI tract and mechanisms of clotting strongly suggests that the acidity within the local environment directly affects outcome of hemostasis. Green et al [15] studied the effects of hydrogen ion concentration on in vitro parameters of platelet function and plasma coagulation. They found that the soluble coagulation system and the platelet-mediated aspect of blood coagulation were exquisitely sensitive to changes in the pH. At a pH of 6.4, platelet aggregation was reduced by over 50%; at a pH of 5.4, platelet aggregation and plasma coagulation essentially did not exist. This study supported the theoretical conclusion that maintaining the intragastric pH close to neutrality in the days following an acute GI bleed facilitates stable clot formation and hemostasis.

Histamine₂-receptor antagonists (H₂RAs) have been used widely to treat patients with acute UGI bleeding, although the literature does not firmly support a role for these agents. A meta-analysis of 27 randomized trials showed that administration of H₂RAs to over 2500 patients with acute UGI bleeding reduced the rates of rebleeding, surgery, and death by 10%, 20%, and 30%, respectively. Of note, the results for surgery and death were only marginally significant [16]. Encouraged by these findings, investigators conducted the first prospective, randomized trial examining H₂RAs for UGI bleeding, which enrolled 1005 patients admitted into 1 of 67 hospitals in the United Kingdom. Famotidine (10 mg bolus plus 3.2 mg per hour) or placebo was administered through a continuous intravenous (IV) infusion for 72 hours to patients with overt UGI bleeding. The two treatment groups did not differ in terms of mortality (6.2% famotidine versus 5.0% placebo), rebleeding (23.9% versus 25.5%), or surgery (15.5% versus 17.1%) (Table 1) [17].

Soon after the famotidine study, the first proton pump inhibitor (PPI), omeprazole, was studied in a double-blind, placebo-controlled, parallel-group trial. This study, also conducted in the United Kingdom, included 1147 patients who were 18 years or older with UGI bleeding for over 40 months. Patients in the active treatment arm received omeprazole

Table 1

Results of a prospective, randomized trial with continuous famotidine or placebo infusion

Outcome	Famotidine (n = 497)	Placebo (n = 508)	Odds ratio (95% CI)
Rebleeding	119 (23.9%)	129 (25.6%)	0.93 (0.68–1.25)
Surgery	77 (15.5%)	86 (17.1%)	0.93 (0.65–1.32)
Death	31 (6.2%)	25 (5.0%)	1.37 (0.77–2.44)

Abbreviation: CI, confidence interval.*Adapted from* Walt RP, Cottrell J, Mann SG, et al. Continuous intravenous famotidine for haemorrhage from peptic ulcer. *Lancet* 1992;340:1058–62; with permission.

intravenously (80 mg bolus plus 40 mg every 8 hours) for the first day and orally (40 mg every 12 hours) for 4 subsequent days or until surgery, discharge, or death. The investigators did not find any differences between the placebo and omeprazole group for rates of transfusion (53% versus 52%, respectively), rebleeding (18% versus 15%, respectively), surgery (11% versus 11%, respectively), or death (5.3% versus 6.9%, respectively). A significant reduction ($P < 0.0001$) in endoscopic signs of UGI bleeding in patients treated with omeprazole (33%) was observed, compared with placebo (45%), however [18].

A few years after the omeprazole study, a similar trial was performed in India using oral omeprazole. Two hundred twenty patients with endoscopic evidence of recent UGI bleeding were assigned randomly to placebo or oral omeprazole (40 mg every 12 hours) for 5 days. The results of this study were in sharp contrast to the preceding study. Significantly fewer omeprazole-treated patients continued bleeding, required surgery, or received transfusions compared with the placebo-treated group (10.9% versus 36.4%, 7.3% versus 23.6%, and 29.1% versus 70.9%, respectively; $P < 0.001$ for all outcomes) [19].

An additional study examined the effect of a continuous infusion of omeprazole (80 mg bolus plus 8 mg per hour) versus placebo for 72 hours in 330 elderly patients at least 60 years old with peptic ulcer bleeding from 20 centers in Sweden and 9 centers in Norway. From days 4 to 21, all patients received 20 mg omeprazole orally once daily. On day 3, the overall outcome (based on transfusion requirement, death, and requirement for surgery) was significantly better in patients who received omeprazole versus patients who received placebo [20]. Potential explanations for the discrepancy between these studies include patient selection, endoscopy in a subset of patients in the first trial obviating the use of acid suppression therapy, and alterations in PPI metabolism based on ethnic differences (eg, Asians are slow acetylators).

Comparing PPIs and H₂RAs

In addition to the aforementioned studies evaluating H₂RAs or PPIs, several trials directly compared H₂RAs with PPIs in patients with UGI bleeding. One double-blind, cross-over study evaluated 12 patients receiving

individually titrated IV infusions of ranitidine, omeprazole, and placebo for 3 days to assess the quantity of medication required to maintain a neutral gastric pH in healthy volunteers. On the first day, the critical dose of ranitidine was fairly high; yet even higher doses were required on days 2 and 3 to maintain neutrality, suggesting that tolerance had developed. In comparison, the dose of omeprazole was reduced over the 3 days but still sustained gastric pH neutrality [21].

Methods and speed of administration also influence efficacy of acid suppressive therapy during the critical first 72 hours. Netzer et al [22] compared the effects of omeprazole infusion (initial bolus of 80 mg plus 8 mg per hour) or injection (initial bolus of 80 mg plus 40 mg every 6 hours) to ranitidine infusion (initial bolus of 50 mg plus 0.25 mg/kg per hour) or injection (100 mg every 6 hours) on gastric pH in 34 healthy volunteers over a 3-day period. They found that on day 1, injections of both drugs were significantly less effective than infusions of both drugs. On days 2 and 3, omeprazole injection was almost as effective as omeprazole infusion, but ranitidine injection and infusion were equally beneficial. The median pH was significantly higher throughout the trial in the omeprazole infusion group compared with the ranitidine infusion group. Moreover, the median pH in the omeprazole infusion group increased from 6.1 to 6.3 over the 3 days but decreased from 5.1 to 2.7 in the ranitidine infusion group. The investigators highlighted two main conclusions: (1) omeprazole infusion is significantly superior to the other three treatment regimens; and (2) the tachyphylaxis associated with ranitidine precludes it from being the appropriate treatment when high intragastric pH-levels are crucial [22]. In addition, although oral PPIs effectively maintain acid suppression, the studies support continuous IV infusion as the administration method of choice to obtain peak levels of the medication quickly.

PPI therapeutic options

Pantoprazole is the only IV PPI available in the United States. Like omeprazole, pantoprazole effectively inhibits gastric acid secretion. In one study, Pisegna et al [23] infused pentagastrin (1.0 µg/kg per hour) in 39 healthy volunteers over a 25-hour phase to stimulate maximum acid output. One hour after infusion, single doses of IV pantoprazole (at 20, 40, 80, or 120 mg), IV famotidine (20 mg), or placebo were administered. The investigators demonstrated a dose-dependent suppression of acid secretion (< 10 mEq per hour) with pantoprazole administration. The 80 and 120 mg doses of pantoprazole suppressed acid output by over 90% in all subjects for more than 21 hours. In comparison, famotidine inhibited acid secretion for 6 hours (Fig. 2). Onset of action was comparable (< 1 hour) between pantoprazole 80 mg and high-dose IV famotidine. Therefore, the investigators concluded that IV pantoprazole is more effective than IV famotidine in providing prompt and long-lasting suppression of acid secretion.

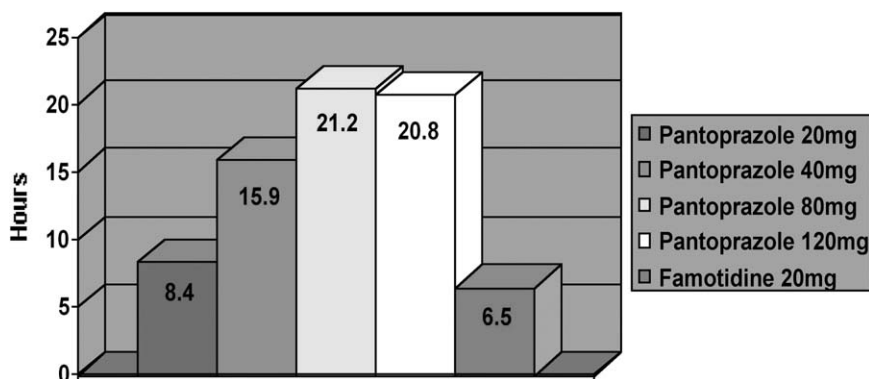


Fig. 2. Duration of effects of pantoprazole and famotidine on acid suppression in 39 healthy volunteers following an infusion of pentagastrin. Duration of response is defined as time from onset until time when acid output levels increased above 10 mEq per hour for at least 1 hour. (Adapted from Pisegna JR, Martin P, McKeand W, et al. Inhibition of pentagastrin-induced gastric acid secretion by intravenous pantoprazole: a dose-response study. *Am J Gastroenterol* 1999;94:2874–80; with permission.)

Another study by Wyeth Laboratories compared the efficacy of oral pantoprazole, IV pantoprazole, and IV famotidine (data on file, Wyeth Laboratories). As shown in Fig. 3, famotidine caused rapid but unsustained acid suppression, while the IV PPI produced rapid and sustained acid suppression. The oral formulation also caused sustained gastric acid inhibition; however, uptake was delayed.

The positive findings in Khuroo et al's study [19] prompted Lau et al [10] to investigate the impact of PPIs in patients after endoscopic treatment of bleeding ulcer. Patients with actively bleeding ulcers or ulcers with non-bleeding visible vessels underwent epinephrine injection followed by heat probe thermocoagulation. Once hemostasis was achieved, patients randomly received either IV omeprazole given as an 80 mg bolus followed by an infusion of 8 mg per hour for 72 hours or placebo. All patients then were given oral omeprazole 20 mg daily for 8 weeks [10].

The primary endpoint, recurrent bleeding within 30 days after endoscopy, was significantly less frequent in the omeprazole group compared with the placebo group by days 3, 7, and 30 ($P < 0.001$ for all time points). Recurrent bleeding occurred most commonly during the drug infusion period but was less frequent in five omeprazole-treated patients (4.2%) versus 24 placebo-treated patients (20%) ($P < 0.001$). In addition, omeprazole-treated patients required significantly fewer units of transfused blood over the 30 days following endoscopy and significantly shorter hospitalized stays compared with the placebo group. A trend toward fewer surgeries and lower mortality rates also was observed in the omeprazole group [10]. A recent pharmacoeconomic study from Canada [25] compared the use of empiric therapy with IV PPI versus endoscopic therapy in patients presenting to the emergency

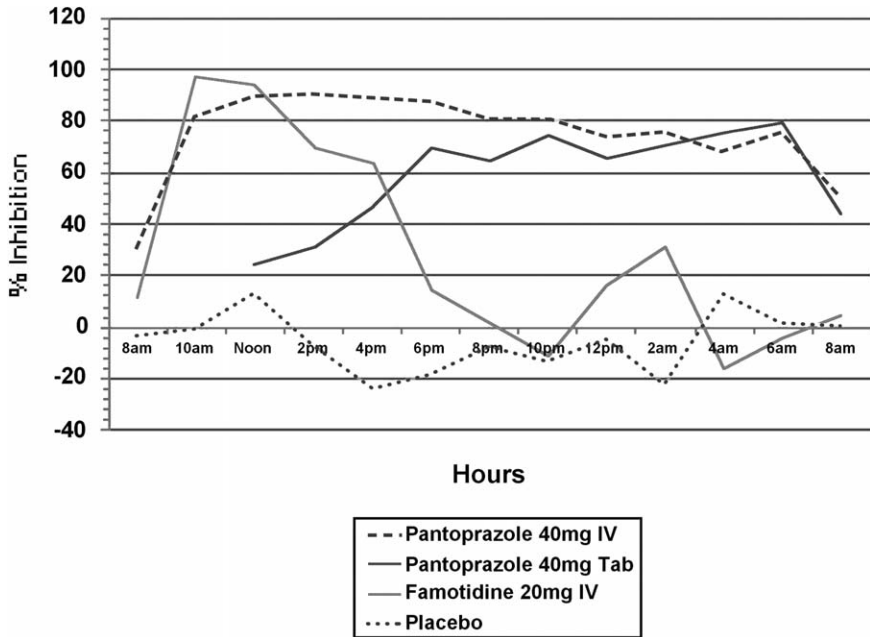


Fig. 3. The effect of oral pantoprazole, IV pantoprazole, and IV famotidine on inhibition of acid output. (Courtesy of Wyeth Laboratories.)

department with UGI bleeding based on results from the Hong Kong study by Lau et al [16]. Rioux et al [24] found that empiric IV PPI therapy reduced hospital stays, decreased the numbers of surgeries, and resulted in significant cost savings when compared with endoscopic therapy, without compromising patient health care. Taken together, these studies provide a strong rationale for the use of IV PPIs to prevent rebleeding in patients who have received endoscopic therapy for UGI bleeding. In addition, IV PPIs may play a role in empiric therapy for management of UGI bleeding.

Stress ulcers

Pathophysiology

Until the last decade, stress-induced UGI bleeding was a rare complication in critically ill patients. With the development of intensive care medicine, however, came a sharp fall in the frequency of this complication. In the 1960s, international research attempted to identify the pathophysiological mechanisms causing stress-induced UGI bleeding and appropriate management for prophylaxis and treatment [25].

Although stress ulceration is speculated as being related to ischemia and impaired mucosal blood flow, particularly during hemodynamic shock, the cause of stress ulcers remains unknown. Other potential causes include

presence of free radicals or bile salts and altered prostaglandin levels [26–28]. Numerous risk factors that predispose patients to the development of stress ulcers have been identified. The list of factors includes mechanical ventilation, coagulopathy, shock, severe sepsis, head trauma, neurosurgery, severe burns, tetraplegia, and multiple organ failure [25].

Role of acid suppression

Despite an incomplete understanding of the mechanism of stress ulcer development, physicians attempt to risk stratify patients and to prevent gastrointestinal (GI) bleeding with pharmacologic agents. A national survey was conducted to determine the rationale for stress ulcer prophylaxis and assess the decision-making process used to select a prophylactic agent. Physicians responding to the questionnaire reported that individuals at high risk for developing stress ulcers (ie, those with burns, shock, and sepsis) were the patients frequently started on prophylaxis. The most commonly used medications were ranitidine, famotidine, sucralfate, and cimetidine. Variables considered in choosing the appropriate agent included ease of administration, formulary availability, adverse event profile, and cost-effectiveness. In general, the authors concluded that no consensus exists among clinicians on the risk stratification and optimal therapeutic approach for stress ulcer prophylaxis [29].

PPI as a therapeutic option

PPIs are recognized as potent acid inhibitors, and their greater acid suppressive ability compared with H₂RAs, along with their good safety profiles, may render them a better option for stress ulcer prophylaxis. Because critically ill patients typically are not able to take oral medications, several preliminary studies have begun to investigate various PPI formulations targeted for use in critically ill patients. One study found that comparable increases in intragastric pH were attained and maintained with omeprazole and lansoprazole granules and simplified lansoprazole suspension [30]. In a pharmacokinetic study evaluating pantoprazole suspension, the investigators concluded that a suspension consisting of the crushed tablet and sodium bicarbonate is a practical formulation to administer to patients inappropriate for IV therapy or unable to swallow a tablet [31]. In another study, patients treated with simplified omeprazole suspension did not experience any clinically significant UGI bleeding, and the 4-hour postomeprazole gastric mean pH was 7.1 [32]. In a comparative study of the suspension and oral forms of omeprazole to IV ranitidine, the investigators concluded that omeprazole, administered orally by mouth or as a suspension through a nasogastric tube, is safe and effective prophylaxis in critically ill patients [33].

An IV PPI represents another option for patients who are not able to take oral medications. Based on the inverse relationship between percentage

of time intragastric pH remains above 4.0 and the incidence of UGI bleeding in ICU patients, a multicenter study comparing four doses of IV pantoprazole (80 mg every 12 hours; 40 mg every 12 hours, and 40 mg every 24 hours) to the standard approved regimen of continuous infusion cimetidine (300 mg bolus plus 50 mg per hour) was recently conducted in critically ill patients. Time to reach an intragastric pH of at least 4.0 and percent of time pH remained at or above 4.0 were calculated. Results, which are shown in Table 2, demonstrate that although there were variations between the doses, pantoprazole quickly achieved and maintained gastric pH above 4.0 and progressively increased percentage of time above 4.0 by day 2. Cimetidine also reached a pH above 4.0 within approximately the same time frame as pantoprazole but was unable to maintain the percentage of time above that acidity level by day 2. Two cases of pneumonia were reported during therapy, one receiving cimetidine and one receiving pantoprazole 40 mg every 12 hours. Also, one patient developed phlebitis while receiving pantoprazole 80 mg every 8 hours [34]. Pantoprazole IV recently has become available in the United States.

Overview of stress ulcer prophylaxis

The relationship between gastric acid suppression and the development of stress ulcers is still an issue of debate. Lack of treatment consensus among

Table 2

Results of a multi-center study comparing intravenous pantoprazole to intravenous cimetidine in patients in the intensive care unit

	Time to reach pH of at least 4 (h)	% of time pH is at least 4 on day 1	% of time pH is at least 4 on day 2	Adverse events
Pantoprazole (n = 6) 80 mg IV q 8 h	6.1	66	77	Phlebitis in one patient
Pantoprazole (n = 7) 80 mg IV q 12 h	4.0	82	86	—
Pantoprazole (n = 6) 40 mg IV q 12 h	4.7	40	62	Pneumonia in one patient
Pantoprazole (n = 5) 40 mg IV q 24 h	2.0	49	59	—
Cimetidine (n = 6) 300 mg bolus IV + 50 mg/h	3.8	75	61	Pneumonia in one patient

Abbreviation: IV, intravenous.

Data from Somberg L, Karlstadt R, Gallagher K, McDewitt J, Graepel J, Paoletti V, Icu Pantoprazole Study Group. *Gastroenterology* 120(Suppl 1):A157–8, 2001.

physicians and dropping incidence of ulcer bleeding with improvement of care in ICUs have been the impetus to perform large-scale clinical trials. H₂RAs are subject to tolerance, which minimizes the impact of these medications. PPIs, however, are not associated with tolerance and, indeed, gastric acid suppression increases after day 1 of administration. Whether PPIs provide the same benefits for stress-related mucosal bleeding as they provide for peptic ulcer bleeding is unknown, but IV PPIs, which are more effective at raising intragastric pH than H₂RAs, likely represent a significant advance in acid suppression. Ongoing clinical studies should show whether this acid suppression effect translates into meaningfully improved clinical outcomes in patients at risk for stress ulcers.

Summary

Peptic ulcer bleeding remains a substantial source of morbidity and mortality in the ICU setting. Endoscopic injection with adrenaline and thermocoagulation is the mainstay of treatment for peptic ulcer bleeds. To enhance healing and overcome limitations of endoscopic therapies, acid suppression therapy is recommended. Although results from a few studies do not support their use fully following an episode of acute UGI bleeding, PPIs have been used successfully to lower transfusion requirements and additional surgical procedures, reduce hospital stays, and lower medical costs. H₂RAs and PPIs have a rapid onset of action when given intravenously; however, patients quickly become tolerant to the effects of H₂RAs, generally requiring increased doses of medication after the first day of administration. PPIs provide persistent acid suppression, maintaining neutral gastric pH, especially during the critical first 72 hours following a bleed. Recent clinical studies further support their use in preventing bleeding in the clinical setting.

Controversy exists over the utility of pharmacologically induced acid suppression in critically ill patients at risk for stress ulcers. Comparative pH studies, however, suggest that IV PPIs such as pantoprazole are more effective in raising intragastric pH than are H₂RAs. Although the clinical benefits of PPIs for stress ulcer prophylaxis have not been established, there is a theoretical framework suggesting that they should be beneficial. Ongoing clinical studies should show whether the theoretical advantage translates into clinically meaningful benefits.

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Pharmacologic features of proton pump inhibitors and their potential relevance to clinical practice

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Five proton pump inhibitors (PPIs) are currently available in the United States. They include omeprazole (Prilosec, AstraZeneca LP, Wilmington, DE), lansoprazole (Prevacid, TAP Pharmaceutical Products, Lake Forest, IL), rabeprazole (Aciphex, Eisai Inc., Teaneck, NJ), pantoprazole (Protonix, Wyeth Pharmaceuticals, Philadelphia, PA), and esomeprazole (Nexium, AstraZeneca LP, Wilmington, DE). PPIs are the most potent acid suppressant agents available and have, therefore, become the drugs of choice for several acid peptic diseases including healing of erosive esophagitis, maintenance and treatment of gastroesophageal reflux disease (GERD), and peptic ulcer disease. Although these agents share many pharmacologic properties, subtle differences do exist among them. This article reviews the potential clinical relevance of the pharmacologic characteristics of PPIs.

Chemical structure of PPIs

All of the PPIs are substituted benzimidazoles (Fig. 1). In addition, all PPIs are chiral compounds, which means their spatial orientation is asymmetrical. When four different atoms are attached to a central atom, such as carbon or sulfur, the central atom is considered a chiral center. In chiral compounds, two structural arrangements that are nonsuperimposable mirror images of each other exist. In the case of PPIs, the chiral center is the

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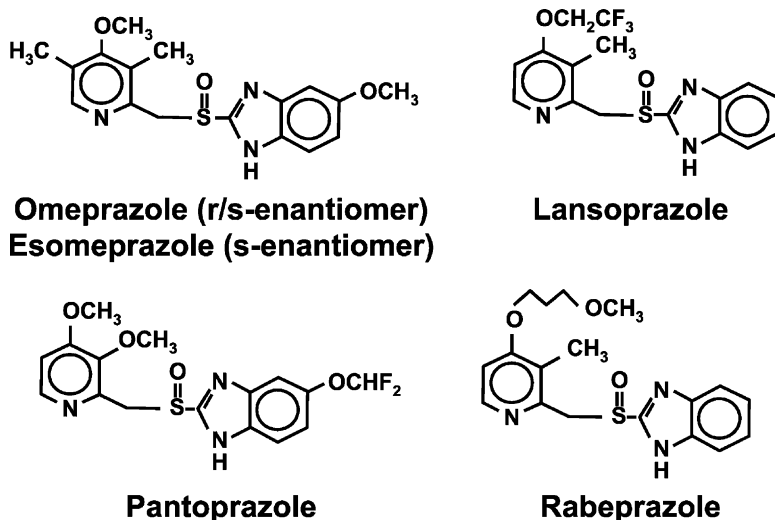


Fig. 1. Structures of proton pump inhibitors.

sulfur atom. The naming of the optical isomers is often confusing, in that there are several classification schemes. One method is to name the isomers in terms of their absolute chemical configuration in reference to the chiral center. (R) and (S) isomers refer to the spatial orientation of the groups to the right (R) and left (S) of the chiral center. One can think of the (R) and (S) isomers (or enantiomers) as right-handed and left-handed forms. Chirality can introduce marked selectivity and specificity into the way the drug is handled by the body and in some cases how the compound interacts with the receptor [1]. Overall, this may lead to variations in pharmacokinetic (PK) and pharmacodynamic (PD) properties and differences in safety and toxicity profiles [2,3].

Most drugs are marketed as racemic mixtures containing equal amounts of (R) and (S) enantiomers. However, recent advances in technology, together with regulatory requirements, have led many pharmaceutical companies to attempt, when relevant and possible, to develop single enantiomeric products. Simplistically, for chiral compounds, pharmaceutical companies now often have the choice of developing (1) racemates that contain equal amounts of both enantiomers, (2) single enantiomeric products, (3) products that contain fixed ratios (not 1:1) of the enantiomers, or (4) single enantiomeric products developed by switching from an approved racemic formulation to a single enantiomeric product (commonly referred to as chiral switching) [4].

The decision to develop single enantiomeric products is dependent on many factors. However, one must carefully weigh whether such a change will have any therapeutic benefit. For example, ketamine, an intravenous anesthetic is currently marketed in the United States as a racemic mixture.

Interestingly, the (S)-enantiomer has superior potency and does not cause psychic emergence reactions (ie, hallucinations, restlessness, or agitation) as compared with the (R)-enantiomer. So, in this case, a single enantiomeric product may be therapeutically desirable [4]. In some cases, however, both enantiomers of a drug have equal efficacy and equal toxicity. Flecaïnide and promethazine fall into this category; separating their racemic mixtures poses no further advantage in the efficacy or safety profiles [2]. In other cases, one enantiomer may be converted in the body to the other enantiomer (ie, chiral inversion). For example, both fenoprofen and ibuprofen undergo significant chiral inversion in the body from the (R)-enantiomer to the more active (S)-enantiomer.

Among the PPIs, omeprazole, lansoprazole, pantoprazole, and rabeprazole are marketed as racemic mixtures of the (R)- and (S)- enantiomers in a 1:1 ratio. The enantiomers of omeprazole display strikingly different pharmacokinetic properties, an observation that led to the development of esomeprazole, a formulation that contains only the (S)-enantiomer of omeprazole. The implications of this difference are highlighted in the pharmacokinetics section of this article.

Mechanism of acid inhibition

Delivery to and activation at the proton pump

Approximately 1 billion parietal cells line the gastric mucosa and secrete acid into the gastric lumen in response to various neurocrine, paracrine, and endocrine factors [5]. One of these factors, histamine, leads to increased hydrogen ion secretion by reversibly binding to histamine-2 (H_2) receptors on parietal cells [5]. H_2 -receptor antagonists (H_2 RAs), such as cimetidine, nizatidine, ranitidine, and famotidine, reversibly block H_2 receptors and decrease basal and meal-stimulated acid secretion [6–9]. However, maximal acid suppression cannot be achieved with H_2 RA administration alone, as these agents only block one pathway involved in acid secretion.

The final step in acid secretion involves a gastric transport enzyme called hydrogen, potassium adenosine triphosphatase, herein known as the proton pump. The proton pump is a heterodimer composed of α and β subunits that traverse the parietal cell membrane [5]. Using adenosine triphosphate energy, the proton pump exchanges potassium ions for hydrogen ions, pumping them across a gradient of 3,000,000:1 [5]. It is here that PPIs exert their mechanism of action and suppress gastric acid secretion.

PPIs, which are acid-activated compounds, are formulated as delayed-release prodrugs that have an enteric coating protecting the drug from degradation in the acidic environment of the stomach. Once the enteric coated product is ingested and reaches the duodenum (pH > 5.6), the enteric coating is removed and the drug is absorbed. The unprotonated PPI then travels by way of the bloodstream. Because it is unprotonated, the PPI

readily transverse cell membranes, including that of the parietal cell. Within the highly acidic environment of the parietal cell's secretory canaliculus, the PPI undergoes acid-catalyzed protonation to the active moiety, the thiophilic sulfenamide [5]. Both (R)- and (S)- enantiomers are converted to the same active moiety, which is not chiral. The highly charged, protonated, active moiety becomes trapped within the secretory canaliculus and binds covalently with cysteine residues on the proton pump, thereby rendering the pump inactive [5]. Binding to cysteine residues cys822 or cys813 in the 5th and 6th transmembrane domain of the α subunit of the proton pump is associated with inhibition of action secretion [10]. While pantoprazole binds to both of these cysteine residues involved with acid production, omeprazole, esomeprazole, rabeprazole, and lansoprazole bind to cys813 as well as to other cysteine residues within the proton pump that do not contribute to acid production (Table 1) [10,11]. Recent *in vitro* data suggest that binding characteristics may confer differences in recovery from pump inhibition, with the investigators predicting that pantoprazole would have a longer duration of action than the other PPIs [12].

Pharmacodynamic characteristics of proton pump inhibitors

As discussed previously, PPIs inhibit proton pumps that are actively secreting acid. Following a meal, only 70% to 80% of proton pumps will be activated at any given time. Therefore, only about 70% to 80% of pumps are inhibited with the first dose of a PPI. Subsequent doses will inactivate active pumps that will include those that were not inactivated the previous day, in addition to any newly regenerated pumps. Overall, approximately 3 to 4 days are required to reach a pharmacodynamic steady state and achieve maximum acid inhibition [13].

The pKa of the PPI may theoretically impact its stability and its rate of activation. Pantoprazole, with a pKa of 3.96, is activated slowly at a high pH, whereas rabeprazole, with a pKa of 5, is activated more rapidly.

Table 1
PPIs and the cysteine residues they bind

PPIs	Cysteine residues
Lansoprazole	813, 321
Rabeprazole	813, 321, 892
Omeprazole/Esomeprazole	813, 892
Pantoprazole	813, 822

Abbreviation: PPIs, proton pump inhibitors.

From Kromer W. Similarities and differences in the properties of substituted benzimidazoles: a comparison between pantoprazole and related compounds. *Digestion* 1995;56:443–54; Besancon M, Simon A, Sachs G, et al. Sites of reaction of gastric H₂ K-ATPase with extracytoplasmic thiol reagents. *J Biol Chem* 1997;272:22438–46; with permission.

Theoretically, this may lead to rabeprazole being activated outside the parietal cell. However, the clinical significance of this characteristic remains to be determined, as the sulfenamide has an exclusively short half-life. Although differences exist in activation rates in vitro at pH values of 5 and higher, one must remember that the parietal cell is the most acidic region in the body. All PPIs are rapidly activated at very acidic pH values, with no substantial differences between them (values ranging from 1.3 minutes for rabeprazole to 4.6 minutes for pantoprazole at pH 1.2) [13–15].

Pharmacokinetic characteristics of PPIs

The PPIs differ from one another in terms of pharmacokinetic characteristics such as bioavailability and metabolism. The PPIs differ in their area under the curve (AUC) values. The slow metabolism of esomeprazole makes its AUC higher relative to that of omeprazole. Two open-label, comparative crossover studies examined the pharmacokinetic profile of the 5 PPIs following single-dose administration. In the data combined from the 2 studies ($n=6$), the average AUCs for the five PPIs were as follows: pantoprazole 40 mg (15.9 ± 8.5 $\mu\text{mol}\cdot\text{h/L}$) omeprazole 20 mg (2.0 ± 1.5 $\mu\text{mol}\cdot\text{h/L}$), esomeprazole 20 mg (2.8 ± 1.8 $\mu\text{mol}\cdot\text{h/L}$), esomeprazole 40 mg (7.3 ± 3.8 $\mu\text{mol}\cdot\text{h/L}$), rabeprazole 20 mg (2.2 ± 0.7 $\mu\text{mol}\cdot\text{h/L}$), and lansoprazole 30 mg (5.2 ± 2.6 $\mu\text{mol}\cdot\text{h/L}$) ($P < 0.05$, ANOVA) [16]. Although the precise clinical relevance of these differences in AUC is unknown, it is well accepted that for a given PPI, AUC correlates with degree of acid suppression [17]. The bioavailability for both omeprazole and esomeprazole is initially low, at 30% and 64% respectively but increases over the first 5 days with repeated administration (Table 2) as a result of decreased first-pass elimination and decreased systemic clearance [18]. In contrast, the

Table 2
Pharmacokinetic parameters of oral PPIs

Parameter	Omeprazole 20 mg	Esomeprazole 40 mg	Lansoprazole 30 mg	Rabeprazole 20 mg	Pantoprazole 40 mg
Bioavailability (%)	30–40	64–90	80–85	52	77
Plasma elimination half-life (h)	0.5–1.0	1.5	1.3–1.7	1.0–2.0	1.0–1.9
Time to peak plasma concentration (h)	0.5–3.5	1.0–1.5	1.7	2.0–5.0	1.1–3.1
Protein binding (%)	95	97	97	96	98

Abbreviation: PPIs, proton pump inhibitors.

From Welage LS, Berardi RR. Evaluation of omeprazole, lansoprazole, pantoprazole and rabeprazole in the treatment of acid-related diseases. *J Am Pharm Assoc* 2000;40(1):52–62. Andersson T, Holmberg J, Rohss K, et al. Pharmacokinetics and effect on caffeine metabolism of the proton pump inhibitors, omeprazole, lansoprazole, and pantoprazole. *Br J Clin Pharmacol* 1998;45(4):369–75; Aciphex (rabeprazole) delayed-release tablets [package insert]. Teaneck, NJ: Eisai Inc., 2000; and Nexium (esomeprazole) delayed-release capsules [package insert]. Wilmington, DE: AstraZeneca LP, 2001.

bioavailabilities for pantoprazole and lansoprazole are in the range of 77% to 85% on day 1 of therapy and do not significantly change over time [19].

Food delays the absorption of pantoprazole and rabeprazole but does not significantly alter the extent of absorption (ie, AUC). In contrast, administration of esomeprazole and lansoprazole following a meal leads to a significant reduction (27% to 50%) in bioavailability (ie, prolonged time to maximum concentration) [20,21]. Studies of a food-effect with omeprazole yield results that are hard to interpret. Pilbrant et al [22], suggest that consumption of food with omeprazole delays absorption and may result in decreased bioavailability. However, Thomson et al [23] found that the $t_{\max}$ was prolonged 1.3 hours ($P < 0.0001$) in the fed versus fasting state with omeprazole 20 mg, although the reduction in AUC in the fed state did not reach significance.

Metabolism

All PPIs are metabolized to varying degrees by the cytochrome P450 (CYP450) enzyme system, specifically CYP2C19 and CYP3A4. The metabolites of PPIs are inactive and do not demonstrate acid suppressing activity [22,24]. Pantoprazole is also the only PPI that undergoes sulfation after CYP450 metabolism. The PPI metabolites are mainly excreted in the urine, with the remainder being excreted in the feces.

CYP2C19 exhibits genetic polymorphism within the population. While most individuals metabolize a PPI rapidly (ie, half-life—1 to 2 hours), a small proportion of the population are “poor” metabolizers. This trait is found in approximately 3% of whites and African Americans and 13% to 23% of Asian populations [17]. Poor metabolizers metabolize the drug slowly (ie, half-life may be up to 10 hours) and therefore have higher serum concentrations of the PPI as compared to most individuals (ie, extensive metabolizers). Because poor metabolizers have higher concentrations of the PPI (ie, greater AUC), they tend to also experience a higher degree of acid suppression compared with fast metabolizers receiving the same dose of a PPI.

PPIs also undergo stereoselective metabolism, resulting in different enantiomers being metabolized at distinct rates. In the case of omeprazole, the (R)-enantiomer is cleared rapidly, while the (S)-enantiomer is metabolized more slowly. These differences are, in fact, the rationale for the single enantiomeric product, esomeprazole, in that the (S)-enantiomer is slowly metabolized, leading to a higher AUC than that achieved when the racemate is administered. For example, Andersson et al [25] reported esomeprazole 20 mg resulted in greater inhibition of acid than did omeprazole 20 mg. Furthermore, this investigation stated that the greater degree of acid suppression with esomeprazole as compared with omeprazole was most likely explained by the fact that the AUC for esomeprazole at steady state was 70% higher than for omeprazole [26].

Tolerance

Tachyphylaxis is commonly associated with continued H₂RA use. The mechanism of this response, although not fully understood, is likely to be related to the enterochromaffin-like (ECL) cell [27]. The ECL cell synthesizes histamine in response to gastrin stimulation. Continued acid suppression, such as that seen with H₂RA use, leads to hypergastrinemia with resultant stimulation of the ECL cell and release of histamine. Since H₂RAs are competitive, reversible inhibitors of the histamine receptor, increasing doses are needed to maintain activity. PPIs, on the other hand, will not be affected by increased histamine release, as they inhibit acid secretion in its final pathway. Thus, one striking difference between PPIs and H₂RAs is that tolerance does not develop with PPIs. In contrast, studies demonstrate that tolerance develops quickly with H₂RA therapy and often cannot be overcome by increasing the dose of the H₂RA [28].

Merki and Wilder-Smith [29] studied 12 healthy volunteers in a 3-day randomized, double-blind, placebo controlled trial. Participants received intravenous doses of either ranitidine or omeprazole or placebo to maintain a target gastric pH above 4. Over the course of 72 hours, the required doses of omeprazole decreased from a mean $\pm$ SD of 235.8 ± 44 mg on day 1 to 134.0 ± 37 mg on day 3. The lower infusion rates over time was most likely because of the increasing number of pumps being inhibited by subsequent omeprazole doses. In contrast, doses of ranitidine progressively increased over the 3 days (from 502.5 ± 76 mg to 541.8 ± 25 mg), indicating tolerance [29].

Rebound acid hypersecretion

Rebound hypersecretion is another phenomenon commonly associated with H₂RAs. Although many individuals thought that rebound and secretion did not occur with PPIs, investigators now appreciate that earlier studies may have attempted to measure rebound hypersecretion too soon after PPI discontinuation. PPIs have a long duration of action, therefore, rebound hypersecretion may not be witnessed until after the pharmacodynamic effects diminish and new proton pumps are generated. Waldum et al [30] were the first to find evidence of a rebound effect in PPIs. In their study, nine patients with GERD were treated with omeprazole 40 mg daily administered for 90 days. Basal and pentagastrin stimulated acid outputs were determined at baseline and 14 days after discontinuation of omeprazole therapy. After 2 weeks without proton pump inhibition, both basal and pentagastrin-stimulated acid output increased significantly ($P < 0.05$ and $P = 0.004$, respectively) [30]. This study demonstrated that rebound hypersecretion does indeed occur in the weeks following PPI discontinuation.

Using pharmacokinetic and pharmacodynamic principles to optimize therapy

Antisecretory efficacy of PPIs is mainly dependent on the proton pump (ie, the number of active pumps in parietal cells and the regeneration of those pumps). Pharmacokinetic properties are also responsible for the antisecretory effects of PPIs, albeit to a lesser degree. Therefore, PPI therapy should be aimed at reaching the maximum number of active pumps available. Administering PPIs approximately 30 minutes before breakfast (or the first substantial meal of the day) should achieve this goal. If more antisecretory action is required, divided doses should be given, keeping this concept in mind.

The pharmacodynamic properties of PPIs also lend themselves to the treatment of patients who are intermittently noncompliant with PPI administration. Permanent inhibition of the proton pump results in the suppression of gastric acid that may continue for several days, until the generation of new pumps has restored the normal acidic environment. This longer duration of effect creates a window in which patients may still derive benefit, even while not taking their medication. This may also apply to patients who take PPIs intermittently because of waxing and waning disease or self-diagnosis.

One important, often misguided, belief is that PPIs can be used for immediate symptom relief. Although PPIs are the most potent agents for gastric acid suppression, maximal inhibition of acid secretion is not achieved until 3 to 4 days into therapy. Khoury et al [31] demonstrated this point in a randomized, open-label, postprandial acid suppression study involving 24 healthy volunteers. Patients were administered 75 or 150 mg of ranitidine or 10 or 20 mg of omeprazole postprandially after gastric pH fell below 4. Time to achieve a pH greater than 4 and the length of time pH remained above 4 were measured over a 360-minute study period. The median time to reach a pH greater than 4 for ranitidine 75 mg and 150 mg was 205 minutes and 186 minutes, respectively. The median time that pH remained above 4 was 93 minutes for ranitidine 75 mg and 144 minutes for ranitidine 150 mg. Omeprazole did not cause pH to rise above 4 during the entire study period, suggesting that a single dose of a PPI is not effective for immediate symptom relief [31]. Thus, the use of PPIs on an as-needed basis is not an effective means of inducing acid suppression or symptom relief.

Drug interactions

There are 2 types of drug interactions that can occur with PPIs. The first involves absorption-based interactions, which are an extension of the pharmacologic activity of these agents. The second type of interaction involves the CYP450 enzyme system.

Absorption-based interactions

Absorption-based or pH-dependent drug interactions can result in either increased or decreased levels of the precipitant drug. PPIs are similar to H₂RAs because they raise the gastric pH, an effect that may influence the absorption of acid or alkaline labile formulations, weak acids, weak bases, or pH-dependent formulations. The absorption of digoxin, nifedipine, aspirin, didanosine, methadone, and acid labile pancreatic enzymes is slightly increased because of decreased degradation of acid labile compounds or increased dissolution of weak acids when given with H₂RAs or PPIs. The increase in absorption, however, is generally not clinically significant [19,32,33].

In contrast, the decreased absorption of drugs that are weak bases in a high pH environment is often clinically significant. Absorption is lowered and treatment failures have occurred with agents such as ketoconazole, itraconazole, cefpodoxime, and indinavir [19,34]. Spacing the administration of these agents with PPIs will not prevent this interaction because of the long effect of proton pump inhibition. Concomitant administration of these agents and PPIs should, if possible, be avoided.

CYP450 interactions

The PPIs differ in their propensity to interact with the cytochrome P450 system. Omeprazole and esomeprazole have been shown to inhibit CYP2C19 and thus have the potential to interfere with the metabolism of other drugs, specifically diazepam, phenytoin, and (R)-warfarin, the less active isomer of warfarin [19,32,33,35]. Lansoprazole increases theophylline metabolism by way of its induction effect on CYP1A2. Rabeprazole and pantoprazole do not seem to interact with the cytochrome P450 system [36].

Summary

In conclusion, PPIs differ slightly in their PK and PD properties and in their propensity to interact with other medications. Inhibition of acid secretion is a function of proton pump inhibition, and PPIs work in a similar fashion to achieve this goal. PK/PD principles can be used to optimize PPI therapy when considering issues related to administration, such as timing of drug delivery relative to the number of active pumps and the drug's AUC.

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Managing gastroesophageal reflux disease: from pharmacology to the clinical arena

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To effectively use the medical treatment options available for the management of acid related disorders, one needs a clear understanding of the physiology governing the regulation of gastric acid secretion and the pharmacology of the potent therapeutic agents commonly used to treat these disorders. This article ties together information about: (1) the basic physiology of acid secretion, (2) the clinical presentation of acid secretory disorders, and (3) the pharmacology of proton pump inhibitors (PPIs) to provide theoretic groundwork for therapeutic approaches to managing gastroesophageal reflux disease (GERD). Indeed, many clinicians may be using these agents inappropriately, perhaps because of a lack of understanding of how the drugs work and a sense of complacency because they are prescribed so frequently.

Physiology of acid secretion

Acid secretion is mediated by 3 principal pathways: neurocrine, paracrine, and endocrine. The primary mediators involved in these pathways are acetylcholine, histamine, and gastrin, respectively [1]. Some acid is produced independently of meal stimulation. Basal acid production follows a circadian rhythm that peaks at about 2:00 to 3:00 AM and is lowest at about 7 AM [2]. Meal-stimulated acid production may be considered a multi-step process that occurs in 3 phases, which overlap to a certain extent [2]: (1) The cephalic phase, in which activation by sensory stimuli results in the release of acetylcholine from vagal postganglionic neurons located in parietal and gastrin cells; (2) The gastric phase, mediated mainly by gastrin. Three main stimuli for gastrin secretion are antral distension, protein, and most

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importantly, elevated pH (over 3.5). This phase accounts for 40% to 50% of acid secretion; and (3) The intestinal (duodenal) phase that contributes about 5% of the acid made during a meal is possibly stimulated by absorbed amino acids and gastrin.

Regardless of the route of stimulation, the final step in acid production is the active transport of hydrogen ions (H^+) mediated by the gastric enzyme H^+ , K^+ -adenosine triphosphatase (ATPase) that is located in vesicles in the parietal cell cytoplasm. This 2-subunit enzyme, once activated, becomes translocated to the parietal cell apical membrane secretory canaliculus, where it exchanges potassium ions (K^+) for H^+ across this membrane [3].

Negative feedback regulation of gastric acid secretion

Stimulation of gastrin leads to an increase in gastric acid secretion, but once the intragastric pH falls below 3.5, gastrin secretion is inhibited (Fig. 1). The decrease in intragastric pH triggers a negative feedback response mediated by the release of somatostatin, presumably in response to the activation of calcitonin gene-related peptide neurons [1]. Somatostatin cells are present in close proximity to antral gastrin cells. Thus, gastric acidity increases the release of somatostatin through a local feedback loop, which inhibits the release of gastrin. Somatostatin also seems to have direct

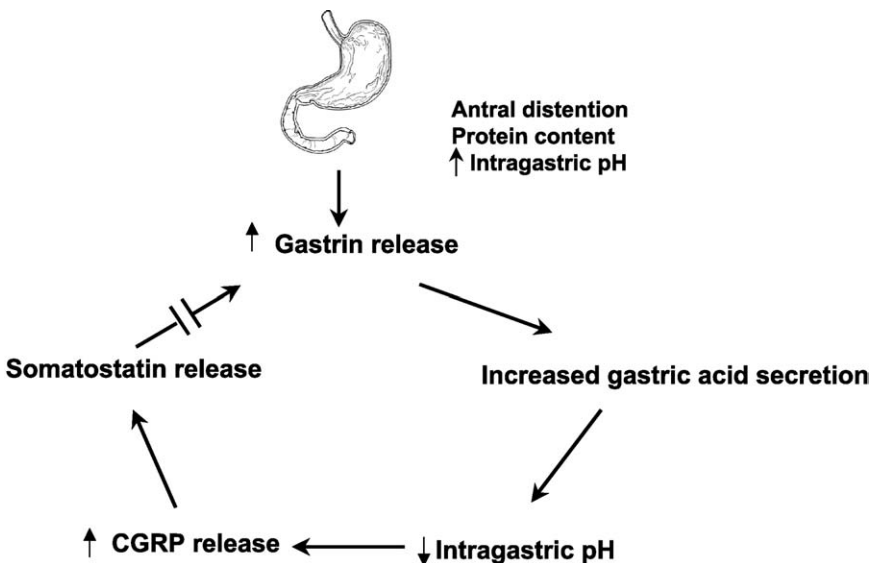


Fig. 1. Negative feedback regulation of acid secretion model where mediators downstream of gastrin release exert a negative feedback loop through somatostatin. CGRP, calcitonin gene-related peptide. (Data from Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. *Gastroenterology* 2000;118:S9–31.)

inhibitory effects on the signal transduction leading to acid production by the parietal cell, and it also may indirectly suppress acid production by inhibiting histamine release from enterochromaffin-like (ECL) cells [1]. Octreotide, the synthetic analog of somatostatin, has been found effective in suppressing acid secretion in patients with Zollinger–Ellison syndrome (ZES) [4].

Clinical presentation of acid secretory disorders

GERD

GERD is the most prevalent gastrointestinal disorder in the western world, affecting approximately 10% of the population. Dent et al [5] on behalf of the Genval Workshop stated that the definition of *GERD*:

...should be used to include all individuals who are exposed to the risk of physical complications from gastroesophageal reflux, or who experience clinically significant impairment of health related well being (quality of life) due to reflux related symptoms, after adequate reassurance of the benign nature of their symptoms.

The pathophysiologic process thought to be responsible for GERD is an abnormally long period of esophageal exposure (ie, duration) to acidic gastric contents that, in turn, relates to the severity (ie, degree) of the disease [6].

A recent American Gastroenterological Association (AGA) telephone survey was conducted in 1000 adults 18 years of age or older who suffered from heartburn at least once per week. Most of the respondents (65%) reported experiencing daytime and nighttime heartburn [7]. Patients with nighttime symptoms report greater decrements in quality of life than those with daytime symptoms in both the physical (38.94 versus 41.52; $P < 0.001$) and mental (46.78 versus 49.52; $P < 0.001$) component summaries [8]. Nocturnal reflux, indicating an increase in acid exposure, is particularly important in the pathogenesis of the disease among patients with severe esophagitis [6].

In the AGA survey, 79% of respondents reported heartburn at night, which amounts to nearly 8 in 10 of all respondents. Of those with heartburn during both the day and night, 50% described the nighttime symptoms as more troublesome, with a large proportion having trouble sleeping and, subsequently, functioning the next day. Of those affected, 71% used over-the-counter medications to control nighttime symptoms and 39% kept medications at bedside. Just under one-half of the respondents (45%) testified that current remedies did not relieve all symptoms, and slightly over half (53%) were amenable to trying something new to control their symptoms [7].

These findings suggest that GERD patients with chronic recurrent symptoms, including not only heartburn, but also dysphagia and hoarseness, represent only a small fraction of sufferers, because the most patients seem

to be experiencing mild intermittent heartburn. Meanwhile, many of these patients may not even inform their physicians about their complaints (Fig. 2). Clinicians need to be sensitive to this profile and to question patients appropriately about symptoms.

Therapeutic approach to GERD

Lifestyle measures such as smoking cessation, excess weight loss, avoidance of specific foods, elevating the head of bed 6 to 9 inches, and avoiding tight-fitting clothing are recommended for most patients at all stages of GERD. However, no large-scale clinical evidence indicates that any or all of these changes are effective treatments. Antacids are also recommended for occasional heartburn, but these medications do not cure reflux esophagitis or prevent nocturnal acid reflux. Thus, antacids are a sub-standard therapeutic choice for treatment of frequent GERD symptoms [9].

Medications frequently used to manage GERD include histamine₂-receptor antagonists (H₂RAs), such as cimetidine (Tagamet, GlaxoSmith-Kline, Research Triangle Park, NC), ranitidine (Zantac, Pfizer Consumer

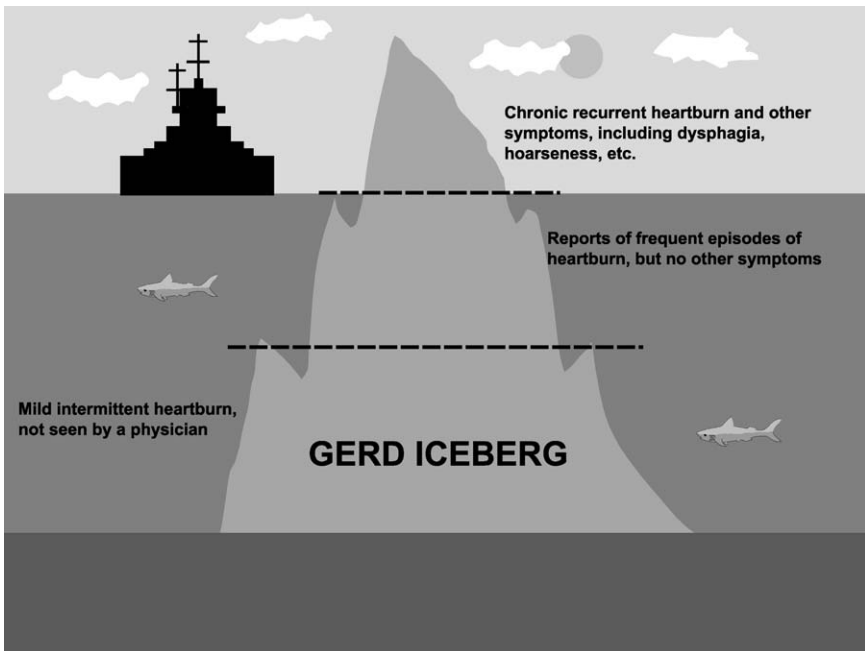


Fig. 2. In this schematic we see that patients who seek medical care for gastroesophageal reflux disease (GERD) represent the “tip of the iceberg.” Most patients do not seek treatment for this condition. (From Castell DO. Introduction of pathophysiology of gastroesophageal reflux disease. In: Castell DO, Wu WC, Ott DJ, eds. *Gastroesophageal Reflux Disease: Pathogenesis, Diagnosis, and Therapy*. New York: Futura; 1985:3–9; with permission.)

Healthcare, New York, NY), famotidine (Pepcid, Johnson & Johnson-Merck Consumer Pharmaceuticals Co., Whitehouse Station, NJ), and nizatidine (Axid, Eli Lilly, Research Triangle Park, NC); and proton pump inhibitors (PPIs), such as omeprazole (Prilosec, Astra Zeneca LP, Wilmington, DE), lansoprazole (Prevacid, TAP Pharmaceutical Products, Lake Forest, IL), pantoprazole (Protonix, Wyeth Pharmaceuticals, Philadelphia, PA), and rabeprazole (Aciphex, Eisai Inc., Teaneck, NJ). Whereas H_2 RAs selectively inhibit histamine-induced acid secretion that reduces basal acid output by 90% and nocturnal acid output by 67% [9], PPIs interfere with the final step in acid production, namely H^+ , K^+ -ATPase mediated release of hydrogen ions, and are thus considered the most potent and effective acid suppressants available [9,10].

There are currently 2 approaches to the medical management of GERD. (A) The “step up” approach calls for initiating minimum therapy with a progressive increase to higher doses or more effective agents until an adequate patient response is achieved. (B) Alternatively, the “step down” approach recommends starting with the most potent therapy and tapering down [10]. Starting with the most effective therapy seems to be the most cost-efficient approach and is, thus, recommended by many clinicians and researchers involved in GERD [5,10]. Patients who remain unresponsive to medical therapy may require more aggressive therapy in the form of endoscopic or surgical procedures.

PPIs for gastric acid suppression

PPIs are prodrugs that are converted to a thiophilic sulfenamide (active form) under acidic conditions. The pH of activation (pK_a) determines the pH at which the PPI is protonated (activated) and varies among the various PPIs. The conversion to the sulfenamide occurs when the pH of the intracellular space, known as the secretory canaliculus, is near the PPI's pK_a . The activated PPI then binds covalently to activated parietal cells, inactivating the enzyme [1,11].

Metabolic pathways

PPIs differ in terms of their metabolism. Although they all undergo hepatic metabolism, the degree to which CYP450 enzymes are involved varies among these agents (Table 1) [11]. While omeprazole, esomeprazole, rabeprazole, and pantoprazole are primarily hydroxylated by the CYP2C19 isoenzyme [12–14]; lansoprazole is primarily metabolized by the CYP3A4 enzyme subtype [15].

These differences in metabolism translate into different drug interaction profiles [11]. Differences in metabolism may also potentially impact PPI efficacy. In certain subgroups, CYP2C19 activity is influenced by genetic polymorphisms. For example, 15% to 30% of Asians are homozygotes

Table 1
Metabolism of various PPIs in relation to polymorphisms of the cytochrome p450 enzyme

PPIs	Primary (secondary) route of metabolism
Omeprazole	CYP2C19 (CYP3A4)
Esomeprazole	CYP2C19 (CYP3A4)
Lansoprazole	CYP3A4 (CYP2C19)
Rabeprazole	CYP2C19 + CYP3A4
Pantoprazole	CYP2C19 (CYP3A4)

Abbreviations: PPIs, proton pump inhibitors.

Data from Prilosec (omeprazole) delayed-release capsules [package insert]. AstraZeneca LP, Wilmington, DE, 2000; Nexium (esomeprazole) delayed-release capsules [package insert]. AstraZeneca LP, Wilmington, DE, 2001; Masa K, Hamada A, Arimori K, et al. Pharmacokinetic differences between lansoprazole enantiomers and contribution of cytochrome p450 isoforms to enantioselective metabolism of lansoprazole in dogs. Biol Pharm Bull 24:274–77, 2001; Aciphex (rabeprazole) delayed-release tablets [package insert]. Teaneck, NJ: Eisai Inc., 2000; and Protonix (pantoprazole) delayed-release tablets [package insert]. Philadelphia, PA: Wyeth Laboratories, 2001.

for the mutation that renders them slow metabolizers of CYP2C19 [16]. These metabolic differences can actually be manipulated to increase the plasma levels of PPIs metabolized by way of this pathway and thus confer a pharmacologic advantage to slow metabolizers. Furuta et al [17] demonstrated the impact of genetic polymorphism on PPI activity in a trial involving 62 patients with peptic ulcer disease (PUD) and *Helicobacter pylori* infection who were treated with omeprazole and amoxicillin. The investigators determined the genotype status of these patients. *H pylori* cure rates were 28.6, 60.0, and 100.0% for rapid, intermediate, and poor metabolizers of PPIs, respectively. Healing rates for PUD followed the same trend, suggesting that the slower the metabolism, the better the rate of eradication of *H pylori*. Similarly, Sagar et al [18] evaluated the impact of polymorphism (wild type or extensive metabolizers and poor metabolizers) on the therapeutic response to PPI therapy. By measuring serum gastrin concentration and pH in patients with endoscopically proven acid-related disease receiving omeprazole 20 mg daily for 8 days, they showed that patients who were heterozygous for extensive metabolism had higher 24-hour intragastric pH (median = 5.5) versus those who were homozygous for extensive metabolism (median = 3.1) ($P < 0.0001$).

Inhibition of acid secretion by PPIs: in vitro data

As noted earlier, PPIs represent the most potent group of acid suppressants available. Fellenius et al [19] established that the proton pump is the final pathway by measuring the effects of administered atropine, cimetidine, PPI, and control to isolated gastric rabbit glands stimulated by histamine, dibutyryl cyclic AMP (DBcAMP), and K^+ using ^{14}C -aminopyrine (^{14}C -AP) as an indicator of acid secretion (Fig. 3). The muscarinic blocker atropine exhibited no inhibitory effect compared with control.

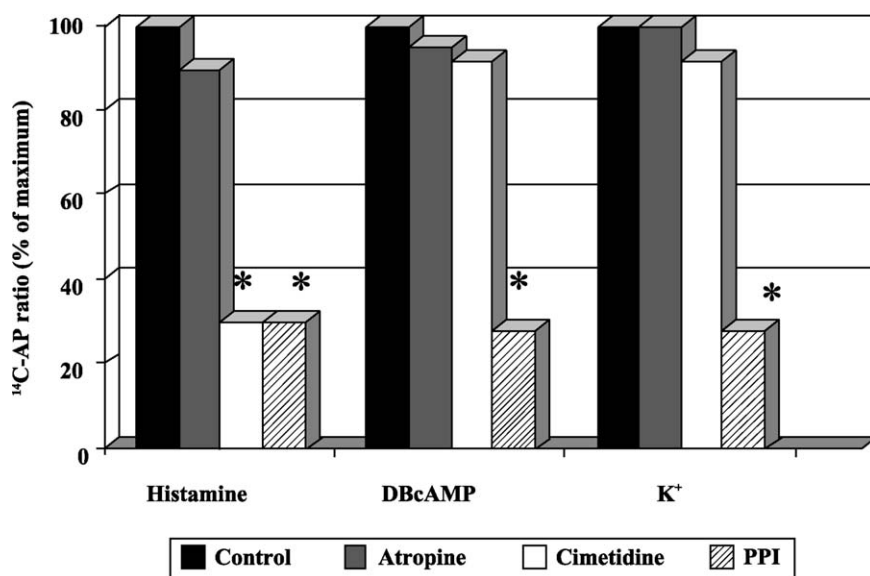


Fig. 3. The effect of atropine, cimetidine, and proton pump inhibitors (PPIs) on ^{14}C -aminopyrine (^{14}C -AP) accumulation induced by histamine (54 μM), dibutyl cyclic adenosine monophosphate (DBcAMP) (1.0 mM), and potassium ion (K^+) (0.1 M) in isolated gastric glands from rabbit mucosa. * $P < 0.05$ vs. control, Student's *t*-test. (From Fellenius E, Berglindh T, Sachs G, et al. Substituted benzimidazoles inhibit gastric acid secretion by blocking (H^+ , K^+) ATPase. *Nature* 290:159–61, 1981; with permission.)

Cimetidine appeared to inhibit histamine, but had no effect on DBcAMP, the postreceptor mediator of histamine, or K^+ , which depolarizes the apical membrane and enables H^+ ion transport. The PPI, however, was able to inhibit the effects of all the stimuli, regardless of whether they worked pre- or postreceptor. These results clearly indicate the greater efficacy of PPIs compared with H_2RAs in inhibiting acid secretion in response to all stimuli.

Inhibition of acid secretion by PPIs: clinical data

Several trials have examined the healing profiles of PPIs and H_2RAs . For example, Chiba et al [20] performed a meta-analysis to determine the comparative profile of PPIs and H_2RAs . Subjects enrolled were patients with Savary–Miller grades II to IV esophagitis, most of whom were receiving PPI or H_2RA therapy. Their study showed that PPIs healed a higher percentage of patients, overall, with erosive GERD regardless of drug dose or treatment period in comparison to H_2RAs ($83.6\% \pm 11.4\%$ vs. $51.9\% \pm 17.1\%$, respectively; $P < 0.0005$, 95% CI). Likewise, they demonstrated that PPIs achieved a healing rate of $31.7\% \pm 3.3\%$ per week after 2 weeks of therapy compared with $15.0\% \pm 6.2\%$ per week for H_2RAs . The speed of healing for PPIs declined over time, but remained higher than the

alternative treatments. The overall healing rate for PPIs ($11.7\% \pm 0.5\%$ per week; 95% CI) was faster than that for H₂RAs ($5.9\% \pm 0.2\%$ per week; 95% CI). Thus, this study clearly illustrated the ability of PPIs to relieve and heal grades II to IV esophagitis nearly twice as fast as H₂RAs.

Approaches to maximizing the effectiveness of PPIs

PPIs are most effective when taken after a prolonged fast, when large numbers of inactive (ie, nonphosphorylated) H⁺, K⁺-ATPase are present, (ie, before breakfast) (Table 2) [1]. Thus, the drugs are systemically absorbed before the meal, at which time a significant majority of proton pumps become activated. While approximately 70% of gastroenterologists recently reported that they dose PPIs before breakfast, only 30% of primary care physicians (PCPs), who write the most prescriptions for PPIs, are aware of this advantage in dosing [21]. Standard once daily administration of PPIs will be effective in 85% to 90% of patients; some refractory patients, however, will require a high dose. The addition of a second dose of PPI in those refractory patients who failed ordinary therapy should be taken before dinner. An indirect assessment of this kind of dosing adjustment occurring in practice can be seen by looking at daily average consumption (DACON) data for PPIs collected from July 2000 through January 2002 in the United States. These data suggest that pantoprazole (1.05 DAICON value for 40 mg) and rabeprazole (1.09 DAICON value) are more likely to provide the desired therapeutic results with a once daily dosing regimen than omeprazole (1.17 DAICON value for 20 mg) and lansoprazole (1.18 DAICON value for 15 mg) [22].

For control of nighttime symptoms, the addition of an H₂RA at bedtime has been suggested by some practitioners; however a consensus from the Genval Workshop indicated that there may be minimal benefit from doubling the “standard ulcer healing dose” of H₂RAs in patients with esophagitis [5]. While the addition of antacid as required (PRN) or H₂RA to the regimen has been recommended, PPIs do not constitute effective PRN

Table 2
Recommended strategies for using PPIs

- Since a steady state is not reached for a couple of days, it is often helpful to take twice daily for the first 2–3 days of therapy
- First dose should be before breakfast
- Second dose, if used, should be before dinner
- Not likely to be effective when used PRN (at time of heartburn)
- Should not be administered with H₂RA, somatostatin, or prostaglandin (concurrently)

Abbreviations: H₂RA, histamine₂-receptor antagonists; PPIs, proton pump inhibitors; PRN, as required.

Data from Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. *Gastroenterology* 118:S9–31, 2000.

therapy because they are optimally taken before the initial daily meal, when H^+ , K^+ -ATPase is being activated. If PPIs are taken at the time when heartburn symptoms become apparent, their effectiveness is reduced because the proton pumps are not maximally activated. H_2 RAs should not be taken together with PPIs because they will place the parietal cell into a nonsecretory state that markedly diminishes the antisecretory properties of the PPI [1].

Summary

GERD is a condition affecting patients throughout the 24-hour period, although the nighttime interval may require special consideration because of the pharmacologic profile of the agents used to treat GERD, and the normal physiologic processes rendering nighttime GERD particularly damaging. GERD patients should be managed with appropriate therapy proportional to the frequency and severity of their symptoms. PPIs are the most potent inhibitors of acid secretion, and with a thorough knowledge of their pharmacologic properties, clinicians can be helped in identifying strategies that can maximize the benefits of their potency (see Table 2). PPIs offer significant benefit to persons requiring longer-term therapy because they are potent agents and offer ease of dosing and favorable drug interaction and adverse effect profiles. However, it is necessary that clinicians understand the physiology and pharmacology of acid secretion to use them appropriately. Inevitably, proper therapeutic treatment demands that variables such as pharmacokinetics, ethnicity (metabolic profile), and the normal physiology of acid secretion be considered when choosing an appropriate PPI.

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