Whatever happened to silent ischaemia?

Introduction

Myocardial ischaemia is a reliable predictor of significant coronary artery disease (CAD). During an episode of myocardial ischaemia, anginal pain may appear late or not at all, even in the presence of ischaemic changes on the electrocardiogram (ECG). This phenomenon of silent ischaemia was first described by Stern and Tzivoni in 1974.[1] As many as 70% of daily ischaemic episodes in stable CAD and 90% of episodes in unstable angina are silent.[2]

Over the past 20 years it has become apparent that the presence of myocardial ischaemia is associated with adverse outcomes in asymptomatic individuals as well as those with symptomatic CAD. The American Heart Association and the American College of Sports Medicine recommend, as a consequence, that apparently healthy men >45 years and women >55 years should have a maximal exercise treadmill test before starting a rigorous exercise regime.[3] Some studies indicate that symptomatic ischaemia is a stronger risk factor than silent ischaemia for future coronary events, others that silent ischaemia has a similar prognostic value. Controversy remains about the importance of silent myocardial ischaemia (SMI), the strategies for testing for it and how to manage this condition in people with and without risk factors for cardiovascular disease.

Types of silent ischaemia

Two forms of SMI have been described.[4] The less common type 1 occurs in patients with obstructive (and sometimes severe) CAD who never experience anginal symptoms and probably have a defective 'warning system'. Patient and physician may be unaware of the presence of ischaemic heart disease until the patient has a silent myocardial infarction or dies. These patients may be identified from the chance finding of ECG abnormalities at rest or during exercise testing (ETT) or on a 24-hour tape while being investigated for arrhythmias. In the Framingham study, 12.5% of all myocardial infarction (MI) patients had type 1 SMI.[5]

In the more common type 2 SMI, patients with stable, unstable or Prinzmetal's angina experience periods of both silent and symptomatic ischaemia. In these patients the total ischaemic burden may be defined as the total period of ischaemia, both symptomatic and asymptomatic.

Episodes of ST segment depression exhibit a circadian rhythm, being most common in the morning. Nocturnal episodes of SMI indicate two or three vessel CAD or left mainstem disease. The highest proportion of silent ischaemia is seen in single vessel disease, particularly left anterior descending artery disease; by contrast, most ischaemia is symptomatic in left mainstem disease.[6]

Silent ischaemia is found in 50% of patients with angina. It is more common among diabetics, especially those with left ventricular hypertrophy,[7] and the incidence of major cardiac events is higher among diabetics with SMI. SMI may also occur more often among patients with hypertension.[8] Some 30–40% of patients on regular haemodialysis experience silent myocardial ischaemia.[9] Among surgical patients, those with very high systolic blood pressures, those undergoing vascular surgery and those patients with a history of hypertension who undergo non-cardiac surgery are at increased risk. Postoperative SMI is strongly associated with pre-operative SMI.[10]

The mechanism of silent ischaemia

The exact mechanism of silent ischaemia is not clear. The following factors may be involved:[4]

- cardiac autonomic neuropathy (in diabetes mellitus)
- a high pain threshold, as exemplified by some patients' tolerance to other painful stimuli such as limb ischaemia
- production of high levels of endorphins, which increase the pain threshold
- less severe ischaemia or a shorter duration of ischaemia in asymptomatic episodes.

Detecting silent ischaemia

There are two common methods of detecting myocardial ischaemia – exercise testing (ETT) and ambulatory ECG monitoring (AECG). In one study the sensitivity of exercise testing in detecting silent ischaemia was 86.2% whereas the sensitivity of 24-hour ECG monitoring was 69.7%.[11] In a small group of patients, however, ischaemic events seem to be detectable only during 24-hour monitoring. The two tests may be used together for maximum sensitivity in detecting SMI although, in apparently healthy asymptomatic subjects, the clinical value of detecting SMI on ambulatory ECG alone is not established.

Prognostic implications

It has been suggested that ST segment changes not associat-

ed with chest pain that occur during stress testing do not necessarily reflect ischaemic changes and are a false positive finding. Such confusion may have arisen because stress tests have been used inappropriately.

However, several studies have shown that silent myocardial ischaemia demonstrated by exercise-induced ST segment depression is associated with subsequent poor outcome. In patients with known coronary artery disease, SMI detected on exercise testing identifies a high-risk group of patients with a greater risk of subsequent events.[12] Ambulatory ECG monitoring has similar prognostic value in unstable angina and post-MI patients. However, in patients with stable angina, stable myocardial ischaemia detected by AECG is less useful. Frequent and accelerating episodes of ST segment depression seen on ambulatory ECG, whether silent or symptomatic, predict a high risk of future events.[13]

In those patients who have never had angina, SMI on treadmill testing has been shown to be associated with a 400–500% increase in cardiac mortality[14] but it is not clear whether an ischaemic ambulatory ECG on its own provides independent prognostic information in these patients.[15]

Interestingly, 25–30% of patients demonstrate predominantly silent ischaemic episodes after coronary artery bypass surgery but they do not have a worse prognosis.[12] The Angina Prognosis Study in Stockholm (APSIS) was a prospective randomised trial involving double-blind treatment with metoprolol or verapamil in patients with chronic stable angina.[16] Ischaemia during ambulatory monitoring showed independent prognostic importance regarding cardiovascular death. Ambulatory electrocardiographic monitoring and exercise testing provided complementary information, but only among patients with marked ischaemia during exercise.

The prognosis in ischaemic heart disease may be determined by the total ischaemic burden rather than by the presence or absence of anginal pain. In a recent study, the functional significance of silent and symptomatic ischaemia was examined by comparing the perfusion abnormalities on SPECT.[17] In those patients with a high likelihood of coronary artery disease, chest pain tended to lose its apparent value as a clinical test parameter.

A recently published study by Laukkanen *et al*[18] investigated the prognostic significance of exercise-induced silent myocardial ischaemia in both high- and low-risk men aged 42 to 60 years with no prior coronary heart disease. In contrast to other studies, patients who developed chest pain during the baseline exercise test were excluded so that the prognostic importance of exercise testing in apparently healthy individuals was observed. Baseline characteristics showed that subjects with SMI had higher serum cholesterol, higher systolic blood pressure, higher maximal heart rate and lower maximal oxygen uptake.

Silent ischaemia during exercise predicted a higher risk of acute coronary events and CHD death, predominantly in those who were at high risk of developing CAD because they had one of the three major coronary risk factors (smoking, hypercholesterolaemia and hypertension). Even after adjustment for conventional risk factors, men with silent ischaemia during exercise still had a significantly increased relative risk of acute coronary events and CHD death. Even when silent ischaemia was detected during the post-exercise recovery phase, it was associated with adverse clinical outcome.

The findings of this study raise important clinical questions. It is obviously not feasible to screen every middle-aged man for silent myocardial ischaemia. The editorial accompanying the study[19] recommends a screening exercise stress test only for high-risk healthy subjects such as those with two or more coronary risk factors. It also recommends that myocardial ischaemia detected on exercise testing should be confirmed by an imaging or stress echocardiography study.

Treatment possibilities

In view of the prognostic importance of silent myocardial ischaemia, it seems clear that it should be treated in order to prevent myocardial infarction, left ventricular dysfunction and malignant arrhythmias. Drugs that are effective in preventing episodes of symptomatic ischaemia (such as nitrates, calcium channel blockers and beta blockers) also effectively reduce and eliminate episodes of silent ischaemia.[20] In one randomised study metoprolol was superior to diltiazem.[21] A combination of beta blocker and calcium channel blocker gives better results than either class of drug alone.[4] In the ASSIST study of 306 patients with asymptomatic or minimally symptomatic ischaemia, atenolol was associated with a significant reduction of silent ischaemia at four weeks compared to placebo. This resulted in a 56% relative reduction in adverse events (death, resuscitated ventricular tachycardia and fibrillation, non-fatal MI and unstable or worsening angina) at one year.[22]

The Asymptomatic Cardiac Ischaemia Pilot Study (ACIP) demonstrated that asymptomatic cardiac ischaemia is common and that it can be suppressed in 40–55% of patients with medication or revascularisation. Revascularisation was most effective in suppressing ischaemia. In addition, at two year follow-up, revascularised patients had a better clinical outcome (death, MI, cardiac hospitalisations) compared to medically treated patients.[23]

Since silent ischaemia, like symptomatic ischaemia, predicts an increased rate of death and myocardial infarction, it has been proposed that a reduced rate of silent episodes should be a basis for approval for drug treatment. The American Food and Drug Administration (FDA) has not approved this suggestion but has concluded that drugs for silent ischaemia need to show an effect on a clinical end point such as survival or rate of new infarction.[24] The recently presented IONA study, dis-

cussed later in this article, is the first large-scale randomised trial to report on the effect of anti-anginal medication on clinical outcomes. The improvement in outcome seen with nicorandil in stable angina patients is encouraging.

In those patients with type 1 SMI who have had a silent MI, it is reasonable to consider secondary prophylaxis with a beta blocker, aspirin and a statin. Their management in terms of coronary angiography and revascularisation should be no different from that of patients with symptomatic ischaemia, depending on the result of the post-MI exercise test.

Mild episodes of silent myocardial ischaemia in stable coronary artery disease do not usually lead to complications and therefore do not need further investigations or treatment.[25] Severe SMI in unstable CAD or SMI leading to (or presenting as) left ventricular dysfunction, MI or ventricular arrhythmias should be managed aggressively.

In diabetics, in whom SMI is common and more damaging, serious thought should be given to its early detection and treatment. Vigorous risk factor modification, including lipid reduction, is the least that can be done in this regard.

IONA: preliminary results show improved outcome

First results from the IONA study (Impact of Nicorandil in Angina) were presented at the American Heart Association meeting in November 2001: they show that nicorandil improves outcome in patients with chronic stable angina.[26] The study was conducted by the University of Glasgow in 5,126 patients with angina who were at higher than average risk of cardiovascular events. Patients were randomised to receive either placebo or nicorandil 10 mg twice daily, increasing to 20 mg twice daily after two weeks, in addition to their usual anti-anginal therapy.

Nicorandil reduced the combined end point of coronary heart disease death, non-fatal MI and unplanned cardiac hospitalisation by 17% (p=0.014). IONA confirms the cardioprotective effect of nicorandil that has been observed in previous studies and suggests that the drug may not only reduce symptoms but also potentially may save lives. These are exciting results which contain the potential for a new understanding of the mechanisms and treatment of myocardial ischaemia.

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