Mechanisms of painless myocardial ischaemia

ABSTRACT—The mechanisms responsible for the frequent absence of pain during episodes of acute myocardial ischaemia are poorly understood. The severity and duration of ischaemia are inadequate predictors of painless ischaemia, and thus it appears likely that important additional mechanisms must be involved. One such mechanism that may be operating in some patients is a generally deficient perception of painful stimuli. Destruction of afferent nerve fibres subserving cardiac nociception is a relevant consideration in some patients with diabetes mellitus and silent ischaemia. Psychological factors may also, in some patients, be important in modulating the ischaemic stimulus. The role of endorphins in the perception of cardiac ischaemic pain is uncertain. It is unlikely that the mechanisms responsible for painless myocardial ischaemia vary from patient to patient and even within the same patient from week to week or from day to day.

Chest pain is the symptom that most frequently causes the patient with ischaemic heart disease to seek medical attention. It is a symptom with which physicians are very familiar. Diagnosis is often predominantly based on this symptom, and it is towards the relief of angina that physicians mainly direct their therapeutic endeavours. However, an increasing body of evidence, accumulated mainly over the past 10 to 15 years, suggests that the heart’s ‘anginal warning system’ frequently fails to be activated during ischaemic events [1–5]. The result is episodes of myocardial ischaemia not accompanied by chest pain or other symptoms recognised by either the patient or the physician. Such asymptomatic ischaemic events are referred to as ‘silent ischaemia’ [1–5].

Painless episodes of myocardial ischaemia are now recognised as occurring frequently in patients with ischaemic heart disease and are a matter of considerable clinical importance. Ambulatory electrocardiographic (ECG) monitoring studies by Schang and Pepine [6] and by Deanfield et al [7] have demonstrated that, in patients with chronic stable angina, 75% of all episodes of transient acute myocardial ischaemia occurring during normal daily activities are unaccompanied by pain. This observation led Deanfield et al, in their landmark 1983 Lancet paper [7], to conclude: ‘... Chest pain seems to be an insensitive indicator of the true frequency of transient myocardial ischaemia, with many episodes remaining undetected by the patient. ...’ A further startling observation regarding the frequent absence of pain during episodes of acute myocardial ischaemia was provided by Kannel and Abbott’s 1984 report that approximately 20% of all myocardial infarctions, occurring in patients enrolled in the Framingham study, were painless [8]. In addition, continuous ECG monitoring studies, performed both in patients with the so-called ‘variant’ form of angina (Prinzmetal’s angina) and in patients with unstable angina in the coronary care unit, have demonstrated that in these patients the prevalence of asymptomatic ischaemic episodes is approximately 75% [3].

It is clear from these reports that the neural mechanisms responsible for alerting the anginal patient to the occurrence of episodes of myocardial ischaemia frequently fail to provide the appropriate warning signal. This is a baffling situation and one that has been the subject of considerable interest over the past 10 to 15 years [1–5]. However, despite much investigation, the mechanisms responsible for the frequent absence of pain during episodes of acute myocardial ischaemia are incompletely understood [3]. In this paper some of the mechanisms that are thought to contribute to the phenomenon of painless myocardial ischaemia are reviewed.

Adequacy of the ischaemic stimulus

It has been postulated that in painless, as opposed to painful, episodes of myocardial ischaemia there may be lesser amounts of myocardium in jeopardy [9]. However, Deanfield, in a study of patients with chronic stable angina, using the technique of position emission tomography, demonstrated large defects in rubidium-82 uptake that were totally silent [7]. Similarly, Maseri et al [10] reported massive defects of thallium scintigraphy in patients with variant angina that were unaccompanied by any symptoms.

A number of studies have compared the severity of ischaemia occurring in painless and painful episodes. Chierchia et al [11] identified 293 episodes of transient acute myocardial ischaemia, of which 84% were asymptomatic. In comparing asymptomatic and symptomatic episodes they found that, on average, the former were shorter in duration and produced less impairment of haemodynamic function. However,
there was a considerable overlap in respect to these measurements between painful and painless episodes. In this study ischaemic episodes were invariably painless when less than three minutes in duration or when associated with increase in left ventricular filling pressure less than 7mm Hg [11]. However, above these levels it was impossible to predict whether an episode would be painful or painless on the basis of duration or severity of ischaemia. Deanfield et al [7], using the technique of ambulatory ECG monitoring, reported that in patients with chronic stable angina, painless episodes were somewhat shorter in duration and less severe when compared with painful ones; but there was again a considerable overlap. Furthermore, in this study most (63%) of the profound (>3mm) episodes of ST segment depression were asymptomatic. Additional evidence against the concept of ‘the inadequate ischaemic stimulus’ as the sole explanation for painless myocardial ischaemia is provided by the recent observations of Davies et al [12]. Using radionuclide techniques, these workers demonstrated that increases in the magnitude and rate of ventricular volume changes were similar during both painful and painless episodes of myocardial ischaemia.

These studies suggest that, although the severity and duration of myocardial ischaemia are related to the production of angina, they do not appear to be particularly accurate predictors of whether or not an acute ischaemic episode will be painless or painful. Consequently, it appears reasonable to suggest that additional mechanisms must be involved in the production of the symptom of angina [3].

Generalised defective perception of painful stimuli

This has been proposed as an important mechanism of painless myocardial ischaemia both by Droste and Roskamm [13] and by Glazier et al [14]. To test this hypothesis, the latter workers identified a group of 12 patients with predominantly painless episodes of myocardial ischaemia both on exercise testing and during ambulatory ECG (Holter) monitoring studies, and a group of 15 patients with predominantly painful ischaemic episodes [14]. Importantly, the severity of ischaemia, as assessed by the ST segment response during exercise testing and Holter monitoring, was comparable in the two patient groups. The study patients were then subjected to a battery of painful stimuli (induced forearm ischaemia, ice-cold water and electrical skin stimulation). For each stressor, two measurements were recorded: pain threshold (the point at which the patient perceived the stimulus as painful), and pain tolerance (the point at which the patient declined to be exposed further to the noxious stimulus). In the group of patients with predominantly painless myocardial ischaemia, the mean threshold and mean tolerance values were significantly greater than those recorded in the group of patients with predominantly painful episodes of ischaemia. Thus, the patients in the former group not only showed a decreased ability to perceive a stimulus as noxious (pain threshold) but also endured perceived pain at higher levels (pain tolerance). However, although the mean threshold and tolerance values between the two groups achieved statistical significance for all stressors, the overlap between the groups was considerable. Therefore, while a generalised defective perception of painful stimuli may well account for painless myocardial ischaemia at one end of the spectrum, other mechanisms must be responsible for the absence of pain, particularly in those patients with painless ischaemia in whom threshold and tolerance for painful stimuli are similar to others with predominantly painful episodes [14].

Endorphinergic mechanisms

A number of investigators [15, 16] have suggested that endorphins may play an important role in painless myocardial ischaemia. Of the several central nervous system (CNS) networks that modulate pain, the endorphin-mediated analgesic system has received considerable attention [17]. When activated this system produces selective suppression of nociceptive dorsal horn neurons, and consequent analgesia [17]. Critical to its activation are the opioid peptides. There is now abundant evidence for an important role for this system in various pain syndromes. However, studies concerning the possible role that endorphinergic systems may play in the modulation of ischaemic cardiac pain have yielded considerably conflicting results. Van Rijn and Rabkin [15] reported that administration of the opioid antagonist, naloxone, resulted in the earlier appearance of ischaemic pain during treadmill stress testing in six patients with exercise-induced angina. Ellestad and Kuan [18], using a similar protocol, studied 10 patients with persistently painless ischaemia on exercise testing. Naloxone failed to unmask anginal pain in any of these 10 patients. Sheps et al [16] measured circulating beta-endorphin levels before and after exercise testing in 25 patients with coronary artery disease. They found that, in comparison to patients who developed angina during exercise testing, those who did not develop this symptom achieved significantly higher peak levels of beta-endorphin. However, the results of this study must be interpreted with caution as the contribution of circulating, as opposed to central, opioid peptides to analgesia has not been established [19].

Damage of nerve pathways responsible for the transmission of cardiac ischaemic pain

This is probably an important mechanism of painless myocardial ischaemia in some patients with diabetes mellitus and coronary heart disease. Silent ischaemic events occur much more frequently in patients with diabetes mellitus and ischaemic heart disease than in
non-diabetic patients with ischaemic heart disease [20]. Faerman et al [21] have observed distinctive histological features in the autonomic nerves of patients with diabetes mellitus dying of painless myocardial infarction (which are not present in diabetic and non-diabetic patients dying with a painful myocardial infarction). The distinctive histological features noted by Faerman et al included:

1. fragmentation of nerve fibres and a decrease in number of fibres;
2. argentophilic spherical swellings;
3. hyperargentophilia;
4. beading and vacuolated thickening of the fibres [21].

These specific nerve lesions may provide a partial explanation for the frequent occurrence of silent ischaemic events in some patients with diabetes mellitus.

Psychological factors

Pain is a private emotion that is influenced by personality, ethnic and social background, previously learned behaviour, emotional state, and psychological expectations [22]. Such influences are hard to measure by conventional scientific methodology. However, the results of a study by Droste and Roskamm suggest that these factors are important in the perception of cardiac ischaemia pain [13]. These authors compared the personality profiles of a group of patients who generally failed to experience pain during ischaemia induced by exercise stress testing and a group who consistently experienced angina in the same setting. The group of patients with painless ischaemia had significantly lower scores for the characteristics of nervousness and excitability [13]. But in this study, too, there was a considerable overlap between the two study groups.

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