



## Chronic Chest Pain

### The Clinical Problem

Angina-like chest pain is an alarming symptom. It is a common reason for presentation to emergency departments and forms the bulk of the workload for cardiologists. Clinical evaluation ranges from simple investigations such as electrocardiograms (ECG) (both at rest and after exercise) and echocardiograms to more expensive and invasive investigations such as coronary angiography and pharmacological stress tests. In patients with recurrent symptoms without an obvious cause, further evaluation excludes cardiomyopathies, microvascular disease, and pericardial disease. However, 10–50% of patients presenting with angina-like chest pain sufficiently severe to warrant invasive cardiac investigations do not have cardiac disease [30] and are classified as having noncardiac chest pain (NCCP).

### Epidemiology and Social and Economic Impact

NCCP is frequent in the Western world. Up to 30% of patients undergoing coronary angiography for chest pain have normal coronary arteries [15]. A recent meta-analysis in 14 separate populations, containing 25,000 subjects, showed a pooled prevalence of NCCP of 13% (95% CI, 9–16). Prevalence was similar in women vs. men but was markedly higher in subjects who also reported gastroesophageal reflux disease (GORD) [19]. Other risk factors include obesity, a family history of GORD, smoking, and analgesic use [13]. Prognosis of patients with NCCP is favorable. Myocardial infarction occurs in at most 1% of cases [31,44], and cardiac death occurs in only 0.6% after follow-up of up to 10 years. In contrast, patients with coronary disease confined to a single vessel have a mortality of 15% at 48 months and 35% at 11 years [10]. The economic burden is significant. In one American study, the health care costs were estimated to be more than US\$315 million annually; because of multiple clinic and emergency room visits, hospitalizations, and prescriptions [36]. In Australia, NCCP accounts for at least \$30 million of the health care budget annually [14].

### Clinical Characteristics of Cardiac and Esophageal Causes of Chest Pain

In patients with NCCP, gastrointestinal, pulmonary, musculoskeletal, infectious, drug-related, and psychological disorders are considered. However, esophageal conditions are considered to be the most common contributing factor for angina-like chest pain of non-cardiac origin [16]. Interestingly, the clinical history often does not distinguish between cardiac and esophageal causes of chest pain because pain of esophageal origin can also be located retrosternally with radiation to the arms, neck, jaws, or back. The pain is often described as squeezing or burning and can be triggered by swallowing, but also by exercise. In patients with angina, the presence of heartburn or dysphagia may increase the likelihood of an underlying esophageal condition [2]; however, as many as 50% of patients with a cardiac cause of chest pain may also have heartburn, regurgitation, or dysphagia [7]. Furthermore, cardiac and esophageal disease may overlap; for instance in patients with coronary artery disease, gastroesophageal reflux may trigger ST segment changes on ECG and chest pain [29]. Hence, the existence of cardiac or esophageal disease cannot be assumed on the basis of clinical presentation alone. Despite these confounding factors, patients with NCCP are usually younger and are more likely to have a normal resting ECG compared to patients with cardiac angina [11].

### Pathophysiology of NCCP

Common causes of chest pain of esophageal origin are GORD, visceral hypersensitivity, and esophageal dysmotility. Of these, GORD is the most common esophageal cause of NCCP. Esophageal pH testing has demonstrated that about half of NCCP patients have abnormal esophageal acid exposure [9,41]. It is unclear why esophageal acid exposure causes heartburn in some patients and chest pain in others. Visceral hypersensitivity is a phenomenon in which conscious perception of visceral stimuli is enhanced. Patients with NCCP, in comparison to healthy control subjects, demonstrate higher pain sensation scores on exposure to a range of esophageal stimuli including balloon distension, acid infusion, and electrical and thermal stimulation [28,35].

Mechanisms proposed to be responsible for esophageal hypersensitivity in patients with NCCP include sensitization of peripheral afferent nerves (peripheral sensitization) and sensitization of spinal dorsal horn neurons (central sensitization [25]). Patients with motility disorders such as symptomatic diffuse esophageal spasm and achalasia may experience retrosternal

angina-like pain, and 30% of NCCP patients have abnormal esophageal manometric findings [8,24]. The relationship, however, between the manometric findings and the chest pain is complex. Patients are generally asymptomatic at the time when the motility abnormalities are identified. Finally, pharmacotherapy with motility-modifying drugs does not correlate with improvement of symptoms [37]. Several studies report a high incidence of psychiatric diagnoses, such as panic disorder, generalized anxiety disorder, depression, and somatization disorder, in patients with NCCP [6,23].

## Diagnostic Evaluation

Gastrointestinal work-up is aimed at demonstrating pathological gastroesophageal reflux, hypersensitivity of the esophagus, or esophageal motor abnormalities.

**Gastroesophageal reflux tests:** (i) *Proton pump inhibitors:* Empirical PPI therapy (the “PPI test”) is recommended prior to any invasive testing to diagnose GORD-related NCCP. The omeprazole doses used in the PPI test range from 40 mg to 80 mg daily over a duration of 7 to 28 days [17,21]. If the symptom score improves by more than 50–75% relative to baseline, the test is considered positive. In different studies, the sensitivity of the PPI test for GORD-related NCCP ranges from 69% to 95%, and the specificity of the test ranges from 67% to 86% [18]. The PPI test is a cost-saving approach that significantly reduces the number of invasive diagnostic tests. (ii) *Reflux monitoring:* Esophageal pH monitoring demonstrates pathological GORD in up to 62% of the patients with NCCP [9,32]. A group of patients may have normal acid exposure, but still have a significant temporal relationship between reflux episodes and chest pain events. These patients are considered to have an acid-hypersensitive esophagus [39]. (iii) *Endoscopy:* Gastrointestinal endoscopy reveals reflux esophagitis in up to 31% of patients with noncardiac chest pain [43]. Endoscopy should be reserved for patients with NCCP and alarm symptoms including dysphagia, odynophagia, weight loss, or anemia.

**Esophageal sensitivity tests:** (i) *Acid perfusion tests:* Hydrochloric acid, infused into the middle third of the oesophagus, is able to induce chest pain. The acid infusion test is positive in 10–38% of patients with NCCP [3,32]. The sensitivity and specificity for the acid perfusion test is 57% and 62%, respectively [20]. (ii) *Balloon distension tests:* A small balloon is placed in the lower esophagus and inflated until patients report pain [35]. Richter et al. and other investigators have observed that balloon distension reproduces chest pain at lower volumes in patients with NCCP than in controls [28,34]. The sensitivity of the test has been reported to vary between 5% and 50% [34].

**Esophageal motility tests:** (i) *High-resolution manometry (HRM)* is the gold standard for recognition and classification of esophageal motility disorders. A significant percentage (48–64%) of patients with achalasia experience chest pain [12]. A recent study using HRM showed that acid-sensitive NCCP patients have a distinct hypermotility pattern in the smooth muscle portion of the esophagus [26]. (ii) *Pharmacological provocative tests:* Provocative tests with edrophonium, ergonovine, bethanechol, and pentagastrin have been developed to identify patients with NCCP of esophageal origin [38]. Overall, pharmacological provocative tests are invasive, are associated with adverse events, are not standardized, have low diagnostic sensitivity for NCCP, and fail to predict therapeutic outcome.

## Treatment of NCCP

Treatment of noncardiac chest pain is challenging because of the heterogenous nature of the disorder. (i) *Acid suppression:* Several open-label studies have demonstrated efficacy of acid suppression with either PPIs or histamine H<sub>2</sub>-receptor antagonists following the first description by DeMeester et al. in 1982 [9]. Since the first double-blind, placebo-controlled study of acid suppression in NCCP by Achem et al. [1,5], similar controlled studies have consistently shown efficacy of PPI treatment in NCCP. (ii) *Smooth muscle relaxants:* Nitrates, phosphodiesterase-5 inhibitors, anticholinergic drugs, and calcium channel blockers have been used in the treatment of NCCP with dysmotility. Most studies included small numbers, and few were placebo controlled, which prevents us from making any firm conclusions about the efficacy of these agents. (iii) *Tricyclic antidepressants (TCAs):* A few clinical trials have evaluated the effect of TCAs in NCCP. In a double-blind, placebo-controlled trial [4] in 60 patients, imipramine (50 mg) significantly reduced chest pain episodes in 52% of patients. Prakash and Clouse [33] demonstrated that 75% of NCCP patients experience symptomatic relief during long-term use of TCAs for up to 3 years. (iv) *Selective serotonin reuptake inhibitors:* In a double-blind, controlled study of sertraline versus placebo in 30 NCCP patients for 8 weeks, sertraline demonstrated a significant reduction in pain score compared with placebo [42]. However, another study [40] found no differences between paroxetine and placebo. (v) *Serotonin-norepinephrine reuptake inhibitors (SNRIs):* Recently, Lee et al. evaluated venlafaxine vs. placebo in a double-blind controlled study in NCCP, reporting that 52% of patients experienced symptom improvement in comparison to 4% of those taking a placebo [27]. (vi) *Miscellaneous treatments:* Symptomatic improvement has been reported in NCCP patients taking adenosine intravenously as well as orally. Small-scale studies have shown improvement with endoscopic injection of botulinum toxin, cognitive-behavioral therapy, and hypnotherapy [22].

## References

- [1] Achem SR, Kolts BE, MacMath T, Richter J, Mohr D, Burton L, Castell DO. Effects of omeprazole versus placebo in treatment of noncardiac chest pain and gastroesophageal reflux. *Dig Dis Sci* 1997;42:2138–45.
- [2] Bak YT, Lorang M, Evans PR, Kellow JE, Jones MP, Smith RC. Predictive value of symptom profiles in patients with suspected oesophageal dysmotility. *Scand J Gastroenterol* 1994;29:392–7.
- [3] Breumelhof R, Nadorp JH, Akkermans LM, Smout AJ. Analysis of 24-hour esophageal pressure and pH data in unselected patients with noncardiac chest pain. *Gastroenterology* 1990;99:1257–64.
- [4] Cannon RO 3rd, Quyyumi AA, Mincemoyer R, Stine AM, Gracely RH, Smith WB, Geraci MF, Black BC, Uhde TW, Waclawiw MA, et al. Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med* 1994;330:1411–7.
- [5] Chambers J, Cooke R, Anggiansah A, Owen W. Effect of omeprazole in patients with chest pain and normal coronary anatomy: initial experience.

- Int J Cardiol 1998;65:51–5.
- [6] Cormier LE, Katon W, Russo J, Hollifield M, Hall ML, Vitaliano PP. Chest pain with negative cardiac diagnostic studies. Relationship to psychiatric illness. *J Nerv Mental Dis* 1988;176:351–8.
- [7] Davies HA, Page Z, Rush EM, Brown AL, Lewis MJ, Petch MC. Oesophageal stimulation lowers exertional angina threshold. *Lancet* 1985;1:1011–4.
- [8] Dekel R, Pearson T, Wendel C, De Garmo P, Fennerty MB, Fass R. Assessment of oesophageal motor function in patients with dysphagia or chest pain: the Clinical Outcomes Research Initiative experience. *Aliment Pharmacol Ther* 2003;18:1083–9.
- [9] DeMeester TR, O'Sullivan GC, Bermudez G, Midell AI, Cimochoowski GE, O'Drobinak J. Esophageal function in patients with angina-type chest pain and normal coronary angiograms. *Ann Surg* 1982;196:488–98.
- [10] Detre KM, Peduzzi P, Hammermeister KE, Murphy ML, Hultgren HN, Takaro T. Five-year effect of medical and surgical therapy on resting left ventricular function in stable angina: Veterans Administration Cooperative Study. *Am J Cardiol* 1984;53:444–50.
- [11] Dumville JC, MacPherson H, Griffith K, Miles JN, Lewin RJ. Non-cardiac chest pain: a retrospective cohort study of patients who attended a Rapid Access Chest Pain Clinic. *Fam Pract* 2007;24:152–7.
- [12] Eckardt VF, Staaf B, Bernhard G. Chest pain in achalasia: patient characteristics and clinical course. *Gastroenterology* 1999;116:1300–4.
- [13] Eslick GD. Noncardiac chest pain: epidemiology, natural history, health care seeking, and quality of life. *Gastroenterol Clin North Am* 2004;33:1–23.
- [14] Eslick GD, Talley NJ. Non-cardiac chest pain: squeezing the life out of the Australian healthcare system? *Med J Aust* 2000;173:233–4.
- [15] Fass R, Achem SR. Noncardiac chest pain: epidemiology, natural course and pathogenesis. *J Neurogastroenterol Motil* 2011;17:110–23.
- [16] Fass R, Malagon I, Schmulson M. Chest pain of esophageal origin. *Curr Opin Gastroenterol* 2001;17:376–80.
- [17] Fass R, Ofman JJ, Gralnek IM, Johnson C, Camargo E, Sampliner RE, Fennerty MB. Clinical and economic assessment of the omeprazole test in patients with symptoms suggestive of gastroesophageal reflux disease. *Arch Intern Med* 1999;159:2161–8.
- [18] Fass R, Ofman JJ, Sampliner RE, Camargo L, Wendel C, Fennerty MB. The omeprazole test is as sensitive as 24-h oesophageal pH monitoring in diagnosing gastro-oesophageal reflux disease in symptomatic patients with erosive oesophagitis. *Aliment Pharmacol Ther* 2000;14:389–96.
- [19] Ford AC, Suares NC, Talley NJ. Meta-analysis: the epidemiology of noncardiac chest pain in the community. *Aliment Pharmacol Ther* 2011;34:172–80.
- [20] Ghillebert G, Janssens J. Provocation tests versus 24-h pH and pressure measurements. *Eur J Gastroenterol Hepatol* 1995;7:1141–6.
- [21] Johnsson F, Weywadt L, Solhaug JH, Hernqvist H, Bengtsson L. One-week omeprazole treatment in the diagnosis of gastro-oesophageal reflux disease. *Scand J Gastroenterol* 1998;33:15–20.
- [22] Jones H, Cooper P, Miller V, Brooks N, Whorwell PJ. Treatment of non-cardiac chest pain: a controlled trial of hypnotherapy. *Gut* 2006;55:1403–8.
- [23] Katon W, Hall ML, Russo J, Cormier L, Hollifield M, Vitaliano PP, Beitman BD. Chest pain: relationship of psychiatric illness to coronary arteriographic results. *Am J Med* 1988;84:1–9.
- [24] Katz PO, Dalton CB, Richter JE, Wu WC, Castell DO. Esophageal testing of patients with noncardiac chest pain or dysphagia. Results of three years' experience with 1161 patients. *Ann Intern Med* 1987;106:593–7.
- [25] Knowles CH, Aziz Q. Visceral hypersensitivity in non-erosive reflux disease. *Gut* 2008;57:674–83.
- [26] Kushnir VM, Prakash Gyawali C. High resolution manometry patterns distinguish acid sensitivity in non-cardiac chest pain. *Neurogastroenterol Motil* 2011;23:1066–72.
- [27] Lee H, Kim JH, Min BH, Lee JH, Son HJ, Kim JJ, Rhee JC, Suh YJ, Kim S, Rhee PL. Efficacy of venlafaxine for symptomatic relief in young adult patients with functional chest pain: a randomized, double-blind, placebo-controlled, crossover trial. *Am J Gastroenterol* 2010;105:1504–12.
- [28] Mehta AJ, De Caestecker JS, Camm AJ, Northfield TC. Sensitization to painful distention and abnormal sensory perception in the esophagus. *Gastroenterology* 1995;108:311–9.
- [29] Mellow MH, Simpson AG, Watt L, Schoolmeester L, Haye OL. Esophageal acid perfusion in coronary artery disease. Induction of myocardial ischemia. *Gastroenterology* 1983;85:306–12.
- [30] Ockene IS, Shay MJ, Alpert JS, Weiner BH, Dalen JE. Unexplained chest pain in patients with normal coronary arteriograms: a follow-up study of functional status. *N Engl J Med* 1980;303:1249–52.
- [31] Pasternak RC, Thibault GE, Savoia M, DeSanctis RW, Hutter AM, Jr. Chest pain with angiographically insignificant coronary arterial obstruction. Clinical presentation and long-term follow-up. *Am J Med* 1980;68:813–7.
- [32] Peters L, Maas L, Petty D, Dalton C, Penner D, Wu W, Castell D, Richter J. Spontaneous noncardiac chest pain. Evaluation by 24-hour ambulatory esophageal motility and pH monitoring. *Gastroenterology* 1988;94:878–86.
- [33] Prakash C, Clouse RE. Long-term outcome from tricyclic antidepressant treatment of functional chest pain. *Dig Dis Sci* 1999;44:2373–9.
- [34] Rao SS, Gregersen H, Hayek B, Summers RW, Christensen J. Unexplained chest pain: the hypersensitive, hyperreactive, and poorly compliant esophagus. *Ann Intern Med* 1996;124:950–8.
- [35] Richter JE, Barish CF, Castell DO. Abnormal sensory perception in patients with esophageal chest pain. *Gastroenterology* 1986;91:845–52.
- [36] Richter JE, Bradley LA, Castell DO. Esophageal chest pain: current controversies in pathogenesis, diagnosis, and therapy. *Ann Intern Med* 1989;110:66–78.
- [37] Richter JE, Dalton CB, Bradley LA, Castell DO. Oral nifedipine in the treatment of noncardiac chest pain in patients with the nutcracker esophagus. *Gastroenterology* 1987;93:21–8.
- [38] Richter JE, Hackshaw BT, Wu WC, Castell DO. Edrophonium: a useful provocative test for esophageal chest pain. *Ann Intern Med* 1985;103:14–21.
- [39] Shi G, Bruley des Varannes S, Scarpignato C, Le Rhun M, Galmiche JP. Reflux related symptoms in patients with normal oesophageal exposure to acid. *Gut* 1995;37:457–64.
- [40] Spinhoven P, Van der Does AJ, Van Dijk E, Van Rood YR. Heart-focused anxiety as a mediating variable in the treatment of noncardiac chest pain by cognitive-behavioral therapy and paroxetine. *J Psychosom Res* 2010;69:227–35.
- [41] Stahl WG, Beton RR, Johnson CS, Brown CL, Waring JP. Diagnosis and treatment of patients with gastroesophageal reflux and noncardiac chest pain. *South Med J* 1994;87:739–42.
- [42] Varia I, Logue E, O'Connor C, Newby K, Wagner HR, Davenport C, Rathey K, Krishnan KR. Randomized trial of sertraline in patients with unexplained chest pain of noncardiac origin. *Am Heart J* 2000;140:367–72.
- [43] Voskuil JH, Cramer MJ, Breumelhof R, Timmer R, Smout AJ. Prevalence of esophageal disorders in patients with chest pain newly referred to the cardiologist. *Chest* 1996;109:1210–4.
- [44] Wielgosz AT, Fletcher RH, McCants CB, McKinnis RA, Haney TL, Williams RB. Unimproved chest pain in patients with minimal or no coronary disease: a behavioral phenomenon. *Am Heart J* 1984;108:67–72.