

# Chest pain of cardiac and noncardiac origin

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## Abstract

Chest pain is one of the most common symptoms driving patients to a physician's office or the hospital's emergency department. In approximately half of the cases, chest pain is of cardiac origin, either ischemic cardiac or nonischemic cardiac disease. The other half is due to noncardiac causes, primarily esophageal disorder. Pain from either origin may occur in the same patient. In addition, psychological and psychiatric factors play a significant role in the perception and severity of the chest pain, irrespective of its cause. Chest pain of ischemic cardiac disease is called *angina pectoris*. Stable angina may be the prelude of ischemic cardiac disease; and for this reason, it is essential to ensure a correct diagnosis. In most cases, further testing, such as exercise testing and angiography, should be considered. The more severe form of chest pain, unstable angina, also requires a firm diagnosis because it indicates severe coronary disease and is the earliest manifestation of acute myocardial infarction. Once a diagnosis of stable or unstable angina is established, and if a decision is made not to use invasive therapy, such as coronary bypass, percutaneous transluminal coronary angioplasty, or stent insertion, effective medical treatment of associated cardiac risk factors is a must. Acute myocardial infarction occurring after a diagnosis of angina greatly increases the risk of subsequent death. Chest pain in women warrants added attention because women underestimate their likelihood to have coronary heart disease. A factor that complicates the clinical assessment of patients with chest pain (both cardiac and noncardiac in origin) is the relatively common presence of psychological and psychiatric conditions such as depression or panic disorder. These factors have been found to cause or worsen chest pain; but unfortunately, they may not be easily detected. Noncardiac chest pain represents the remaining half of all cases of chest pain. Although there are a number of causes, gastroesophageal disorders are by far the most prevalent, especially gastroesophageal reflux disease. Fortunately, this disease can be diagnosed and treated effectively by proton-pump inhibitors. The other types of non-gastroesophageal reflux disease-related noncardiac chest pain are more difficult to diagnose and treat. In conclusion, the cause of chest pain must be accurately diagnosed; and treatment must be pursued according to the cause, especially if the cause is of cardiac origin.

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## 1. Introduction

Although chest pain seems to have been mentioned by Erasistratus of Chios (ca 304-ca 250 BC), William Heberden [1] provided the first medical description of chest pain, which he called *angina pectoris*, in July 1768. It is significant, however, that Heberden appeared to have “no inkling of the fact that these chest pangs had any connection with the heart, much less with the coronary artery” [2].

The relationship between angina pectoris and heart and/or coronary diseases was shown in 1809 by Allen Burns [3],

who championed the view that “heart pain is an insufficient blood supply.” In 1950, however, D Rhodes Allison [4] showed that “mistakes are frequent and 16% of patients referred to hospitals with a diagnosis of angina are found in fact to be suffering from pain arising in the chest wall only, with no evidence whatsoever of underlying heart disease.” Today, it is uniformly recognized that chest pain is one of the symptoms most frequently driving patients to their primary care physician's office or to hospital emergency services. The US National Center for Health Statistics reported that, in 2002, chest pain prompted 11.2 million visits to physicians' offices [5]. In 2004, chest pain brought 6 million patients to emergency departments and was the second most common reason for emergency department visits [6] (behind only stomach and abdominal pain and cramps).

Most patients who visit physicians' offices or emergency services for chest pain are driven by fear of a myocardial infarction, but many such patients are actually free of heart

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disease. It has been reported that in 50% of patients referred to cardiologists, chest pain was noncardiac in origin [7]. Another study [8] reported the distribution of diagnoses among 10 689 patients presenting with chest pain at the emergency departments of 10 hospitals over a 7-month period. A little more than half, 55.3%, of the patients had chest pain of noncardiac origin. Among the 44.7% whose chest pain was of cardiac origin, 23.7% of the patients had ischemic cardiac disease and 21.0% had nonischemic cardiac disease.

In this review, chest pain due to ischemic cardiac disease (especially coronary heart disease) and other cardiovascular disorders will be discussed, as well as chest pain of noncardiac origin. The occurrence of chest pain in women will also be addressed, as its presentation and impact are often different from those in men. The role of psychological and psychiatric factors will be evaluated and discussed, as it has been shown that depression, panic disorders, and other such manifestations may follow the occurrence of chest pain and even in some instances trigger or worsen the chest pain.

Although chest pain most commonly occurs in middle-aged or older adults, it must be noted that chest pain of cardiac or noncardiac origin can also occur in children and adolescents [9]; it requires careful and extensive examination. If a specific cause can be identified, the corresponding therapeutic course must be followed. However, in many instances, “the lack of significant pathology ... makes reassurance (of the parents and patients) the mainstream therapy.”

## 2. Chest pain of cardiovascular origin

### 2.1. Chest pain of coronary heart disease (ischemic) origin

Although chest pain can be caused by a number of cardiovascular disorders, chest pain due to coronary heart disease, called *angina pectoris*, is by far the most common. Coronary heart disease is a dominant public health problem, as shown by the 2005 prevalence of self-reported coronary heart disease in Table 1. In the United States in 2006, 445 687 [10] deaths were attributed to coronary heart disease. Many of these deaths occurred suddenly in ambulatory patients. Because most patients with myocardial infarction have a history of angina, it is important to pay attention to and correctly diagnose this form of chest pain. Furthermore, information about the high prevalence of coronary heart disease and its association with chest pain and myocardial infarction is widely disseminated to the public, which explains (and justifies) the

fear of myocardial infarction in patients suffering from chest pain, irrespective of the cause.

Angina pectoris is clinically divided into “stable angina” and “unstable angina.” Stable angina is pain that comes on slowly with activity or stress; it goes away rapidly with rest or medication, but returns with new activity or stress. This form of angina is usually detected and treated by primary care physicians, especially new cases. The frequency of stable angina episodes varies greatly among patients; but the higher the frequency, the greater the patient’s physical limitation and the poorer the quality of life [11]. Unstable angina is pain that develops suddenly, sometimes without apparent cause such as during sleep, and progressively worsens. Unstable angina signals an increase in risk of an acute myocardial infarction, and most myocardial infarctions are preceded by unstable angina.

Although not all chest pain is due to ischemic cardiac disease, missing this diagnosis or failing to institute proper treatment can be deadly for patients. In one large study [8], 41 patients with ischemic cardiac disease were mistakenly discharged from the hospital; their mortality 30 days after discharge was significantly higher than that in the patients who were correctly hospitalized (risk adjusted ratio of 1.9). This observation demonstrates the risk associated with not identifying the correct cause of chest pain [12–15]. In this regard, hospitalization must be carefully considered to obtain a correct evaluation of a patient’s chest pain and distinguish between all the potential causes. Noncardiac chest pain (NCCP) can occur in a patient with coronary artery disease, and vice versa [13]. In addition, physicians more frequently fail to make a correct diagnosis in, and to hospitalize, black patients with chest pain due to ischemic disease compared with white patients (5.8% vs 1.2%) [8].

A number of studies have investigated the accuracy of the bedside findings to establish a correct diagnosis. One study [12], based on 64 English-language publications that included thousands of patients with stable angina or unstable angina with myocardial infarction, concluded that the description of the patient’s pain is the most compelling predictor of typical stable angina (ie, relief of pain within 10 minutes of rest or after taking nitroglycerine). The electrocardiogram (ECG) findings were found to be the most reliable predictor of unstable angina and myocardial infarction, especially the presence of ST-segment elevation greater than 1 mm. The reality, however, is that patient history, current symptoms, physical examination, ECG findings (ST-segment elevation or depression, inverted T wave, and new Q waves), biomarkers (troponin I, creatine kinase–MB), angiography, and computed tomography angiography all have a role in achieving an accurate diagnosis [15–17]; but the selection of test(s) performed depends on the clinical manifestations of the patient and other external conditions.

As mentioned earlier, angina may be the first indication of coronary heart disease and, in many patients, the early manifestation of ischemic cardiac disease and myocardial

Table 1  
 US 2005 prevalence of self-reported coronary heart disease

Diagnosis	n (in millions)	%
Myocardial infarction	8.874	4.0
Angina	9.762	4.4
Both myocardial infarction and angina	14.421	6.5

Percentage of 221.86 million: age >18 years, men and women. Based on *MMWR* (2007;56[06]:113–118) and US Census Bureau, Division of Population.

infarction. Buckley and Murphy [18] compared the prognosis of coronary artery disease patients with angina alone to those who had an acute myocardial infarction. Although patients with angina alone did slightly better, the difference was not significant; and the authors concluded that the “prognosis to death or cardiac outcomes for patients with angina alone was similar to those with previous acute myocardial infarction and/or revascularization, while health status was poorer.” Another study by Buckley et al [19], based on a primary care incident cohort, underscores the risk of subsequent negative outcomes (myocardial infarction, cardiac and all-cause mortality) in the 5 years following newly diagnosed angina. It found that this risk is greater in men and is highly related to age, obesity, smoking, and concomitant medical conditions such as hypertension and diabetes. Invasive therapeutic interventions (coronary grafting, percutaneous transluminal coronary angioplasty, and stent insertion as needed) did not significantly reduce the 5-year risk. Other investigators [20] have shown that 1 year after the initial diagnosis of angina, there was no difference in the frequency of chest pain between patients receiving optimal medical therapy alone and those treated with the same medical therapy plus percutaneous coronary intervention. After 4 to 6 years of follow-up, there was no difference in death or myocardial infarction rates between the 2 groups, although a number of patients in the medical therapy group required a percutaneous coronary intervention, including stent insertion as needed.

## *2.2. Chest pain, angina, and coronary heart disease in women*

The evaluation of chest pain in women is as important as in men. However, there are many reports showing that less attention is paid to chest pain in women; and therefore, they may be less thoroughly treated. Although chest pain may have more varied characteristics in women than in men, fewer angiographic verifications of its cause are performed. It is therefore essential that the evaluating physician carefully look for associated risk factors and conditions, such as diabetes, which may be predictors of coronary heart disease [21].

Multiple studies have provided data on the incidence and prevalence of angina among women, data that contradict the traditional belief that coronary heart disease is a “men’s disease” [8]. In fact, we now know that the incidence and prevalence of angina and myocardial infarction are the same in men and women. A study by Hemingway et al [22] concluded that, in the general population, women and men have a similar incidence of angina; however, fatal coronary diseases, nonfatal myocardial infarction, and all-cause mortality were higher in men than in women. A follow-up study [23] reported data from 31 countries and confirmed earlier observations made in single countries that “women have a similar, or slightly higher prevalence of angina than men.” A wide range of myocardial infarction

death rates were reported among the 31 countries; but in all cases, mortality was higher in men than in women. The data from this study are very similar to those reported in another single-country study of patients registered in primary care practices [19].

A study of 136 247 patients pooled from 11 clinical trials compared a variety of factors between men and women including 30-day mortality rates from acute coronary syndromes [24]. Mortality in women was 9.6% compared with 5.3% in men; but after adjusting for clinical characteristics of the patients, the mortality differences between men and women became insignificant (odds ratio, 1.06). However, the differences in mortality remained significant when the patients were grouped by ECG findings (ie, ST-segment elevation vs no ST-segment elevation) and also in patients showing only unstable angina. After further adjustment based on angiographic findings (ie, number of diseased vessels), the 30-day mortality was lower in women than in men (odds ratio, 0.96), except in patients presenting ST-segment elevation. The authors of the study pointed out that clinical presentation, as well as differences found in specific examinations (ECG, angiography), impacts markedly on the prognosis of men and women with acute coronary syndromes, including unstable angina. In this study, both men and women had been participants in clinical trials; and thus, the most optimal treatments had been given equally to both sexes.

In other situations, however, treatments differ significantly between the sexes. As indicated, stable angina alone cannot always be related to coronary heart disease on the basis of chest pain; yet one study [25] showed that men were much more likely to receive the necessary follow-up tests (both noninvasive and invasive procedures) to confirm a diagnosis. Furthermore, once the diagnosis was ascertained, women were also significantly less likely to receive optimal medical therapy recommended by guidelines. During the follow-up period, the hazard ratio of death from myocardial infarction for women was 2.7 ( $P = .01$ ). A 2009 review of many studies on the therapeutic approach to stable angina and ischemic cardiac diseases confirmed these findings [26].

## *2.3. Psychological and psychiatric factors in coronary heart disease*

In 1980, it was reported that type A behavior and suppressed hostility may be involved in the pathogenesis of coronary heart disease in both men and women [27]. Since then, many studies have been devoted to the association between psychological/psychiatric factors and coronary heart disease and its associated chest pain. Panic disorders and severe stress have been found to be associated with an increased risk of coronary heart disease or sudden cardiac death in men [28] and in women [29]. Panic disorders may provoke ischemic pain (or worsen it) by increasing heart rate, blood pressure, and even resistance in small coronary vessels [30]. Anxiety appears to act as an arrhythmogenic factor

because of its effect on the heart’s sympathetic innervations and, over time, affects some coronary heart disease risk factors such as diabetes, hypertension, and cholesterol. Another study examining the role of panic attacks in chest pain among postmenopausal women found an increased occurrence of chest pain among women with a recent history of panic attacks. However, evidence of ST-segment abnormality was not related to the frequency of panic attacks [31], except perhaps in the case of patients with preexisting ischemia.

Whether depression and anxiety are independent risk factors for coronary heart disease and chest pain remains controversial, but there is good evidence that these psychological/psychiatric factors are aggravating factors of heart disease, increasing morbidity and mortality [32]. When chest pain, which in itself can be a symptom of depression, is recurrent, further examination, such as angiography, is required. A correlation between severe depression and abnormal angiography findings has been described [33]. It should be noted that psychological factors also have a significant impact on NCCP [34], and therapy for depression should be implemented in both cases [35,36].

2.4. Chest pain of nonischemic cardiac disease origin

As mentioned earlier, about 20% of all cases of chest pain are due to nonischemic cardiac disease. Often, these patients have symptoms similar to those reported by patients with acute coronary disease or myocardial infarction [37], a fact that underscores the necessity to reach an accurate diagnosis as quickly as possible. The most common nonischemic cardiac conditions causing chest pain are discussed below. In most cases, the differential diagnosis with ischemic cardiac disease is based on specific characteristics of the patient’s history [12,14,37,38], the description of the chest pain, ECG findings, and chest radiography and/or magnetic resonance imaging.

Focusing on chest pain characteristics, for example, in *aortic dissection*, the pain is sudden and unrelenting. It is sharp, tearing, and stabbing. It can easily be confused with the pain of myocardial infarction. Aortic dissection occurs mostly in older patients (50–70 years) and is associated with a history of hypertension in the majority of patients. In *acute pericarditis*, chest pain is the most common symptom of the disease, which is due to viral or bacterial infection. The pain is sudden and sharp. It is maximum in the anterior chest, but it radiates to the back and the shoulders. It worsens in the supine position and during inspiration; but it is relieved by leaning forward or sitting, and often it is associated with dyspnea. In *mitral valve prolapse*, chest pain can be sharp and stabbing. It does not become worse with activity, but it is persistent. Its incidence is significantly higher in young women than in elder ones and than in men irrespective of age. Women presenting with mitral valve prolapse often have a long history of undiagnosed chest pain. Although the characteristics of chest pain in a mitral valve prolapsed

patient cannot be ignored, electrocardiography is the main test for the diagnosis of this condition. *Heart failure* is a common disease occurring mostly in elderly patients who have a significant antecedent of heart disease. The chest pain that has varied quality is inconsistent, but it occurs frequently. *Post-stent insertion* is very often followed by nonischemic cardiac chest pain that is due to the overexpansion of the vessel receiving the stent. In most instances, it lasts about 24 hours; but it may be severe. It is described as continuous, squeezing, and located deep in the chest [39]. Evidently, the specific treatment of all the nonischemic cardiac diseases varies greatly; each is also different from the treatment of the varied expression of coronary heart disease.

3. Noncardiac chest pain

*Noncardiac chest pain* is defined as recurrent angina-like pain without demonstrable evidence of coronary heart diseases by conventional testing such as angiography or positive troponin assay. The causes of NCCP are many, as shown in Table 2. The study by Pope et al [8] shows that half or more of the patients visiting emergency departments for chest pain are found to have NCCP; similar findings have been reported in other Western countries [40,41].

Gastroesophageal disorders are the most frequent causes of NCCP [42], followed by chest wall syndromes [43] and psychosomatic disorders [7]. Other conditions such as pulmonary embolism, pneumonia, and pneumothorax are often associated with substernal discomfort or even severe pain; but these conditions present specific symptoms that lead to their identification. Gastroesophageal disorders are varied [44], but by far the most frequent cause of NCCP is gastroesophageal reflux disease (GERD). Gastroesophageal reflux disease is usually associated with chest pain at rest or during a change in position; however, in GERD patients, chest pain rarely occurs during exercise testing [45], even in subjects with coronary heart disease. However, chest pain may appear during exercise in healthy young volunteers. It has been reported that GERD may produce angina, as it may cause a reflex decrease of the coronary blood flow. Other

Table 2  
Noncardiovascular causes of chest pain

Gastrointestinal diseases:
Gastroesophageal reflux
Esophageal spasm
Peptic ulcer
Pancreatitis
Biliary colic
Pulmonary embolism
Pneumonia
Pneumothorax
Chest wall syndromes
Nerve root compression
Panic disorder/depression

All may occur in patients with ischemic cardiac disease.



gastroesophageal disorders also cause chest pain, albeit to a different degree [42,44,46]. Esophageal dysmotility plays a very limited role in NCCP; sustained esophageal contractions of long duration are associated with pain. Psychosocial factors are said to play a very important, perhaps essential, role in the perception of intraesophageal events; it has been reported that 17% to 43% of patients with NCCP may suffer from psychological abnormalities [46].

The high prevalence of GERD has led to distinguishing GERD-related NCCP from non-GERD-related NCCP; however, the mechanism of pain in both groups remains elusive [47]. Although treatment of NCCP is difficult because of its variety of sources and expressions, GERD-related NCCP responds to a high dose of proton-pump inhibitor, which is actually an effective way to confirm, if not make, the GERD diagnosis [48]. Non-GERD-related NCCP does not respond to proton-pump inhibitors, but there is evidence that adenosine-receptor inhibitors may be effective in reducing the severity and frequency of the chest pain in patients affected by non-GERD-related NCCP [44,49]; pain modulators are also a treatment to be considered.

#### 4. Conclusion

The proportion of patients suffering from chest pain in most Western countries is impressive; in the United States, this amounts to millions of patients each year. Nearly all patients with chest pain experience a decreased functionality and quality of life irrespective of the cause of the pain because most patients fear that their chest pain is a harbinger of an imminent myocardial infarction. The causes of chest pain are many; and frequently, it is difficult to identify the cause based on the patient's description and characteristics of the pain. Yet it is essential to obtain an accurate diagnosis to apply a specific treatment without delay. There are many approaches to effectively and accurately diagnose chest pain due to ischemic cardiac disease. They range from ECG, exercise test, angiography (ordinary or computed tomographic angiography), and biomarkers. Once the diagnosis is reached and the severity of the disease is established, appropriate treatment can be applied and monitored to assess effectiveness. Treatment can be percutaneous coronary intervention and/or optimal medical treatment or coronary grafting. Similarly, there are diagnostic and therapeutic approaches specific to other causes of chest pain: nonischemic cardiac disease, noncardiac diseases (eg, GERD), and psychological and psychiatric disorders. In the case of the noncardiac diseases, the evaluation of experts in the field is warranted.

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