Commentary

Atypical chest pain: looking beyond the heart

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Summary

Chest pain is common, and tends to be overinvestigated. Patients with normal coronary anatomy have a low mortality, but remain significantly incapacitated. We discuss ways of improving the management of such patients. An early diagnosis of a non-cardiac cause of pain should be made, ideally by the general practitioner, taking account of risk factors for cardiac as well as psychological disorders, the quality of the pain, the patient’s concerns and worries and the presence of stressful life events. The minimum of investigation should be performed. Cardiological referral should be considered for patients with a high a priori risk of ischaemic heart disease. Otherwise referral, if necessary, should be to a gastroenterologist, psychiatrist or clinical psychologist, as appropriate. Treatment options are medications with musculoskeletal or oesophageal activity, cause of pain should be made, ideally by the general practitioner, taking account of risk factors for cardiac as well as psychological disorders, the quality of the pain, the patient’s concerns and worries and the presence of stressful life events. The minimum of investigation should be performed. Cardiological referral should be considered for patients with a high a priori risk of ischaemic heart disease. Otherwise referral, if necessary, should be to a gastroenterologist, psychiatrist or clinical psychologist, as appropriate. Treatment options are medications with musculoskeletal or oesophageal activity, simple or repeated reassurance, cognitive therapy, psychiatric drugs, and respiratory retraining. We suggest that a multidisciplinary chest-pain clinic may improve the care of such patients.

Introduction

Chest pain occurs frequently in the community and is usually benign. Despite this, myocardial ischaemia remains important, because it is potentially fatal. This leads to an understandable tendency to overinvestigate, so that as few as 11–44% of patients referred to cardiac outpatient clinics have evidence of organic disease, and up to 31% of patients receiving coronary angiography are shown to have normal coronary anatomy (NCA). Although the mortality and morbidity from coronary angiography are small, an erroneous diagnosis of coronary disease is difficult to revoke. Patients are frequently not reassured by investigation, and there is some evidence that the process of investigation itself may entrench the idea of cardiac disease. One half remain or become unemployed, one half remain on cardiac medication and about three-quarters continue to experience pain. The aim should, therefore, be to make an authoritative diagnosis of non-cardiac pain as early as possible allowing appropriate management with the minimum of cardiac-orientated investigation. In this paper, we discuss the possible causes of pain in these patients and suggest improved methods of assessment and management. We also make proposals for future research.

Reasons for avoiding undue cardiac bias

Causes of pain

Unitary explanations are not always applicable in patients with NCA. Historically these patients have been subclassified according to the quality of the pain, and the ECG changes either at rest or on exercise. Thus, it is generally (although not univer-
sally) accepted that patients with chest pain and ST segment depression on the ECG on exertion may sometimes have a cardiac cause for pain, while those with ‘atypical’ pain and no electrocardiographic evidence of ischaemia are more likely to have a non-cardiac cause. The small subgroup with LBBB may develop a dilated cardiomyopathy.6 Beyond this there are grave difficulties of classification. The clinical and research literature is beset by terms such as ‘typical pain’, ‘atypical pain’, ‘typical pain with atypical features’, all of which have different meanings to different cardiologists. The criteria for an abnormal exercise test are arbitrary, and the poor specificity of these changes is well known. It is obvious that factors other than ischaemia can cause ST segment depression, among them digoxin, cardiac fibrosis and hypokalaemia. Myocardial perfusion imaging is not a complete answer, because of the problem of false-positive results.7 Research has tended to start with the premise that chest pain must be caused by ischaemia. In the absence of significant stenoses of the epicardial arteries, there has been a search for biochemical disorders, small-vessel disease or abnormalities of the precapillary arterioles.8 Many studies have been limited by incomplete control groups and faulty methodology. Thus, lactate extraction was used for at least 12 years to diagnose myocardial ischaemia9, until Gertz et al.10 studied an asymptomatic normal control group and showed that 7 (44%) of 16 subjects had criteria for ischaemia at rest or during pacing. Evidence of reduced flow reserve using thermodilution catheters11 was not corroborated by studies with more accurate nuclear techniques12,13 and remains unsupported by modern work using positron emission tomography.14 There is some evidence for coronary spasm or reduced coronary reserve (‘microvascular angina’) in a small proportion of patients with normal coronary arteries,4 but we must guard against the attempt to explain all chest pain in cardiocentric terms. This has led to suggestions that even in the absence of ischaemia, the release of adenosine or other substances into the coronary vasculature might cause pain.15 This cardiocentricity begins worthily enough in the desire not to miss patients with treatable coronary disease, but ends in ever more complex attempts to interpret absent or incomplete evidence.

In fact, a large proportion of patients with NCA have pain which is atypical of a cardiac origin,16,17 and there is now a wealth of evidence that non-cardiac factors can cause chest pain. For example, about 50% of all patients with chest pain and normal coronary anatomy have oesophageal reflux or motility disorders,4 approximately 60%16,17 have evidence of breathing disorders, and 60%, psychological abnormalities.18,19 These possible causes are benign and consistent with the mortality of zero in most long-term series.20,21 However, the situation is not straightforward. There may appear to be a robust relationship between a demonstrated abnormality and pain in some individuals, but this is lacking in research populations either of oesophageal22,23 or respiratory disorders.24,25 Furthermore, the response to therapy is variable. Despite a significant reduction in intra-oesophageal pressure, nifedipine is no more effective than placebo in abolishing pain in patients with nutcracker oesophagus.26 On the other hand, there may be a good response to antireflux medication, although with no clear relationship to the degree of reflux.27 There is also a large overlap in the possible causes of chest pain, with over one half having two or more of an oesophageal, respiratory or psychiatric abnormality.28 It may then be difficult to decide which is the aetiologically relevant factor. Thus psychological treatments have been found to be effective,29 sometimes in the presence of continuing organic abnormalities.30 In fact, to speak of unitary causation like this is naive. There is evidence of subtle interactions between (often multiple) physical and psychological abnormalities, and the patient’s perception and interpretation of somatic sensations is often overlooked.31,32 There is also evidence that a benign somatic or emotional trigger can reproduce previously experienced pain as a result of altered thalamic function.33 This may explain some cases where chest pain recurs after bypass grafting. These mechanisms are expected to be in flux, and to interact to varying degrees in different individuals or at different times within the same individual.

How to establish a diagnosis of non-cardiac chest pain

Assessment

The crucial first step is to make a confident diagnosis of a non-cardiac cause of pain as early as possible, preferably within 1 year of the onset of symptoms. Patients presenting to a general practitioner need to be assessed under four categories.

Cardiac risk factors

If the 10-year risk of a coronary event is higher than 20%, based on published charts,34 it is reasonable to investigate, however ‘atypical’ the chest pain. The symptoms may be coincidental and even myocardial infarction is ‘silent’ in around 11% of cases.35

Quality of the chest pain

There is surprisingly little work on such a fundamental symptom. However, we have recently
Atypical chest pain

shown\textsuperscript{17} that three questions helped to differentiate patients with normal coronary anatomy from those with significant coronary disease. If the answers to all three questions were ‘atypical’, the chance of coronary disease using a logistic regression was only 2% in patients aged under 55 years, and 12% in those aged over 55 years. This model is now being tested prospectively, but if confirmed might guide referral from the community to a cardiologist, and thereafter might help in the decision whether to offer coronary angiography.

Risk factors for psychological and other disorders

Symptoms of gastric disease do not appear to discriminate adequately.\textsuperscript{17} However, if the initial assessment is that a cardiac cause is unlikely, this ancillary history can reasonably be used to guide further investigation or explanation. Although anxiety is more common in patients with normal anatomy (58–70%) than coronary disease (9–23%), there is often considerable overlap.\textsuperscript{18} However, one group was able to classify 82% of patients correctly using the Millon questionnaire,\textsuperscript{36} and the presence of psychiatric symptoms may be particularly important in individuals. A psychiatric aetiology is suggested if there is a situational (or phobic) component to the somatic symptoms. For example, anxiety and panic are common in certain situations such as crowds, public transport, queues and lifts. A fear of experiencing symptoms in these situations leads to avoidance of them, and considerable limitation of activities may occur.

Asking specific questions about panic attacks is important. For example, ‘have you ever had a panic attack, when you suddenly felt frightened, anxious or extremely uncomfortable? When you last had chest pain, what was the first thing that you noticed? During the attack did you notice that you were short of breath, dizzy, heart racing, trembling or shaking, chest pain?’ This sort of enquiry is designed to establish a positive diagnosis of panic disorder. It is also worth asking if the patient has ever experienced or received treatment for panic attacks or agoraphobia in the past.

Patients’ concerns and worries

It is important to elicit the patients’ beliefs and attitudes about the chest pain. Some patients entertain abnormal attitudes and beliefs about their symptoms. These include exaggerated fears of death, marked conviction of disease despite negative findings, and intense bodily preoccupation. A sample question might be: ‘when you experience chest pain, what is your worst fear?’

Stressful life events

There is a considerable body of research evidence that attests to the importance of distressing life events as precipitants of anxiety and depressive disorders.\textsuperscript{37} Questions about life events before the onset of the chest pain are not routinely sought by physicians. Events signifying loss, threat, and rejection are of particular importance. Open questions are useful, e.g. ‘tell me about any changes or setbacks that occurred in the months before your symptoms began.’

When and how to investigate

Patients with a low a priori risk of coronary disease (e.g. young, female with no hypercholesterolaemia) and atypical pain do not usually need cardiac investigation. Patients with an intermediate or high risk (e.g. middle-aged male) should usually have non-invasive investigation even if the chest pain is apparently atypical of a cardiac origin. It may be necessary to refer to a cardiologist if open-access non-invasive investigation is not available. At this level, the minimum of reasonable investigation should be performed. A normal exercise test at high workload in a patient with atypical pain is probably reasonable, with a myocardial perfusion scan as back-up for equivocal cases. Coronary angiography should be a rare necessity for those in whom non-invasive investigation suggests disease or for those, for example bus-drivers, whose livelihoods depend on the diagnosis. A certain number of normal angiograms is inevitable. However, there is a wide range in the incidence of normal studies, between 6% and 31% for individual hospitals,\textsuperscript{18,20} and between 0% and 71% for individual cardiologists at one centre.\textsuperscript{38} The implication is that rationalizing criteria for investigation would reduce variability in practice.

If hospital referral is necessary in patients at low risk of coronary disease, for example because of continuing severe symptoms, it should then be to the specialist suggested by the additional history; this may be a gastroenterologist, rheumatologist, or psychiatrist/clinical psychologist. This should obviate the very real problem of creating iatrogenic cardiac disease.

How to manage non-cardiac chest pain

Organic treatments

In some patients, obvious musculoskeletal problems can be treated conventionally, for example with non-steroidal anti-inflammatory agents. There is uncertainty about the status of oesophageal abnormalities.
However, acid reflux is common and some patients respond well to H$_2$ receptor antagonists or proton-pump inhibitors. We have shown that pain may resolve completely in as many as one third.$^{39}$ We therefore use a proton-pump inhibitor as an initial therapeutic trial in patients with NCA. If there is no evidence of conspicuous psychological abnormality, we ask for oesophageal function testing which reveals a small number of patients with motility disorders or acid reflux unresponsive to first-line medication. These may need specialist gastroenterological referral.

**Psychological treatments**

For the remaining patients with no evidence of organic oesophageal disease, psychological treatment in the form of reassurance has been the mainstay of the management of non-cardiac chest pain. Most patients with persistent non-cardiac pain are happy to accept that they do not have a serious condition, provided that they are given a satisfactory alternative explanation for the pain.$^{40}$

In some patients, however, reassurance is unsatisfactory, especially those with continuing abnormal beliefs about the pain, or with conspicuous psychiatric problems, e.g. depression. Such patients require an alternative strategy, and the treatment of choice is cognitive behavioural therapy (CBT). This treatment identifies the distinctive pattern of symptoms, misinterpretations, and anxiety involved in the patient’s chest pain. It challenges evidence supporting the patient’s negative interpretations, and experiments with patient behaviour to provide additional support for non-catastrophic explanations of symptoms and anxiety, and to provide an opportunity to minimize the patient’s worst fears.

This treatment was effective in three randomized controlled trials,$^{29,41,42}$ including one in a group setting.$^{42}$ Patients who underwent the group therapy had significantly improved outcomes in terms of reduction in the frequency and severity of chest pain, reduced functional disability as measured by the SF36, less psychological distress and improved exercise tolerance. Significantly, patients who continued to attribute their pain to heart disease had poorer outcomes. These findings, which were maintained at 6-month follow-up, have important economic implications for the management of patients with non-cardiac chest pain. In another recent study$^{43}$ of patients with chest pain and normal coronary arteries, CBT was found to be ineffective, partly as a result of intervening too early, immediately after catheterization. It appears that it may be more helpful for patients to have some time to absorb the results of the tests, discuss the findings with their family or the general practitioner, and then be offered an individualized intervention at a later stage, perhaps 2–6 weeks later.

We believe that an essential component of further treatment studies of patients with NCA or negative investigations by the cardiologist should include a full discussion with the patient before angiography to discuss the possibility and meaning of a negative test. For example, it might be appropriate to inform patients that one in five angiograms reveal normal arteries and that other non-cardiac causes of pain are common. Further studies exploring the possible benefits of interventions of this type are needed.

**Pharmacological treatment**

Tricyclic antidepressant drugs have been shown to benefit patients with chronic pain,$^{44}$ independent of any effect on mood. This analgesic effect was harnessed in a study of 60 consecutive patients with chest pain and normal coronary arteries, who were randomized to a three-week trial of clonidine, imipramine 50 mg nightly, and placebo.$^{35}$ There was a mean reduction in frequency of chest pain episodes by 50% in the imipramine group, which occurred independently of baseline levels of psychiatric morbidity and oesophageal abnormalities. Furthermore, repeat assessment of sensitivity to cardiac pain while the patients were receiving treatment showed significant improvement only in the imipramine group.

Alprazolam has also been shown to decrease panic frequency as well as levels of anxiety and depression in an open trial of eight patients with atypical chest pain and panic disorder.$^{46}$ This drug does however carry the risk of dependence and withdrawal symptoms.

**Respiratory retraining**

A behavioural treatment aimed at restoring normal respiratory physiology has also been shown to reduce the frequency of functional cardiac symptoms in patients ‘with functional cardiac symptoms who demonstrated signs of hyperventilation syndrome’.$^{37}$ Because the treatment involved not only slow diaphragmatic breathing (breathing retraining), but also reattribution of the cardiac symptoms to hyperventilation, it is unclear which of these components was more beneficial, although the authors noted a strong relation between a reduction in respiratory rate and treatment success.

**The case for a multidisciplinary chest pain clinic**

A more imaginative approach is needed for the assessment and management of patients with chest pain. General practitioners should be helped to make
decisions about referral of patients as well as for managing those referred back from cardiologists after a diagnosis of non-cardiac pain.

Invasive investigation by cardiologists needs to be reduced by the appropriate use of risk analysis and non-invasive investigation. Further research in the validity of chest pain and other questionnaires is needed. If normal coronary anatomy is found at angiography, the patient should be re-assessed after 4–6 weeks, when a ‘stepped’ approach to management should be adopted. This may best be undertaken in a multidisciplinary chest pain clinic run jointly by a cardiologist, psychiatrist and possibly also a gastroenterologist. A high proportion of patients with non-cardiac chest pain will have co-existing psychological problems, and experience shows that they accept the presence of a psychiatrist at a combined clinic more readily than the offer of referral to another part of the hospital. A combined clinic might also be expected to be effective for those numerous patients with both organic and psychological abnormalities. However, management strategies are not yet clear and work continues on the relative place of physical and psychological methods.

References


