PART 1
Symptoms, Syndromes, and Scenarios
CHAPTER 1
Heartburn and noncardiac chest pain

Tiberiu Hershcovici¹ and Ronnie Fass¹,²
¹Neuroenteric Clinical Research Group, Southern Arizona VA Health Care System, Tucson, AZ, USA
²University of Arizona College of Medicine, Tucson, AZ, USA

KEY POINTS
- Heartburn is described as a retrosternal burning sensation that moves orad from behind the xiphoid bone upward to the neck and is the cardinal symptom of patients with gastroesophageal reflux disease (GERD)
- Non-cardiac chest pain (NCCP) is defined as recurring, angina-like, retrosternal chest pain of non-cardiac origin. NCCP may be a manifestation of a gastrointestinal (GI) or non-GI-related disorder. GERD is the most common esophageal cause of NCCP
- The typical reflux syndrome can be diagnosed on the basis of symptoms characteristic without diagnostic testing. Symptom response to antireflux treatment is used to further cement the diagnosis of GERD prior entertaining any invasive investigation
- Patient’s history and characteristics do not reliably distinguish between cardiac and esophageal causes of chest pain

Introduction
In this chapter, heartburn and non-cardiac chest pain are discussed in tandem for each subsection. The objective is to provide comparisons and contrasts in each category discussed. Noncardiac chest pain (NCCP) is a different symptom complex from heartburn, yet, as discussed subsequently, gastroesophageal reflux is the most common cause of NCCP. In other words, reflux may result in typical heartburn or, in more atypical discomfort, NCCP. Heartburn is the cardinal symptom of patients with gastroesophageal reflux disease (GERD). In patients with heartburn as the predominant symptom, GERD is the likely cause in at least 75% of individuals [1]. In a US population-based study, the prevalence of at least one episode of heartburn over 1 year was 42% and weekly episodes of heartburn was 20% [2]. However, the majority of patients with heartburn will never seek medical attention and treat their symptom with over-the-counter medications.

NCCP is defined as recurrent chest pain that is indistinguishable from ischemic heart pain after a reasonable work-up has excluded a cardiac cause. Sir William Osler, in 1892, described “esophagismus,” or pain secondary to spasms of the esophagus, which may have initiated the clinical concept that esophageal pain can mimic cardiac angina. It has been estimated that the US prevalence of NCCP is 23% [2]. NCCP is a benign condition, although the associated morbidity, and the economic burden resulting from inability to work and healthcare utilization, are significant.

What is it?
Heartburn
Heartburn is described as a retrosternal burning sensation that moves orad from behind the xiphoid bone upward to the neck. It most often occurs within 1 to 2 hours after a meal, particularly a large volume or fatty meal, exacerbated by bending over or assuming the recumbent position, and is typically relieved by antacids.

Heartburn may be associated with other GERD symptoms such as water brash and sour or bitter taste in the mouth. Additionally, heartburn often disturbs the sleep of affected individuals and significantly impairs patients’ quality of life. Neither heartburn frequency nor severity is predictive of the presence or absence of erosive esophagitis in the individual patient [3,4].

The word “heartburn” does not translate literally between most languages. Consequently, different words for the same condition are used by patients and physicians in many countries [5]. It is important during history-taking to ensure that the patient and physician alike have similar understanding of the term “heartburn”.

NCCP Patients may report squeezing or burning substernal chest pain that may radiate to the back, neck, arms, and jaws. There are many causes for NCCP, which are not limited to the esophagus, and these include musculoskeletal, pulmonary, cardiovascular, infectious, drug-related, and psychological as well as other gastrointestinal disorders (Table 1.1) [6].

Rome III Criteria do not specifically address NCCP but rather a subset of patients with NCCP termed “functional chest pain of presumed esophageal origin” [7]. These are patients with recurrent episodes of substernal chest pain of visceral quality with no apparent explanation using currently available tests. As with all other functional esophageal disorders, GERD and esophageal dysmotility should be ruled out before the diagnosis is established.

A patient’s history and characteristics do not reliably distinguish between cardiac and esophageal causes of chest pain [8]. Therefore, all patients who present with chest pain, regardless of its character, should initially undergo a proper cardiac evaluation before being referred to a gastroenterologist. The cardiologist’s first priority is to exclude any acute life-threatening...
The incidence and prevalence of NCCP have scarcely been studied. Several population-based studies have demonstrated that the prevalence of NCCP ranged between 20 and 25% [2,12]. It appears that NCCP is a very common disorder, regardless of gender or ethnicity. While most tertiary referral-based studies report a female predominance, a population-
based study showed no gender predilection [2]. However, women with NCCP tend to consult healthcare providers more often than men and are more likely to present to hospital emergency departments [13,14]. Whilst there are no gender differences regarding chest pain intensity, women tend to use terms like “burning” and “frightening” more often than men [15,16].

Information about risk factors that are associated with NCCP is scarce. Patients with GERD-related NCCP are likely to share the same risk factors as the general GERD population (Table 1.2). Otherwise, psychological factors such as anxiety, panic disorder, major depression, and somatoform disorders have all been demonstrated to be closely associated with NCCP.

Pathophysiology

Pathophysiology of heartburn

The mechanisms responsible for the development of heartburn remain poorly understood. It has been postulated that sensitization of esophageal chemoreceptors, either directly by exposure to acidic or weakly acidic reflux or indirectly through release of inflammatory mediators, is responsible for the generation of heartburn [17]. Both animal models and human studies have demonstrated dilatation of intercellular spaces in acidic or weakly acidic exposed tissues, and this might permit an increase in paracellular permeability, allowing acid to reach sensory nerve endings that are located within the esophageal mucosa [18]. However, this prevailing hypothesis does not fully explain symptoms in patients with heartburn, primarily because more than 95% of acid reflux events are never perceived by patients with GERD.

Several luminal mechanisms have been identified to facilitate perception of a reflux event: proximal migration, lower pH nadir, larger pH drops, larger volume and longer acid clearance time, and preceding higher esophageal cumulative acid exposure time. Overall, acidic reflux (pH < 4) is more commonly the cause of heartburn than nonacidic reflux (pH ≥ 4). Central factors such as psychological comorbidity, anxiety and poor sleep have all been demonstrated to also facilitate perception of reflux events.

Triggers

Physiologically, the most common trigger for GERD symptoms is a meal, particularly if it contains a large amount of fat. However, the mechanisms by which luminal fat and possibly other nutrients modulate the perception of esophageal stimuli remain to be elucidated. Fat causes a reduction in lower esophageal sphincter (LES) basal pressure and delay in gastric emptying. Additionally, fat may also exacerbate symptoms of GERD by heightening perception of intraesophageal acid. Enteric hormones such as cholecystokinin or other gut neurotransmitters and enzymes are believed to mediate the effect of fat on the lower esophageal sphincter and sensory afferents. Furthermore, non-reflux-related intraesophageal stimuli may also lead to the development of heartburn. For example, esophageal balloon distensions have been shown to induce heartburn symptoms in a subset of normal subjects and reproduce typical heartburn in half of the patients with GERD [19], suggesting that mechanical distension of the esophagus per se, may also result in heartburn even in the absence of actual acid reflux.

This suggests that heartburn is not stimulus specific, and that non-reflux-related intraesophageal events may lead to this type of symptom as well. These poorly understood events are likely the causes of functional heartburn. Simultaneous intraesophageal impedance and pH measurements have demonstrated that nonacidic reflux (weakly acidic or weakly alkaline that is a pure liquid or a mixture of gas and liquid) also plays a role in the pathophysiology of heartburn, more commonly in patients who failed proton pump inhibitor (PPI) treatment. Central factors, such as psychological comorbidity (anxiety, depression, etc.), stress, and poor sleep have all been shown to modulate esophageal sensitization and thus cause patients to perceive low-intensity esophageal stimuli as being painful (Figure 1.1).

Pathophysiology of NCCP

GERD is the most common esophageal cause of NCCP, as abnormal 24-hour esophageal pH monitoring and/or positive endoscopic findings are present in up to 60% of the patients [20]. This is further supported by the efficacy of acid suppressive therapy in relieving patients’ symptoms and the reproducibility of chest pain by esophageal acid perfusion studies. Acid perfusion into the distal esophagus has been demonstrated to alter the perception of painful stimuli in the distal

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**Figure 1.1** The “Fass & Tougas” conceptual model for esophageal symptom generation in nonerosive reflux disease (NERD). Proposed causes of heartburn – interactions between intraesophageal stimuli and the brain. (Reproduced from Fass R, Tougas G. Functional heartburn – the stimulus, the pain and the brain. Gut. 2002;51:885–892, with permission from BMJ Publishing Group Ltd.)
portion of the esophagus (primary hyperalgesia) as well as the proximal portion of the esophagus (secondary hyperalgesia) in patients with NCCP.

**Motility**
The increased prevalence of esophageal motility disorders in patients with NCCP suggests that chest pain may also result from stimulation of mechanoreceptors within the esophageal wall. Approximately 30% of patients with NCCP demonstrate some type of esophageal dysmotility. The motility abnormalities include diffuse esophageal spasm, nutcracker esophagus, achalasia, nonspecific esophageal motor disorder, hypertensive and hypotensive lower esophageal sphincter [21]. However, there is a poor temporal correlation between esophageal motility disorders and episodes of chest pain, suggesting that the presence of esophageal dysmotility during esophageal manometry may be a marker for an underlying motor disorder rather than the direct cause responsible for the patient’s symptoms. Furthermore, in NCCP patients who underwent simultaneous esophageal manometry and pH testing, chest pain was more commonly associated with acid reflux events than motility abnormalities [22]. High-frequency intraesophageal ultrasonography has revealed a strong correlation between spontaneous and edrophonium-induced chest pain and sustained esophageal contractions (SECs). These contractions are caused by shortening of the longitudinal muscle of the esophagus and thus are not readily detected by traditional esophageal manometry. SECs have been suggested to be the motor corollary for esophageal chest pain. However, it is still unclear whether SECs are the direct cause of chest pain or simply an epiphenomenon.

**Esophageal hypersensitivity**
Cerebral-evoked potential studies in patients with NCCP using esophageal balloon distention protocols demonstrated abnormal cerebral processing of esophageal stimuli. The recorded cerebral-evoked potentials (marker of central nociceptive processing) were of lower quality and amplitude and with longer latency compared with those of control subjects. Peripheral and central sensitization of esophageal sensory afferents and spinal cord neurons has been suggested to cause increased responses to innocuous and noxious intraesophageal stimuli. It has been postulated that inflammation or other injuries to the esophageal mucosa set off a cascade of events that leads to the up-regulation of receptors and induces the development of esophageal hypersensitivity through peripheral and central sensitization. Patients with NCCP appear to have decreased thresholds for sensation, discomfort and pain for various esophageal stimulations.

**Psychological factors**
Up to 75% of NCCP patients have been observed to have an increased association with psychological disorders, including depression, anxiety, somatization and panic disorder [23]. These patients often report chest pain or tightness under stress, possibly due to sympathetic nervous system arousal. Studies have been inconsistent when the frequency of panic disorder, anxiety, and depression were compared between NCCP patients and those with coronary artery disease (CAD). Some studies reported increase in the prevalence of psychological disorders in NCCP patients, while others found no significant difference between the two groups [24,25].

For many NCCP patients, psychological co-morbidity may contribute to the emergence of chest pain by heightening the perception of intraesophageal events [26]. In addition, psychological comorbidity may affect patients’ personal attitude towards the disease, response to treatment, and relapse.

**Causes/differential diagnosis**
In addition to GERD, functional heartburn, eosinophilic esophagitis, achalasia, peptic ulcer disease or esophageal/gastric malignancy can lead to heartburn symptoms. Furthermore, a sudden and isolated attack of heartburn may be caused by pill-induced esophageal injury, or even caustic injury to the esophageal mucosa. The most important diagnosis to be excluded during the evaluation of a patient with chest pain is ischemic heart disease (Figure 1.2). The potential causes of NCCP (besides esophageal disorders) include gastric and gallbladder disorders, musculoskeletal abnormalities, pulmonary and pericardial disorders, and psychiatric abnormalities (primarily panic disorder) (Table 1.1).

**Symptom complexes**
Heartburn, as the predominant symptom, is highly specific for the diagnosis of GERD. However, other symptoms are also commonly found in patients with GERD and are outlined below.

**Regurgitation**
Regurgitation is defined as the perception of flow of refluxed gastric content into the mouth or hypopharynx [5]. Although regurgitation is less prevalent than heartburn in patients with GERD, in some it may be the sole presentation of the disorder. Regurgitation is particularly severe at night, when patients are recumbent, or when bending over. Among patients with regurgitation, abnormally low LES basal pressure, gastroparesis, and esophagitis are more common. For these reasons regurgitation appears to be more difficult to control medically than heartburn. It should be emphasized that regurgitation may also be a presentation of a pharyngeal pouch, esophageal obstruction, or gastric outlet obstruction.

**Water brash**
Water brash is the sudden filling of the mouth with clear, slightly salty fluid due to secretions of the salivary glands in response to intraesophageal acid reflux events.
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Presence should raise suspicion for an alternative esophageal cause, especially infections (Candida, herpes) or corrosive (pills) induced injury. A milder variant is a sensation that the patient can feel solids and liquids passing down the esophagus without pain.

Diagnosis

The typical reflux syndrome can be diagnosed on the basis of the characteristic symptoms without diagnostic testing. Symptom response to antireflux treatment should be used to further cement the diagnosis of GERD prior entertaining any invasive investigation [5]. Tools that are currently available for diagnosing GERD include the PPI test, barium esophagram, upper endoscopy, esophageal pH monitoring, and multichannel intraluminal impedance with pH sensor (MII-pH). In contrast, clinical history does not help to distinguish esophageal from cardiac chest pain. Both esophageal and cardiac chest pain can produce a pressure-like squeezing or burning substernal chest pain. Both may improve with nitrates or calcium channel blockers. Additionally, both may be exertional in nature. The presence of heartburn, regurgitation and pain relieved with antacids may suggest an esophageal etiology in patients with NCCP.

**Globus sensation**

Globus is the constant sensation of a lump or fullness in the throat, which improves transiently during swallowing. Globus usually occurs in the absence of dysphagia.

**Dysphagia**

The term dysphagia refers to the sensation that food is being hindered in its normal passage from the oral cavity to the stomach. In patients with GERD, sensation of dysphagia may be perceived below the breast bone anywhere up to the sternal notch. The latter is commonly referred sensation from a lesion in the distal part of the esophagus. Dysphagia may be referred cephalad to the site of the obstruction but never caudal. Dysphagia in a patient with heartburn may suggest the presence of erosive esophagitis, peptic stricture, ulceration, or malignant tumor of the esophagus.

**Dyspepsia**

Many patients with predominantly heartburn symptoms may also complain of dyspeptic symptoms, such as epigastric pain or discomfort, bloating, early satiety, nausea, and even vomiting. These symptoms are reported at a similar frequency by patients with or without esophageal mucosal injury. It is unclear whether these symptoms represent an overlap with functional dyspepsia or are part of the GERD symptom complex.

**Odynophagia**

Odynophagia is pain during swallowing. It occurs occasionally in patients with severe erosive esophagitis. However its presence should raise suspicion for an alternative esophageal cause, especially infections (Candida, herpes) or corrosive (pills) induced injury. A milder variant is a sensation that the patient can feel solids and liquids passing down the esophagus without pain.

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**The proton pump inhibitor (PPI) test**

**GERD** The PPI test is a simple, noninvasive diagnostic tool for GERD that is widely available to community-based physicians [27]. The test is a short course (1–4 weeks) of high-dose
PPI given two to three times daily for the diagnosis of GERD. If symptoms disappear or markedly improve with therapy and then return when medication is discontinued, then GERD could be assumed as the diagnosis, and no further testing is required. Several trials in patients with typical symptoms of GERD have demonstrated that the sensitivity of the PPI test ranges from 66% to 89% and the specificity from 35% to 73%. However, there is still no consensus about the desired level of symptom response (cut-off level), optimal dose, frequency, or duration of the PPI test for GERD. In the absence of warning signs, the PPI test is a safe and reasonable first step in diagnosing and treating GERD.

**NCCP** The PPI test is recommended for diagnosing GERD-related NCCP prior to any invasive or noninvasive testing. In a meta-analysis, the overall sensitivity, specificity, and diagnostic odds ratio for the PPI test vs. endoscopy and 24-hour esophageal pH monitoring in diagnosing GERD in NCCP patients were 80%, 74% and 19.35, respectively [28]. The PPI test is a cost-effective diagnostic strategy for GERD-related NCCP primarily due to significant reduction in the usage of invasive diagnostic tools [29].

**Barium esophagram**

Barium esophagram should not serve as the primary test for the evaluation of patients with heartburn. The test is considered positive for GERD diagnosis if reflux is witnessed during examination or if there is morphologic evidence of reflux esophagitis. However, the test has a low sensitivity and specificity for the diagnosis of GERD. The presence of barium reflux does not necessarily denote GERD, as 20% of normal subjects may demonstrate similar abnormality during esophagram. Barium esophagram may be helpful and should be considered as the first diagnostic tool in patients with GERD who develop dysphagia. In patients with NCCP without alarm symptoms, barium esophagram has never been shown to be of value.

**Upper endoscopy**

**GERD** According to most guidelines and consensus statements, upper endoscopy is recommended for GERD patients who do not respond to therapy, those with recurrent or alarm symptoms and to exclude Barrett’s esophagus [30]. Endoscopy is the gold standard for diagnosing erosive esophagitis, Barrett’s esophagus, peptic stricture, and adenocarcinoma of the esophagus. Furthermore, the test allows assessment of the degree of esophageal mucosal injury, provides an opportunity for histopathologic diagnosis, and allows assessment of response to antireflux therapy. Upper endoscopy has a low sensitivity for diagnosing GERD, because 50–70% of reflux patients do not demonstrate any evidence of esophageal mucosal injury. The clinical roles of new endoscopic technologies including narrow band imaging, chromoendoscopy, confocal endomicroscopy, magnification and high-resolution endoscopy, capsule endoscopy and ultrathin unsedated transnasal endoscopy are under investigation. However, early studies have suggested that these techniques may increase the sensitivity for diagnosing GERD in patients with normal endoscopy.

**NCCP** Upper endoscopy in the absence of alarm symptoms, while commonly performed in clinical practice, has been shown to provide little useful information in the initial evaluation of NCCP. In the largest study thus far addressing the role of upper endoscopy in NCCP, 44% of the NCCP patients had a normal endoscopy. Endoscopic findings in those with abnormal endoscopy were GERD-related and included hiatal hernia (28.6%), erosive esophagitis (19.4%), Barrett’s esophagus (4.4%), esophageal stricture or stenosis (3.6%), and peptic ulcer (2%) [31].

**pH testing**

**GERD** Twenty-four-hour esophageal pH monitoring or the wireless pH capsule are sensitive tests for the diagnosis of GERD but should not be considered as the gold standard. The wireless pH capsule has extended the duration of the test to 48 hours and has somewhat improved its sensitivity. The original role of esophageal pH testing was to objectively diagnose GERD in patients with heartburn but normal endoscopy. However the empiric use of PPIs in this group of patients has altered its role. Presently, pH monitoring use is limited to patients who have not responded to at least a double dose of PPI, patients with normal endoscopy who are candidates for antireflux surgery, and patients who have had antireflux surgery but report recurrence of GERD symptoms. In patients with atypical or extraesophageal manifestations of GERD, pH monitoring should be performed in those who have failed treatment on at least double-dose PPI given over a period of at least 3 months (the test is done on treatment) [30]. The pH test may be uncomfortable to patients (because of the pH probe), costly, and may not be readily available to community-based physicians.

**NCCP** The use of 24-hour esophageal pH monitoring in NCCP has been transformed in the past decade, primarily owing to increased usage of empiric PPI therapy or the PPI test. Presently, the test has been reserved for NCCP patients in whom objective evidence of GERD is required (off therapy) or in whom response to a therapeutic PPI trial is equivocal or negative (on therapy). In patients with NCCP, 24-hour esophageal pH monitoring on therapy has a therapeutic predictive value in addition to its diagnostic merit. Patients with greater esophageal acid exposure appear to have a greater response to antireflux treatment [32]. Extending pH monitoring to 48 hours by using the wireless pH capsule improves detection of reflux-associated chest pain symptoms.

The sensitivity of pH monitoring in NCCP is unknown, but approximately 50–60% of patients with untreated NCCP demonstrated increased distal esophageal acid exposure and/or a positive symptom index alone.
Esophageal manometry
GERD Esophageal manometry should not be used to establish the diagnosis of GERD. It may identify manometric abnormalities commonly found in GERD (for example ineffective esophageal motility and reduced LES basal pressure). However, these findings are absent in the majority of GERD patients. The role of esophageal manometry in patients with reflux symptoms is primarily to assist in the placement of a pH measuring device and to exclude achalasia.

NCCP Esophageal motility abnormalities have been identified in 30% of patients with NCCP. Hypotensive lower esophageal sphincter (61%) is the most common motility abnormality diagnosed, followed by hypertensive lower esophageal sphincter, nonspecific esophageal motor disorder, and nutcracker esophagus (10% each). Achalasia and diffuse esophageal spasm are very uncommon in NCCP [21]. The presence of a motility abnormality during esophageal manometry is rarely associated with reports of chest pain, raising a question about the exact relationship between the aforementioned motility findings and chest pain.

Multichannel intraluminal impedance (MII)
The MII + pH sensor can determine the nature (liquid, gas, or mixed), proximal extent, and acidity of a reflux event. The technique has been shown to be primarily useful in identifying weakly acid or alkaline reflux in GERD patients who failed PPI twice daily [33]. MII + pH sensor has not been evaluated in NCCP patients, and thus its value in this condition remains unknown.

Provocative tests
Provocative tests for NCCP include the Bernstein or acid perfusion test (reproducing chest pain by infusing acid into the mid esophagus), the Tension test (reproducing chest pain by inducing augmented esophageal contractions using intravenous edrophonium, an acetylcholine esterase antagonist), and the balloon distention test (reproducing chest pain by using graded esophageal balloon distensions). At present, provocative tests are rarely used in clinical practice, due to low sensitivity, discomfort and potential adverse events.

Future directions
Despite current advances in the understanding of the pathophysiology, diagnosis, and treatment of patients with heartburn and NCCP, the exact underlying mechanisms for these symptoms remain poorly understood. The lack of association between symptom severity and anatomical as well as pathophysiological findings remains perplexing. Future investigation should bring further understanding of the peripheral and central factors that may modulate perception of heartburn or NCCP. New or refined imaging techniques will be introduced and their value in diagnosing GERD will be determined. Further focus of investigation will be on non reflux causes for heartburn and the underlying mechanisms for functional chest pain. The value of multichannel intraluminal impedance as well as other new diagnostic techniques will be assessed in special GERD groups and patients with NCCP.

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