Gastroenterology

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Unexplained (non-cardiac) chest pain

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Non-cardiac chest pain is considered to be central chest pain that resembles angina yet, after appropriate investigation, its cause appears unrelated to the heart. The problem is common: one in four of the population have at least one episode over the course of a year and patients with chest pain account for about 5% of all presentations to primary care physicians and emergency departments.[1] Even among those patients referred for coronary angiography, a significant proportion has no evidence of ischaemic heart disease (IHD). The terminology can be confusing and, because of the possibility that such pain may still result from thus far unrecognised cardiac disease, the term 'unexplained chest pain' (UCP) is preferred to the more usual 'non-cardiac chest pain' and certainly preferable to the vague term 'atypical chest pain'. When IHD has been excluded, the prognosis for these patients is usually excellent.[2] However, despite the potentially beneficial effect of reassurance resulting from negative investigations, many such individuals continue to experience symptoms, seek medical advice and accrue considerable healthcare costs.[1]

Clinical assessment

UCP can be caused by a variety of conditions (Table 1). Clinical diagnosis can be difficult due to the non-specific character and location of the symptoms. Moreover, many patients with proven IHD also have non-cardiac pain.[3] Therefore it is necessary to exclude cardiac ischaemia by ECG and measurement of troponin. Where doubt remains that there may be a cardiac cause, more specialised investigation such as non-invasive cardiac stress tests may be appropriate, and a specialist cardiology opinion sought when the general physician remains uncertain.

Clinical re-evaluation is often worthwhile. Further history and examination may reveal typical reflux symptoms (or prompt relief with antacids), pain on palpation of the chest wall or hyperventilation and panic attacks. Psychosocial problems often accompany UCP, especially in patients referred for specialist medical attention.[4] Patients with psychiatric illness are highly sensitive and attentive to visceral symptoms and tend to label these as 'painful' and indicating life-threatening disease.[4]

Table 1. Causes of unexplained (non-cardiac) chest pain. Reproduced with kind permission of Blackwell Publishing.[1]

- Oesophageal (40–60%)
  - Gastro-oesophageal reflux disease (acid and non-acid)
  - Visceral hypersensitivity
  - Oesophageal motor dysfunction ± bolus escape
    - Nutcracker oesophagus, oesophageal spasm, achalasia
    - Weak and/or ineffective peristalsis
- Musculoskeletal (10–20%)
  - Fibromyalgia, costochondritis, spinal problems
- Psychological (20–60%)
  - Panic attacks, anxiety, depression, somatisation, hypochondria
- Miscellaneous
  - Pulmonary disease, breast conditions, herpes zoster
  - Cardiac disease

Investigation

William Osler suggested in 1892 that the oesophagus may be a source of episodic chest pain. He would have emphasised the need to keep other diagnoses in mind ('medicine is a science of uncertainty and an art of probability'), but systematic reviews have confirmed that oesophageal disease is the most common identifiable cause for UCP, accounting for at least two-thirds of cases.[1] It is important to identify UCP patients with serious underlying pathology, but National Institute for Health and Clinical Excellence guidelines indicate that endoscopic investigation is not necessary for patients presenting with dyspepsia (definition includes UCP) without dysphagia, weight loss or evidence of bleeding.[5] A prospective study of dyspeptic patients referred for endoscopy found that the presence of these 'alarm features' identified 92% of those with occult malignancy; in contrast, in dyspeptic patients with reflux symptoms or UCP the likelihood of cancer or peptic ulcer disease was even lower than in the general population with dyspepsia.[6]

Chest pain can be triggered by a variety of oesophageal stimuli, including acid reflux, distension and motor dysfunction. Many UCP patients have evidence of visceral hypersensitivity, a mechanism by which the perception of

visceral events is heightened such that even normal physiological events may be experienced as painful.

Gastrointestinal investigations

Various gastrointestinal investigations are available (Table 2) but many lack diagnostic sensitivity in UCP whereas others are time-consuming and poorly tolerated.

Endoscopy

Endoscopy is usually normal, with reflux oesophagitis revealed in only 10–25%. There is a very low pick-up of more serious disease.

Barium studies

Barium studies are even less likely to provide useful information unless dysphagia accompanies chest pain.

Ambulatory monitoring

The single most useful investigation in UCP is ambulatory 24-hour pH measurement. It is not known why some patients complain of heartburn and others of chest pain in response to oesophageal acid, but 40–60% of patients with UCP have pathological levels of acid exposure diagnostic of gastro-oesophageal reflux disease (GORD). Other patients complain of chest pain in association with isolated acid reflux events (indicative of visceral hypersensitivity). Some of these experience UCP only a few times a week and require prolonged pH monitoring to increase diagnostic sensitivity.

The clinical impact of pH studies is that patients with a proven association between acid reflux events and UCP are significantly more likely to respond to acid suppression than those without such findings (Fig 1).[7,8]

Multichannel intraluminal impedance

The combination of multichannel intraluminal impedance and pH catheters detects both acid *and* non-acid reflux and follows bolus transport through the oesophagus. Overall in GORD, this technique improves the ability to associate symptoms and reflux events by 10–20%.[9] The ability to detect non-acid reflux may be particularly useful in UCP patients because a high proportion have heightened sensitivity not only to acid reflux but also to oesophageal distention by non-acid 'volume reflux' and bolus escape on swallowing.[10]

Table 2. Gastrointestinal investigations for suspected oesophageal causes of chest pain.

- Endoscopy (in the presence of 'alarm symptoms')
- Barium studies (*not often indicated)*
- Endoscopic ultrasound (detects oesophageal wall thickening ± spasm)*
- Ambulatory, 24-hour oesophageal pH studies
  - Assesses association between symptoms and reflux episodes
  - (improved by 48-hour study (eg catheter-free Bravo® system*))
  - Combined pH and impedance study (acid and non-acid reflux)
- Oesophageal manometry
  - Ambulatory 24-hour manometry
  - High-resolution manometry*
- Provocative tests (*not generally recommended*)
  - Acid perfusion (reflux provocation), edrophonium (spasm provocation)

*not widely available.

Conventional manometry

Up to a third of patients with UCP undergoing conventional manometry have abnormal findings. In the absence of dysphagia, however, major oesophageal dysmotility such as occurs in achalasia is rare and the importance of many other findings questionable.[11] This is because 'non-specific motor dysfunction', including the condition known as nutcracker oesophagus, is common in GORD and many patients obtain symptomatic relief with acid suppression even though motor function is unchanged. Also, medications that relax oesophageal smooth muscle rarely improve symptoms. Studies have shown that manometric abnormalities in UCP are associated with acid reflux and visceral hypersensitivity but are not a common cause of symptoms unless bolus transport is disturbed or there is extremely high contractile pressure (>300 mmHg).[10]

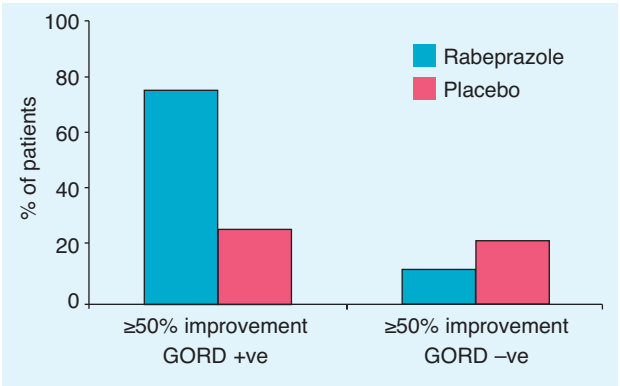

Fig 1. Response to proton pump inhibitor (PPI) therapy in patients defined as gastro-oesophageal reflux disease (GORD) positive and GORD negative on the basis of the findings on upper gastrointestinal endoscopy and 24-hour pH studies. GORD positive patients' symptoms improved on twice-daily rabeprazole therapy (p<0.03) whereas GORD negative patients experienced no benefit (p=0.66). Similar results have been produced with other high-dose PPIs (eg omeprazole 20 mg bd). Reproduced with kind permission of Blackwell Publishing.[8]

Oesophageal sensitivity

Measurement of oesophageal sensitivity is not routine, but in many UCP patients the presence of symptoms in the absence of severe GORD or motor dysfunction indicates that visceral hypersensitivity is a key feature of their condition. Studies of brain activity during oesophageal stimulation have described discrete abnormalities of peripheral (visceral afferent), central (spinal) and psychological function in this patient population.[12] It may be possible in the future to use this information to direct individual treatment of neuropsychologic pathology in UCP.

Therapeutic trials and treatment

In principle, it would be possible to subject all those affected by UCP to comprehensive investigations in an attempt to reach a definitive diagnosis before starting treatment, but this approach is neither practical nor cost-effective.[13] In practice, most commentators recommend a policy of 'therapy as investigation'.

Proton pump inhibitors

Acid suppression is the single most effective treatment of UCP. The proton pump inhibitor (PPI) test assesses the symptomatic response to a short course of high-dose acid suppression (eg 14 days omeprazole 20–40 mg twice daily). Such treatment provides complete or partial (>50%) resolution of symptoms in up to 80% of patients with UCP and GORD on 24-hour pH testing, but only 20% of those with no evidence of GORD.[6] A recent meta-analysis reported a pooled sensitivity and specificity of the PPI test for GORD-related UCP of 78% (95% confidence interval (CI) 61–95) and 86% (95% CI 67–100), respectively.[14] The risk ratio for continued symptoms after PPI was only 0.54 (95% CI 0.41–0.71), representing a number-needed-to-treat (NNT) of less than 3 (Fig 2).[14]

A therapeutic trial of PPI in unselected patients with UCP is both safe and cost-effective.[13] If successful symptom relief is achieved with high-dose treatment, the lowest effective maintenance dose should be continued. The prevalence of visceral hypersensitivity means that effective acid suppression is important. Some patients require continuous use of high-dose PPI over the long term. H_2-receptor antagonists are substantially less effective than PPIs.

Smooth muscle relaxants and prokinetics

The evidence from trials that treatment of oesophageal motor dysfunction is successful in treating UCP is rather weak. A key problem is low efficacy – there is a relative lack of treatments that inhibit or enhance oesophageal contractions as effectively as PPIs suppress acid secretion. In addition, it is difficult to predict from conventional manometry which patients will respond to particular treatments. Individual UCP patients with 'nutcracker oesophagus' may respond to calcium-channel blockers (eg nifedipine) but placebo-controlled trials have not shown

Key Points

- **Between 40 and 60% of patients presenting with unexplained chest pain (UCP) may have an oesophageal cause for their symptoms**
- **A 14-day trial of high-dose treatment with a proton pump inhibitor is appropriate as a therapeutic trial before planning further investigations**
- **Upper gastrointestinal endoscopy and barium studies are usually unhelpful in the clinical investigation of UCP**
- **Referral for ambulatory pH monitoring and oesophageal manometry should be strongly considered, especially in centres where more sophisticated manometric techniques are available, as they increase the diagnostic sensitivity**
- **Smooth muscle relaxants are often disappointing but, as in other functional gut conditions, trials of low-dose antidepressants can be useful; predicting which patients will respond is tricky**

KEY WORDS: ambulatory pH monitoring, chest pain, gastro-oesophageal reflux disease, oesophageal motility disorders, proton pump inhibitor, visceral hypersensitivity

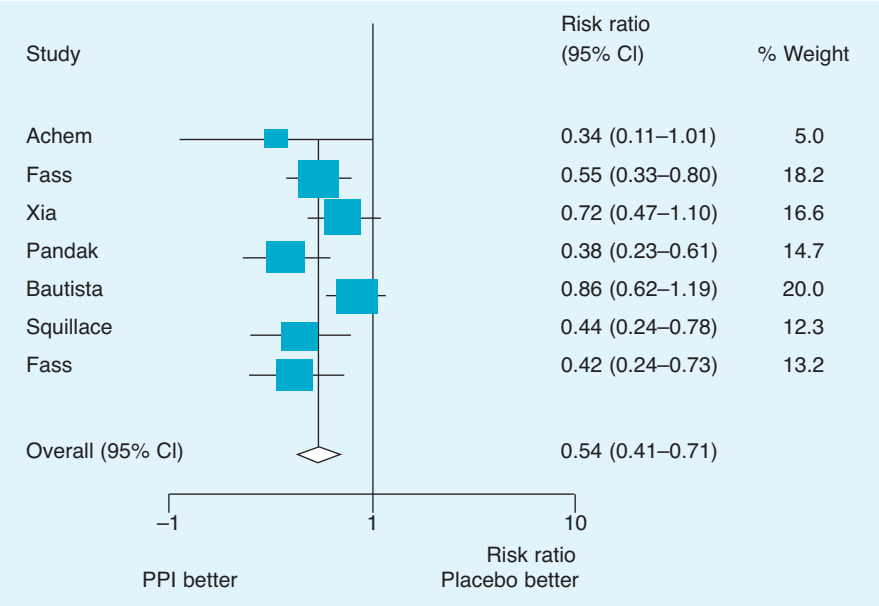

Fig 2. Meta-analysis showing the effect of proton pump inhibitor (PPI) treatment in non-cardiac chest pain. The overall relative risk for continued chest pain after PPI treatment was 0.54 (95% confidence interval (CI) 0.41–0.71; number-needed-to-treat <3). Reproduced with kind permission of Blackwell Publishing.[14]

convincing benefits. Nitrate donors (eg glyceryl trinitrate) may have a role in the treatment of 'oesophageal spasm', but their use is limited by side effects and tachyphylaxis. Until its withdrawal from use, cisapride provided quite effective treatment in UCP patients with weak oesophageal function and GORD. Other modern 5-HT_4 agonists (eg tegaserod) with prokinetic effects on the oesophagus and stomach, but without adverse cardiac effects, may become available soon.

Visceral analgesics and psychological treatments

The beneficial effects of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors in UCP have been established by randomised controlled trials.[15] These medications act as visceral analgesics without necessarily affecting mood and their effects are independent of oesophageal motor function. Low-dose TCAs are taken at night-time (eg amitriptyline 10–25 mg) to avoid daytime drowsiness. Patients must be encouraged to persist with treatment because side effects tend to decrease after several days' treatment and they should be advised that beneficial effects may take 6–8 weeks to become fully apparent.

Psychological approaches

No trials of cognitive-behavioural therapy or other psychological approaches have been performed in UCP patients but these treatments are effective in other functional bowel diseases.[16] Patients learn to cope with their symptoms by diverting attention away from gastrointestinal sensations and unhelpful thoughts and behaviour related to their condition.

Conclusions

Chest pain is a common presenting complaint in primary and secondary care. After exclusion of cardiac ischaemia, strong evidence supports an empirical trial of high-dose acid suppression. A positive PPI test provides both diagnosis and effective therapy. If symptoms do not improve, a 'test and treat' approach is recommended (Fig 3) both to define underlying pathology and to direct management. Even when effective treatment is not available an explanation often allows the affected individual (and their doctor) to come to terms with UCP and can be therapeutic in itself. Alternatively, if the patient wishes to avoid invasive tests, empiric trials of low-dose TCA and/or other medications can be attempted *before* investigation of oesophageal structure and function.

Looking ahead, ongoing research is attempting to identify clinically relevant oesophageal motor and sensory dysfunction in UCP that will direct effective medical and psychological management when acid suppression fails.

Acknowledgement

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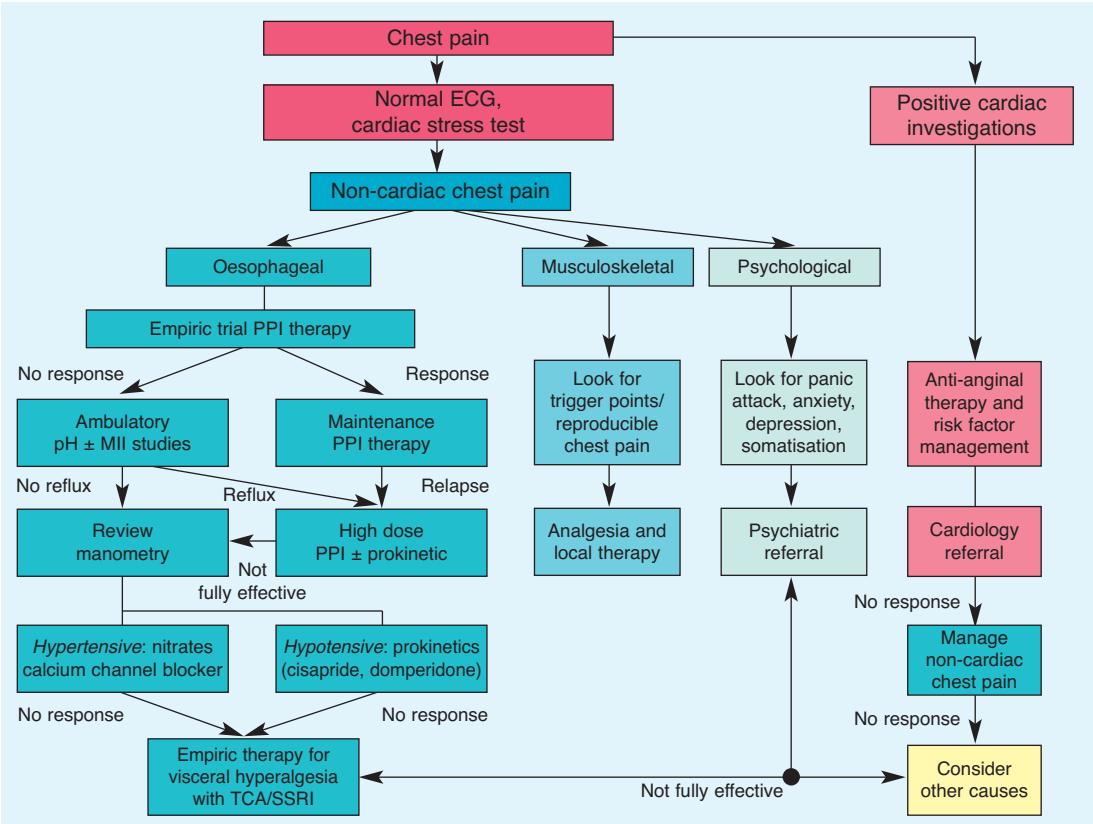

Fig 3. Algorithm for unexplained (non-cardiac) chest pain management. MII = multichannel intraluminal impedance; PPI= proton pump inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

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Treating functional lower gastrointestinal symptoms

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The most frequently occurring lower gastrointestinal (GI) symptoms can be considered in three groups:

- abdominal pain and/or bloating
- altered bowel function symptoms: constipation, increased bowel frequency or looser consistency stools
- rectal symptoms: the sensation of incomplete evacuation and the increased passage of mucus.

Symptoms tend to occur in clusters: for example, the irritable bowel syndrome (IBS), loosely definable as abdominal pain associated with any of the above symptoms. The frequent occurrence of these symptoms can be gauged from population-based studies showing a UK prevalence of approximately 20%.

Aetiology

The aetiology of lower GI symptoms is the focus of much research and it is clear that there are multiple relevant factors at peripheral gut, spinal and central nervous system levels. Advances in the understanding of how stress and mood disorders may influence the autonomic nervous system, visceral sensitivity and motility have led to a combined hypothesis that psychological factors and gut physiological abnormality may combine to result in functional symptoms (Fig 1).[1] No single treatment is likely to help all symptoms in these syndrome clusters so treatment is generally directed at individual symptoms, primarily pain, constipation and diarrhoea.

General management

The key to successful management of functional bowel disorders is strong, empathic reassurance, individually directed according to the patient's particular symptoms, beliefs and anxieties. A central component is provision of a simple explanation of the benign nature and prognosis of the condition. Patients should be advised that fewer than 2% of patients need functional diagnosis revision at 30 years of follow-up. The less good news is that 88% of patients have recurring episodes of GI symptoms, so reassurance should be tempered by awareness of their chronic and recurrent nature.[2]

The presence of alarm features mandates serological and luminal investigation to exclude organic disease. It is important not to overinvestigate younger patients as this may both exacerbate anxieties and undermine confidence in the clinician. One important diagnosis to consider, especially in the presence of low-grade anaemia, is coeliac disease. Approximately