MECHANISMS AFFECTING THE SYMPTOMATIC EXPRESSION OF MYOCARDIAL ISCHAEMIA

M.D. Thesis

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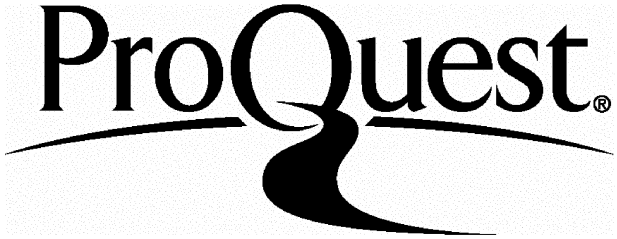

ABSTRACT

The symptomatic expression of myocardial ischaemia varies between and within patients and mechanisms are poorly understood. The aim of this thesis has been to determine factors which account for this variation in patients with stable angina and acute myocardial infarction.

In stable angina, myocardial ischaemia will only provoke symptoms if the magnitude of the ischaemic stimulus exceeds the sensory threshold for experiencing angina and this explains much of the within patient variation. Ischaemic mass may also account for the between patient variability, although in diabetic patients, perceptual dysfunction caused by subclinical neuropathy plays an additional role. Endogenous opiates do not appear to influence the perception of myocardial ischaemia. Other factors affecting the symptomatic expression of myocardial ischaemia include environmental temperature and cold-intolerant patients appear to have impaired baroreceptor function which may result in a greater increase in heart rate in the cold.

In acute myocardial infarction, cold also appears to play a role, with more infarcts occurring on colder days in both summer and winter. Following acute myocardial infarction, myocardial ischaemia is common and frequently silent. Damage to the innervation of the myocardium may account for the low level of symptoms in the early post-infarction period, but does not account for the variation between and

within patients. As in stable angina, the magnitude of the ischaemic stimulus is an important determinant of symptoms in these patients.

Comparison of patients with stable angina and acute myocardial infarction demonstrates an association between circadian variation in sympatho-vagal balance and episodes of ambulatory myocardial ischaemia. Thus patients with stable angina have a peak in sympatho-vagal balance in the waking hours which corresponds with a peak in ambulatory ischaemia. This is in distinction to patients with acute myocardial infarction, in whom the circadian variation in sympatho-vagal balance and ambulatory ischaemia is reduced.

In most patients with stable angina, the absence of symptoms during an episode of myocardial ischaemia probably reflects an inadequate intensity of ischaemia. A logical consequence may be that it is relatively unimportant to detect and treat asymptomatic myocardial ischaemia. However, in some patients, particularly those with diabetes, a subclinical neuropathy may impair the perception of myocardial ischaemia despite what would be considered an adequate stimulus in another patient. It may be worthwhile screening such patients for myocardial ischaemia even if symptoms are not prominent.

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INTRODUCTION

1.1 CARDIAC PAIN AND MYOCARDIAL ISCHAEMIA

Understanding of the link between cardiac pain and myocardial ischaemia has been a dynamic process which remains incomplete more than two hundred years after angina was first described by William Heberden[1] in 1768. As early as 1866, Potain associated the sensation with that from ischaemic skeletal muscle[2], and in 1903, Colbeck recognised the association of coronary atheroma with angina, suggesting that atheroma led to chronic subclinical myocardial damage[3]: "*The areas of degenerated ventricular wall are thus unable to take their proper share in resisting the increased intra-cardiac pressure and in consequence undergo more or less distension and stretching. Herein lies the explanation of the pain*". Parry was the first to suggest that myocardial ischaemia was responsible for the pain[2]. Of diseased coronary arteries he said: "*though a quantity of blood may circulate through these arteries, sufficient to nourish the heart, as appears, in some instances, from the size and firmness of that organ, yet there may probably be less than what is requisite for ready and vigorous action*". This view was supported by Keefer and Resnik[4], and Lewis[2] proposed that a chemical mediator, "substance P", was produced in ischaemic myocardium and was responsible for the pain. However, while not ruling out ischaemia as a cause of cardiac pain, Martin and Gorham[5] demonstrated that mechanical stretch of the coronary artery could elicit chest pain in dogs. Over the last 50 years, the association between pain and

ischaemia has become firmly established, although it is increasingly appreciated that these two variables are not necessarily interdependent: angina can occur without myocardial ischaemia, and myocardial ischaemia frequently occurs without angina.

1.2 DEFINITION OF SILENT MYOCARDIAL ISCHAEMIA

Colbeck[3] was perhaps the first to recognise that the pathophysiological changes usually associated with angina may not always be accompanied by pain, and he attributed "*angina sine dolore*" to destruction of nervous tissue in the myocardium. In the last two decades, it has been increasingly recognised that myocardial ischaemia is not invariably associated with anginal symptoms, a scenario described as silent myocardial ischaemia. Cohn[6] has defined this as "*objective evidence of myocardial ischaemia (by direct or indirect measurements of left ventricular function, perfusion, metabolism, or electrical activity) without chest pain or other anginal equivalents*", and few authorities would disagree with this[7].

Cohn has considered three types of silent myocardial ischaemia[8] which vary in prevalence and prognosis. Type 1 includes patients with objective evidence of myocardial ischaemia who have never experienced angina, type 2 incorporates patients with a previous myocardial infarction who are now asymptomatic and type 3 comprises patients who have angina in addition to episodes of silent ischaemia. The distinction between types 1 and 3 may be artificial: group 1 may simply be at

one extreme of a spectrum. However, the three groups can be usefully considered separately in the following discussion, as they differ in prevalence and detection, and possibly also in pathophysiology.

1.3 PREVALENCE OF SILENT MYOCARDIAL ISCHAEMIA

1.3.1 Silent Myocardial Infarction

Myocardial infarction without symptoms has been recognised for many years[9]. The Framingham study found evidence of myocardial infarction based on changes on the resting electrocardiogram in 259 people, over 18 years of follow-up[10]. Sixty (23%) of these were unrecognised but in 28, a careful history revealed symptoms compatible with myocardial infarction; hence, 32 (12%) were truly silent.

1.3.2 Type 1: Asymptomatic Patients

The prevalence of silent myocardial ischaemia in an asymptomatic population without prior history of cardiac disease is more difficult to determine. Erikssen et al[11] screened 2014 apparently healthy asymptomatic middle aged (40 - 59 years) Norwegian men; 50 had positive exercise stress tests and angiographically proven coronary artery disease, a prevalence of 2.5%. Froelicher et al[12] found a similar prevalence in 1390 asymptomatic male United States Air Force Personnel.

1.3.3 Type 2: Following Acute Myocardial Infarction

Petretta et al[13] detected ST segment depression in 64 of 270 (24%) asymptomatic patients during ambulatory Holter monitoring performed a mean of 13 days after an uncomplicated first myocardial infarction. Ouyang et al[14] studied 59 patients 4 days post-infarction and found episodes of ST segment depression in 27, all of which were asymptomatic. Fox et al[15] reported on 359 post-infarction patients who underwent a pre-discharge sub-maximal treadmill stress test. 185 patients developed ST segment changes which were silent in 103 cases (56%). These results are similar to those of de Belder et al[16], who detected ST segment depression in 104 of 262 patients during a limited treadmill test at a median of 11 days post-infarction. Ischaemia was silent in 67 (64%). Thus ischaemia is common in the early post-infarction period and is often silent.

1.3.4 Type 3: Stable Angina Pectoris

Stern and Tzivoni[17] were one of the first investigators to report a high frequency of painless ischaemia on ambulatory Holter monitoring and there have been numerous studies examining the relation between ST segment depression and symptoms[18-25]. The largest of these (Mulcahy et al[23]) included 150 patients with angina and documented coronary artery disease and found that 85% of patients with ST segment depression had episodes of silent ischaemia; 30% had only silent episodes. Cecchi et al[20] studied 39 patients without proven coronary disease and found silent ischaemia in 75%. Most studies have found that 75% of ischaemic episodes are silent[20,24], although this figure tends to be lower in studies where patients had angiographically confirmed coronary artery disease[22,25]. Thus

symptoms represent the tip of the ischaemia iceberg, and the term "total ischaemic burden" has been used to denote the sum of painful and painless myocardial ischaemia[26].

There have been few studies comparing the perception of ischaemia between patients with stable angina and those in the post-infarction period. A recent study by Taylor et al[27], however, suggested that perception may be reduced after myocardial infarction. These investigators reported that chest pain during coronary angioplasty was twice as likely to occur in patients with stable angina than in those with recent myocardial infarction (64 versus 30%), although the degree of ischaemia was similar in the two groups as judged by changes in ST segment and pulmonary capillary wedge pressure.

1.4 METHODS OF DETECTING SILENT ISCHAEMIA

The ability of any test to identify patients with a disease is measured by the positive predictive value. According to Bayes theorem[28], this is dependent on the sensitivity, specificity, and the prevalence of the disease in the population under study. Thus the value for a given test will depend greatly on the population to whom it is applied. In a population with a high probability of disease, such as elderly patients with typical exertional angina the specificity becomes much more critical than the sensitivity. On the other hand, in screening a less selective population, such as patients with atypical chest pain, a high sensitivity is essential.

From the discussion in section 1.2, it can be seen that a diagnosis of silent myocardial ischaemia requires objective evidence of ischaemia. Ischaemia, defined as an imbalance between myocardial oxygen supply and demand, is not measured directly, but rather its pathophysiological sequelae. Nesto and Kowalchuk[29] have described an ischaemic cascade where diastolic dysfunction and then systolic dysfunction precede electrocardiographic changes and then angina. Chierchia et al[30] studied six patients with angina at rest associated with ST-T wave changes and found that pain, when it occurred, was a late phenomenon in relation to a fall in coronary sinus oxygen saturation, a rise in left ventricular end diastolic pressure and electrocardiographic changes. During the more controlled but less physiological situation during percutaneous transluminal coronary angioplasty, Hauser et al[31] found that following balloon inflation, changes in ventricular wall motion occurred after 19 seconds, ST segment changes at 30 seconds, and chest pain at 39 seconds. Hence the method of detection will influence the diagnosis of ischaemia. These methods may be considered in four categories: 1, demonstration of reversible myocardial perfusion defects, 2, left ventricular wall motion abnormalities, 3, detection of ST segment changes on electrocardiography and, 4, detection of myocardial metabolites.

1.4.1 Myocardial Perfusion

Thallium scintigraphy, either planar or using computerised tomography, is now widely used for assessing myocardial perfusion with a sensitivity of 80 - 90% and a specificity of 90%or more[32,33]. However, despite this high level of diagnostic performance, where the pretest probability of coronary disease is very low, false

positive results are common. Dipyridamole or dobutamine may be used as an alternative to a conventional exercise protocol, and has the advantage of allowing some quantification of the extent of myocardial ischaemia[34]. However, significant radiation exposure occurs during thallium scintigraphy and this becomes increasingly important when repeated tests are performed. Positron emission computerised tomography using rubidium-82 has a high sensitivity and specificity for the detection of coronary artery disease, and its short half-life allows repeated studies in the same individual[24,35,36].

1.4.2 Ventricular Wall Motion

Any technique capable of evaluating ventricular function, such as exercise echocardiography[37,38] and digital subtraction ventriculography[39], may be useful in identifying myocardial ischaemia. In recent years, there has been increasing experience of ambulatory radionuclide ventriculography using a device known as the VEST[40,41], a portable battery powered device incorporating a radionuclide detector and a Holter electrocardiogram[42]. Technetium-99m, which has a half life of 7 hours, is injected at the beginning of the study, and the patient may be ambulant for several hours during which data are accumulated and stored. As well as providing details of changes in systolic left ventricular function and ST segments, changes in ventricular filling may be observed, affording a measure of early ischaemia[29,41]. Use of this technique suggests that up to 20% of silent and 50% of painful episodes would not be diagnosed by ambulatory ST segment monitoring alone[41].

1.4.3 ST Segment Changes

Ambulatory Holter monitoring and exercise stress testing rely on ST segment changes to detect myocardial ischaemia; haemodynamic responses[43] and symptoms[44] may provide additional information. Although there have been many studies assessing the sensitivity and specificity of these techniques for diagnosing ischaemic heart disease, the results do not necessarily reflect the reliability of the tests for detecting myocardial ischaemia. ST segment changes on the surface electrocardiogram have been reported to have poor sensitivity for myocardial ischaemia, perhaps reflecting their late occurrence in the ischaemic cascade. Thus, Friedman et al[45] found that of 21 patients undergoing coronary balloon angioplasty who developed ST segment changes detected by an intra-coronary electrode, only nine had changes on the surface electrocardiogram. Stern and Tzivoni[17] were the first to use Holter monitoring for detection of ischaemia in the ambulatory setting, and it has now been used in numerous studies of angina and silent ischaemia[18,20,25,46-51]. Advances in technology mean that both AM and FM recorders can be used, but adequate assessment of the ST segment is very dependent on the frequency response and phase shift characteristics of the equipment used as well as the playback speed[52]. The prevalence of ST segment changes unrelated to myocardial ischaemia can be inferred by examining a normal population[12,53-56]. Eggeling et al performed Holter monitoring in 100 healthy medical students and 24 children[55]. Only six subjects (five female) developed ST segment changes with no apparent cause. No subject in this study had evidence of postural ST segment changes. Deanfield et al[54] studied 80 asymptomatic volunteers and 20 patients with non-cardiac chest pain and normal coronary arteries. T wave changes were

common, and ST segment elevation occurred in five subjects; these could be reproduced in three of the patients by postural changes. However, only two men had ST segment depression, and each episode lasted less than 20 beats. Thus, these studies have shown a low prevalence of ST segment depression in a population with a low pre-test likelihood of coronary artery disease. In contrast, Armstrong et al[56] found ambulatory ST segment depression in 30% of 50 asymptomatic middle aged men, but little data are available on the duration of these episodes and coronary artery disease was not excluded in these subjects.

In order to confirm that ST segment depression on Holter monitoring represented myocardial ischaemia, Deanfield et al[36] performed simultaneous Holter monitoring and positron emission tomography using rubidium-82 and found that over 97% of episodes of ST segment depression were associated with perfusion defects. This study also demonstrated that the degree of ST segment depression reflected the severity of the perfusion defect. In a study of Holter monitoring, Günther et al[50] found a sensitivity of 62% in 79 patients with documented coronary disease, comparable to their findings of 68% on exercise testing. Thus, Holter monitoring may not have a high specificity in the diagnosis of coronary artery disease, but it provides a reliable means of detecting episodes of ischaemia in patients with documented coronary disease.

The sensitivity of exercise stress testing in the diagnosis of coronary disease ranges from 40 to 95%, depending on the study and the severity of disease[57]. The protocol chosen for exercise stress testing may also influence the result; thus a

high level test, such as the Bruce protocol, is more sensitive than a low level test[58,59]. The choice of leads may also affect sensitivity[43], for example the use of lead CMV_5 can improve sensitivity at the expense of decreasing specificity.

Specificity may be improved by the combination of diagnostic tests[32] and utilising detailed analysis of the shape of the ST segment[60]. Further improvements may be made by discounting ST segment elevation[53,54,61,62], up-sloping ST segment depression[54], down-sloping ST segment depression during tachycardia[53] and transient episodes of ST segment change lasting less than 1 minute[54]. Excluding patients with postural[54,63] and resting ST segment abnormalities, electrolyte disturbances, hyperventilation, left ventricular hypertrophy, pre-excitation syndromes, intra-ventricular conduction defects, mitral valve prolapse and those taking drugs such as cardiac glycosides, can further enhance the specificity[12].

1.4.4 Detection of Myocardial Metabolites

Non-ischaemic myocardium preferentially metabolises free fatty acids rather than glucose, but the reverse is true in the ischaemic myocardium. Positron emission tomography can detect ischaemia as a decrease in perfusion using a marker such as nitrogen-13 ammonia in association with an increased uptake of ^{18}F-2-fluoro-2-deoxyglucose, a marker of glucose metabolism[64]. This technique remains a research tool[65], but simple though more invasive techniques, such as measurement of lactate in the coronary venous system, have been used to diagnose and quantify myocardial ischaemia[66,67].

1.5 PROGNOSIS OF SILENT ISCHAEMIA

The clinical importance of detecting silent ischaemia remains contentious. Nevertheless, the concept that patients with silent ischaemia may lack the "warning" of pain, predisposing them to malignant arrhythmias, is certainly a cause for concern[68,69]. Turitto et al[70] studied 60 patients with angina and ischaemia on Holter monitoring and found that as well as having greater total ischaemia, patients with ventricular arrhythmias had a higher proportion of painful ischaemia. However, in the arrhythmia prone group, 13% of silent episodes were associated with ventricular arrhythmias.

Ischaemia is a marker of coronary artery disease, and may predict the need for revascularisation, acute cardiac events and death. Whether this is true only of symptomatic ischaemia, or whether it also applies to silent ischaemia is uncertain. However, the concept of total ischaemic burden (the sum of painful and painless ischaemia) is being considered increasingly important both as a marker of prognosis[26,71,72] and a target for treatment[21,49,71-75]. It is helpful to consider the three types of silent myocardial ischaemia separately.

1.5.1 Type 1: Asymptomatic Patients

Patients with type 1 silent ischaemia may have critical coronary disease[76], and at increased risk of cardiac events. Thus, a population study in Malmö ("Men born in 1914") reported an increased incidence of fatal and non-fatal myocardial infarction among 98 of 394 asymptomatic 68 year old men with ST segment depression

during 24 hour ambulatory electrocardiography[77], and findings have been similar in asymptomatic populations screened by exercise stress testing[72,78].

1.5.2 Type 2: Following Myocardial Infarction

Ischaemia in the post-infarction setting is clearly associated with an adverse prognosis[15,16,79-83], but direct comparisons of events in patients with painful and silent ischaemia on exercise stress testing have shown no significant difference[15,16,82]. However, de Belder et al[16] found a trend towards a higher incidence of death and non-fatal myocardial infarction in patients with silent ischaemia, while Fox et al[15] found a trend in the opposite direction. From the currently available data, it is not clear if patients with painless ischaemia following acute myocardial infarction have a different outcome from their symptomatic counterparts, and their optimal management remains unknown. Until further data are available, an understanding of the mechanism whereby some patients are asymptomatic may help to rationalise management.

1.5.3 Type 3: Angina Pectoris

The high event rate in unstable angina makes it possible to compare outcomes in relatively small numbers of patients, with and without silent ischaemia. A consistent finding has been that ST segment depression during and after unstable episodes is a marker of poor prognosis. Thus, Gottlieb et al[84] found silent ischaemia on Holter monitoring to be the strongest predictor of myocardial infarction (better than coronary anatomy) over 1 month follow-up in 70 patients with unstable angina. Wilcox et al[85] performed Holter recordings in 66 patients with unstable angina

during the first 24 hours of admission and found that transient ST segment depression predicted myocardial infarction and death with a specificity of 92% and a sensitivity of 25%.

Tzivoni et al[86] followed up 56 patients with stable angina and a positive exercise test for a mean of two years and found a higher incidence of myocardial infarction and death in the 43 patients with ischaemia on ambulatory monitoring regardless of symptoms. Studies of exercise stress testing in patients with angiographically proven coronary disease have shown that the prognosis of patients with silent ischaemia is similar to[87] or worse than[88] of those with painful ischaemia.

Given the low rate of myocardial infarction and death in patients with stable angina[89] the numbers required to compare prognoses in groups with and without silent ischaemia are inordinately large. A multi-centre pilot study is currently recruiting 600 patients with coronary artery disease, ischaemia on exercise stress testing and at least one episode of ischaemia on 48 hour Holter monitoring[90]. Patients are randomised between symptom directed medical therapy, ischaemia directed medical therapy (both placebo controlled), and revascularisation. The primary end point in this pilot study is ischaemia on Holter monitoring at 12 weeks, and if warranted, a full scale mortality study will follow. The TIBET (Total Ischaemic Burden European Trial) is also examining the effect of medical therapy on prognosis in patients with myocardial ischaemia, but the results of this trial too are still awaited. Thus current data do not permit a direct comparison of prognosis of anginal patients with purely symptomatic and those with combined symptomatic

and asymptomatic ischaemia. To target therapy at relieving symptoms, when 75% of ischaemic episodes during daily activities may be silent, seems to be under-treatment, particularly as silent ischaemia has been shown to precede myocardial infarction, at least in patients with unstable angina[84,91]. On the other hand, to recommend revascularisation to a relatively asymptomatic patient with ischaemia on non-invasive testing cannot be justified at present[92]. Again, until further data are available regarding the prognosis of silent ischaemia and the consequences of treatment, an understanding of the underlying mechanism may help in the management of this condition.

1.6 THE MECHANISM OF ANGINAL PAIN

1.6.1 Variation Between and Within Patients

There is a wide variation in symptoms both between and within patients with coronary artery disease[93]. Thus, patients with type 1 silent ischaemia, who never experience pain, lie at one end of a spectrum, and at the other extreme are those patients who experience symptoms with every episode of ischaemia. In addition, within a given patient, symptoms may occur with one episode of ischaemia and be absent with another. Any theories of pain perception in myocardial ischaemia must take account of these variations.

There are two groups of patients who may be particularly prone to silent myocardial ischaemia; the elderly and diabetic patients.

Miller et al[94] studied 35 patients with ischaemia and angina on exercise testing and found that the time from onset of ischaemia to onset of angina was positively correlated with age, independent of severity of coronary disease or changes in left ventricular function. Umachandran et al[95] found a similar correlation in 82 patients, and also observed that autonomic function correlated with age, a finding supported by other workers[96]. Callaham et al[97] reported exercise test findings in a heterogenous population of 1773 patients, and found an increasing prevalence of silent ischaemia with age, from 7% in those under 50 years to 36% in those ≥ 70 years, although only 326 patients underwent coronary angiography.

Silent myocardial infarction is more common in diabetic patients[10,98] particularly those with autonomic neuropathy[99,100]. Several studies have suggested that silent ischaemia is also more prevalent in diabetic patients[101,102], but this has not been a consistent finding[97,103]. Nesto et al[101] compared symptoms during exercise thallium-201 scintigraphy in 50 diabetic and 50 non-diabetic patients; most had a history of angina, others had atypical chest pain, recent myocardial infarction or were asymptomatic. Angina during exercise testing was less common in the diabetic patients (28% versus 68%), but there was no angiographic confirmation of coronary disease. Naka et al[102] recently reported a study of exercise testing in 172 diabetic patients and 168 controls recruited from a hypertension clinic, all asymptomatic. Although similar numbers of patients in each group had ST segment depression on exercise treadmill testing (41 versus 42), coronary angiography demonstrated a significant stenosis in 14 of the diabetic patients compared with six controls. This study, therefore, suggests that type 1 silent ischaemia is more

common in the diabetic patients, and also serves to highlight the potential pitfalls of relying on non-invasive tests for diagnosing coronary artery disease in an asymptomatic population. Callaham et al[97] found no difference in the prevalence of silent ischaemia on exercise testing between patients with and without diabetes. However, the diagnosis of diabetes was based on pharmacy prescriptions so that patients not on hypoglycaemic therapy were classified as non-diabetic, and the conclusions must be treated with caution. Chipkin et al[103] found a similar prevalence of silent ischaemia in diabetic and non-diabetic patients undergoing treadmill testing. However, the number of diabetic patients was small (26), and less than half the patients underwent coronary angiography. In summary, therefore, the data are conflicting and it remains unclear to what extent, if any, diabetic patients are more prone to silent myocardial ischaemia.

1.6.2 The Noxious Stimulus and Nociception

Since Lewis[2] proposed that ischaemic pain was mediated by "substance P", there has been considerable support for the chemical hypothesis, although Martin and Gorham's mechanical hypothesis[5] has never been disproved. Bradykinin, potassium, lactate and adenosine are all potent algesic agents under experimental conditions[104,105], and have been postulated as mediators of ischaemic pain. Adenosine can provoke angina when given intravenously and by intra-coronary injection[106]. Crea et al[106] have shown that patients with silent ischaemia tolerated a longer infusion of adenosine and reported less severe pain. However, this may reflect a general hyposensitivity to pain, rather than supporting a definite pathophysiological role for adenosine. Intra-coronary bradykinin may also produce

pain[107] and Kurita et al[108] found reduced levels of plasma bradykinin in patients with silent ischaemia, compared with those with angina during treadmill testing. Lactate levels increase during myocardial ischaemia, but it seems unlikely that this is the cause of pain since patients with McArdles syndrome, who are unable to synthesise lactate, may still experience pain in ischaemic muscle[105].

As well as uncertainty regarding the form of the noxious stimulus, there are also questions concerning the nature of receptors and transmission to the central nervous system. Malliani and Lombardi[109] were the first to apply the 'specificity' and 'intensity' theories of nociception to myocardial pain. The 'specificity' theory suggests that nociceptors are specific and will only respond to a noxious stimulus, whereas the 'intensity' hypothesis suggests that adequate stimulation of non-specific receptors may elicit pain. Teleologically, it seems unlikely that receptors in the myocardium would exist for the single purpose of mediating pain. In addition, such specific receptors would be expected to have no background discharge, until a noxious stimulus was applied. Somatic receptors of this type have been identified[110], but despite extensive investigation of the cardiac afferent supply, Malliani found no evidence of recruitment of silent fibres, even with injection of intra-coronary bradykinin[107], indicating that the "specificity" theory does not apply to cardiac pain[111].

Malliani has expanded on the "intensity" theory by proposing the "spatio-temporal pattern" hypothesis[112,113], suggesting that episodes of myocardial ischaemia may activate different afferent codes as a result of interaction of complex mechanical

and chemical events, the nature of which remain to be determined. Droste and Roskamm[114] have suggested that this may account for the observation that a small area of myocardium with intense ischaemia may provoke pain more readily than a large area of less intense ischaemia.

1.6.3 Afferent Cardiac Nerve Supply

The myocardial afferent nerve supply runs from receptors in the atria and ventricles via the vagus but more importantly by means of the sympathetic supply to the heart[109]. Ventricular sympathetic afferents are small myelinated or unmyelinated fibres with spontaneous impulse activity which respond to haemodynamic stimuli; vagal fibres are unmyelinated. These pathways provide a potential site for modification of nociception, and may be particularly affected in acute myocardial infarction[100] or in diabetic patients with neuropathy. There have been many studies aimed at elucidating associations between silent ischaemia and neuropathy in diabetic patients, but results have been contradictory[115-120]. Spinal transmission is largely by the spinothalamic tracts and at this level there are complex stimulatory and inhibitory processes which allow for the modulation of sensation by efferent signals and spinal reflexes[121]. Sheps et al[122] have demonstrated that mean arterial pressure correlated with somatic pain tolerance and suggested that baroreceptors may have a mediating role in somatic pain perception.

1.6.4 Central Processing

There are two endogenous pain inhibitory systems, one neural and the other hormonal[114]. The neural pathway descends via the periaqueductal grey matter with

met-enkephalin and adrenaline acting as synaptic neurotransmitters. The humoral system releases beta-endorphin from the anterior pituitary gland, particularly during exercise and also as part of the stress response[123]. There have been several studies aimed at elucidating the role of endogenous opiates but the results have been contradictory[124-131].

Cognitive factors play an important role in mediating painful symptoms[132], and there have been several studies examining psychological factors and silent ischaemia[133-135]. Janne et al[133] applied three self rating psychological scoring systems to patients with coronary artery disease and ischaemia on thallium scintigraphy. Asymptomatic patients tended to have higher scores, implying an under-complaining tendency. However, whether this was causal, or a consequence of lack of symptoms was not established. Light et al[134] have shown an association between symptoms on treadmill testing and a high depression score, but Freedland et al[135] found that patients with silent ischaemia tended to have reduced awareness of bodily functions (measured by the Autonomic Perception questionnaire) but no difference in the tests which influence symptom reporting behaviour or measure denial of symptoms.

1.7 OUTLINE OF THESIS

The association between myocardial ischaemia and chest pain is variable. A number of potential mechanisms may account for this variability, but their relative

importance both within and between patients remains poorly understood. In this thesis, mechanisms affecting the symptomatic expression of myocardial ischaemia have been explored. Attention has been directed towards patients with stable angina pectoris (Section 1: chapters 2 - 5) and patients with acute myocardial infarction (Section 2: chapters 6 - 9). Chapter 2 examines the interaction of ischaemic and perceptual factors in a group of patients with stable angina. In chapter 3, the influence of endogenous opiates has been studied in the same patients, with emphasis on their potential role in modulating the perception of cardiac pain and their involvement in the physiological response to stress. Chapter 4 investigates mechanisms of silent ischaemia in diabetic patients while in chapter 5, the variable effects of cold exposure on ischaemic cardiac pain is examined. In section 2 (chapter 6), circadian, seasonal and temperature influences on the pathogenesis of myocardial infarction have been studied. Chapter 7 examines the interaction of ischaemic and perceptual factors in the post-infarction period, and chapter 8 compares mechanisms affecting the perception of ischaemic cardiac pain in patients with stable angina and patients with recent acute myocardial infarction. In chapter 9, circadian variations are used again to elucidate the influence of the autonomic nervous system on ischaemia in these patients. The final chapter summarises the results and their possible implications as well as suggesting further useful research projects.

In this thesis, two techniques have been used for the diagnosis of myocardial ischaemia: exercise treadmill testing and 48 hour ambulatory Holter monitoring. Exercise treadmill testing was chosen over a more specific test such as thallium-

201 myocardial scintigraphy because patients were required to undergo repeated testing and, although the radiation dose is low, it was not felt ethically justified to expose patients to unnecessary radiation for research purposes. Holter monitoring was chosen as a second measure of myocardial ischaemia as it allowed assessment in the ambulatory setting when supply driven ischaemia may be important.

In order to optimise the specificity of these tests for ischaemia, in addition to standard inclusion and exclusion criteria, the study population was restricted to patients with proven ischaemic heart disease either by coronary angiography or previous myocardial infarction. In addition, patients with stable angina were included only if the resting electrocardiogram was normal (with the exception of some patients in chapter 4). In the post-infarction patient, ST segment elevation and reciprocal ST segment depression is not a reliable indicator of ischaemia, and for the purposes of these studies, such episodes were not therefore considered ischaemic[61,136,137].

SECTION 1

STABLE ANGINA

CHAPTER 2

INTERACTION OF ISCHAEMIC AND PERCEPTUAL VARIABLES IN THE PERCEPTION OF ANGINA

2.1 INTRODUCTION

In patients with symptomatic coronary artery disease, there is a variable association between myocardial ischaemia and the provocation of symptoms. Indeed a majority of patients with stable angina have episodes of ischaemia which are entirely asymptomatic, although the relative frequency of painful and silent episodes shows considerable variation between patients[23]. Thus any mechanism of angina must account for this variation between patients and also for the variation within patients, whereby some episodes of ischaemia are associated with pain, while others are silent.

Data presented in part to the American College of Cardiology, Anaheim 1993

There are two main theories that may account for the variable symptomatic expression of myocardial ischaemia. The "intensity theory" of pain proposes that a sufficient stimulus is required to induce pain. In the context of angina, this has been called the "mass" theory which states that a critical amount of myocardium needs to be rendered ischaemic before the patient experiences symptoms. In support of this, Iskandrian et al[138] have shown that exertional increments in left ventricular ejection fraction are less pronounced in patients who experience no angina during treadmill testing, suggesting that ischaemia in this asymptomatic group is less extensive. Chierchia et al[139] performed haemodynamic monitoring and electrocardiography in 14 patients with unstable angina and found that asymptomatic episodes of ischaemia were shorter and produced less impairment of left ventricular function. Similarly, Hendler et al[34] evaluated the results of exercise thallium scintigraphy in 152 patients with exertional ST segment depression and found a smaller ischaemic thallium score in the silent, compared with the symptomatic episodes. However, Cohn et al[140] studied left ventricular function using radionuclide ventriculography in 40 patients with coronary artery disease at rest and at peak exercise and found no difference between symptomatic and asymptomatic patients.

A second explanation is that silent ischaemia represents abnormalities in pain perception, either peripheral or central[141]. Patients with silent ischaemia on treadmill testing have a tendency to impaired somatic pain sensation[142] and this may be explained in two ways. Firstly by a destruction of nociceptive pathways as suggested by the increased prevalence of silent ischaemia in diabetic[117] and elderly

patients[95] with impaired autonomic function. Secondly by a difference in pain discriminating ability, perhaps mediated centrally by beta-endorphin, as evidenced by the finding of increased circulating levels in some patients with silent ischaemia[124].

This study aims to re-examine mechanisms of angina in patients with symptomatic coronary artery disease. Particular attention has been given to defining the relative contributions of ischaemic and perceptual factors in order to provide an integrated theory that accounts for the variable association between myocardial ischaemia and the provocation of symptoms. The role of endogenous opiates has also been studied in a double blind placebo controlled study of naloxone and placebo. The placebo limb provides the data presented in this chapter, and the role of endogenous opiates is presented in chapter 3.

2.2 METHODS

2.2.1 Patient Selection

Patients were recruited consecutively from those undergoing exercise treadmill testing for the assessment of angina. All patients were required to have had stable angina for at least 3 months without unstable symptoms or acute myocardial infarction in the preceding 6 months. Patients with a normal resting 12 lead electrocardiogram (ECG), who developed ≥0.1mV of planar or down-sloping ST segment depression on exercise treadmill testing, were eligible. All patients

underwent routine coronary angiography to confirm significant coronary disease (defined as at least one stenosis of >50% luminal diameter in one or more major coronary arteries). Patients with diabetes were excluded if there was any clinical evidence of neuropathy, retinopathy or micro-albuminuria. Patients with symptoms or clinical signs of peripheral or autonomic neuropathy, any other neurological disease, or a history of alcohol abuse were also excluded. Normal electrolytes, renal and liver function, and haemoglobin, were confirmed in all cases. The study group comprised 43 patients who fulfilled these clinical, angiographic and laboratory criteria.

2.2.2 Study Design

Anti-anginal medication was withdrawn 5 days before the study with the exception of short acting nitrates which were disallowed only on the day of the study. No medication was taken on the morning of the study. All studies took place at the same time of day (09.00 hours) with the patient fasted. Patients underwent somatic pain tests (reported in chapter 3), autonomic function tests, and an exercise treadmill test. Wax ear plugs were worn during the study, in order to minimise distraction from background noise during treadmill stress testing. In addition, 48 hour ambulatory Holter monitoring was performed for analysis of ST segments and heart rate variability.

2.2.3 Exercise Treadmill Test (See Appendix A)

This was performed according to the Bruce protocol[43], using a Marquette Case 12 treadmill. A 12 channel ECG was monitored continuously and recorded at

baseline and every 30 seconds throughout the study. Heart rate was monitored throughout the test and blood pressure was recorded at baseline, at the end of each stage, and at peak exercise. In order to obtain objective measurement of the onset of pain, no communication was made with the patient during the test, and the patient indicated the onset of angina by pressing a buzzer. Exercise was stopped when the patient pressed the buzzer for the second time, or if any of the following occurred: a fall in systolic blood pressure >10mmHg, significant ventricular arrhythmias, or >0.5mV ST depression. The anginal latency was calculated as the time from the onset of electrocardiographic ischaemia (0.1mV of planar or down-sloping ST segment depression, measured 80 milliseconds after the J point) to the onset of angina.

2.2.4 48 Hour Ambulatory Holter Monitoring (See Appendix A)

On a separate occasion patients underwent 48 hour ambulatory Holter monitoring of ST segments. This was also performed while the patient was withdrawn from anti-anginal therapy. Before the recording, 12 lead electrocardiograms were recorded in the sitting, standing, supine and left and right lateral positions, to ensure that ST segments did not change with posture. Leads CMV_5 and modified lead II were used; recordings were made on magnetic tapes (TDK D120) using frequency-modulated dual channel recorders (Marquette Series 8000). The occurrence of anginal symptoms was indicated by pressing a button on the recorder, and maintaining a diary. Tapes were analysed using a Marquette Holter Acquisition Module (software version 5.8) after careful review and relabelling of ECG complex morphology. Episodes of ST shift were identified on the computer-

generated trend analysis and validated manually by examination of representative electrocardiographic strips. All tapes were analysed by a single investigator, and the results reviewed with a second investigator. An ischaemic episode was defined as ≥0.1mV planar or down-sloping ST segment depression 0.08 seconds after the J point that persisted for more than 1 minute. An interval of 2 minutes was required after return of the ST segment to baseline before another discrete episode was counted. The proportion of silent ischaemia was calculated by dividing the duration of episodes of ischaemia which were not associated with angina, by the total duration of ischaemia.

2.2.5 Autonomic Function Tests

Five standard tests were performed according to the protocol of Ewing and Clarke[143]; heart rate variation during deep breathing (six breaths over 1 minute), Valsalva ratio (mean of three manoeuvres), lying to standing heart rate ratio (maximal R-R interval at or around the 30th beat divided by the shortest R-R interval at or about the 15th beat), systolic blood pressure response to standing from supine and rise in diastolic blood pressure with sustained hand grip (for up to 5 minutes). R-R intervals were calculated electronically from an ECG obtained via a signal amplifier, using custom written software (RR Medical Electronics Ltd.), and blood pressure was measured manually by sphygmomanometry. Repeatability of these measures has been confirmed previously[144].

2.2.6 Heart Rate Variability (See Appendix B)

Spectral and non-spectral measures of heart rate variability were made by analysis of the first 24 hours of Holter recordings using Marquette heart rate variability software version 1. The measures calculated were: amplitude of low (0.04 - 0.15 Hz) and high (0.15 - 0.40 Hz) frequency spectral analysis, proportion of adjacent R-R intervals more than 50 milliseconds different (pNN50), root-mean square of the difference of successive R-R intervals (RMSSD), mean of all 5-minute standard deviations of R-R intervals (SD), standard deviation of 5-minute mean R-R intervals (SDANN), and the standard deviation of all R-R intervals from the mean (SDRR). Repeatability of measures of heart rate variability has been established in normal subjects[145,146].

2.2.7 Coronary Angiography and Ventriculography

Patients underwent routine coronary angiography to confirm the presence of coronary artery disease. Five standard views were taken of the left and three of the right coronary arteries. Coronary disease was quantified using two methods. Firstly, the number of main vessels with a percentage diameter stenosis greater than 50% were counted, and secondly using Gensini's coronary score[147] to give a measure of the amount of myocardium at risk of ischemia. Left ventricular function was assessed by standard contrast ventriculography performed in the right anterior oblique projection, and ejection fraction was calculated by the area method.

2.2.8 Statistical Analysis

All averaged results are expressed as mean values with standard error of the mean (SEM) in parentheses. Groups A and B, silent and painful episodes of ischaemia on Holter, and patients with single versus multi-vessel disease were compared using the unpaired t-test for normally distributed variables, and by the Mann-Whitney U test for other variables (proportion of silent ischaemia on Holter, Gensini score, left ventricular ejection fraction, exercise time on treadmill, low frequency peak in heart rate variability, pNN50, and the duration of episodes of ischaemia on Holter monitoring). The relation between anginal latency, the proportion of silent ischaemia on Holter and Gensini score were examined using Spearman correlation. Severity of coronary disease and the distribution of diabetic patients in groups A and B were compared using the χ^2 test. Two-sided p values were considered significant at the 5% level.

2.2.9 Ethical Approval

The study was approved by the Newham Health District Ethics Committee, and written informed consent was given by all patients.

2.3 RESULTS

2.3.1 Patient Characteristics

There were 34 men and nine women, with a mean age of 62 years (SEM 1, range 37 - 77). Of these, 14 had single vessel and 29 multi-vessel coronary artery

disease; 13 patients were diabetic, four had a history of hypertension and one had previous coronary artery bypass grafting. The resting ECG was normal in every case.

2.3.2 Treadmill Stress Testing: Group A versus Group B (Table 1)

Patients were subdivided into those who experienced angina on the treadmill (n=34, group A) and those who did not (n=9, group B). Group A was younger, had more extensive coronary artery disease and a significantly lower exercise tolerance than group B. Anginal latency in group A was 79 (15) seconds and was significantly more prolonged in patients with single vessel compared with multi-vessel disease (144 (31) versus 55 (16) seconds, p=0.01).

2.3.3 Autonomic Function: Group A versus Group B (Table 2)

In group B, clinical tests of autonomic function tended consistently towards the borderline abnormal range, while spectral and non-spectral measures of heart rate variability were significantly reduced compared with group A. The distribution of diabetic patients between the groups showed no significant difference (9 versus 4, p=0.52).

Table 1: Comparison of angiographic and exercise variables between symptomatic (group A) and asymptomatic (group B) patients.

	GROUP A n=34	GROUP B n=9	P VALUE
Age (years)	61 (2)	66 (2)	0.04
Single / multi-vessel disease	9/25	6/3	0.03
Gensini score	48.8 (5.9)	34.3 (12.9)	0.13
Left ventricular ejection fraction (%)	57 (1)	56 (2)	0.35
Heart rate (beats min^{-1})			
Rest	82 (3)	77 (5)	0.42
Peak	132 (3)	142 (8)	0.16
Systolic blood pressure (mmHg)			
Rest	140 (4)	143 (8)	0.72
Peak	166 (4)	166 (8)	0.99
Peak rate pressure product (mmHg beats.$minute^{-1}$ x 10^3)	201 (8)	208 (20)	0.72
Time to 0.1mV ST depression (s)	190 (18)	272 (41)	0.05
Exercise time (s)	322 (22)	461 (55)	0.03

Table 2: **Comparison of clinical tests of autonomic function and heart rate variability between symptomatic (group A) and asymptomatic (group B) patients.**

	GROUP A n=34	GROUP B n=9	P VALUE
Autonomic function; clinical tests			
Valsalva ratio	1.61 (0.05)	1.48 (0.10)	0.26
Lying-standing heart rate ratio	1.15 (0.02)	1.07 (0.03)	0.04
Heart rate variation during deep breathing (beats minute^{-1})	16.0 (1.2)	14.5 (3.4)	0.60
Fall in systolic blood pressure from lying to standing (mmHg)	9.1 (1.4)	12.8 (3.5)	0.28
Increase in diastolic blood pressure with sustained handgrip (mmHg)	24.7 (1.2)	22.8 (1.8)	0.46
Autonomic function; heart rate variability			
Low frequency peak (ms)	24.3 (2.0)	18.5 (1.8)	0.04
High frequency peak (ms)	10.4 (0.9)	8.1 (0.7)	0.26
SDANN (ms)	127 (6)	112 (10)	0.25
rMSSD (ms)	26.6 (3.1)	19.4(1.8)	0.04
pNN50 (%)	6.54 (1.66)	2.56 (0.81)	0.10
SD (ms)	53.7 (3.4)	46.6 (2.7)	0.11
SDRR (ms)	140 (6)	124 (11)	0.23

2.3.4 Holter ST Monitoring: Group A versus Group B

Ischaemic ST segment depression was recorded in 35 patients during 48 hour monitoring. Group A had a significantly lower proportion of silent ischaemia during 48 hour monitoring than group B (0.66 (0.07) versus 0.99 (0.01), $p=0.005$).

2.3.5 Holter ST Monitoring: Painful versus Silent Episodes (Table 3)

Of 337 ischaemic episodes in 35 patients, 56 (17%) were painful. Nineteen patients experienced both painful and silent episodes and these are compared in table 3. In these 19 patients there were a total of 226 ischaemic episodes of which 47 (21%) were painful. Painful episodes were longer and associated with more ST segment depression than silent episodes. In addition, painful episodes were associated with a greater percentage increase in heart rate from the onset of ischaemia to peak ST segment depression.

2.3.6 Holter ST Monitoring: Severity of Coronary Disease

Patients with multi-vessel disease had a lower proportion of silent ischaemia than those with single vessel disease (0.59 (0.08) versus 0.88 (0.05), $p=0.02$). In addition, there was a negative correlation between the Gensini coronary score and the proportion of silent ischaemia on Holter monitoring ($r=-0.48$, $p=0.007$).

Table 3: **Comparison of painful and painless episodes of ischaemia on Holter monitoring in 19 patients.**

	PAINFUL EPISODES	PAINLESS EPISODES	P VALUE
Mean duration (minutes)	12.0 (4.6)	2.1 (0.4)	0.05
Maximum ST depression (mV)	0.26 (0.03)	0.22 (0.02)	0.04
Heart rate pre-episode ($minute^{-1}$)	84 (2)	80 (1)	0.08
Heart rate at peak ST depression ($minute^{-1}$)	106 (3)	91 (4)	0.001
% increase in heart rate at peak ST depression	26 (3)	13 (4)	0.001

2.4 DISCUSSION

In this study, mechanisms of angina in patients with coronary artery disease have been studied. Simple variables obtained during treadmill testing, Holter monitoring and cardiac catheterisation have provided indirect evidence to suggest that myocardial ischaemia will only provoke angina if the stimulus is of sufficient magnitude to exceed the patient's perceptual threshold. The data indicate that the magnitude of the stimulus is principally determined by the mass of ischaemic myocardium and also the intensity of ischaemia as reflected by its severity and duration. The perceptual threshold is a sensory function mediated by the central nervous system and its afferent supply. This interaction of ischaemic and perceptual mechanisms may account for much of the variability between patients with coronary artery disease, whereby some experience more symptomatic ischaemia than others, and also the variability within individuals, whereby some ischaemic episodes provoke pain and others do not.

Between-patient variability was apparent on treadmill testing, during which most patients experienced angina but 21% (group B) did not, and on Holter monitoring, in which the proportion of silent ischaemia in different patients ranged from 0 to 100% during episodes of ST depression. The most simple unifying mechanism to account for the variability between patients is that a critical mass of ischaemic myocardium is required to provide sufficient stimulus to induce angina. Thus patients with single vessel disease (in whom the mass of ischaemic myocardium is likely to be smaller than in patients with multi-vessel disease) were significantly

more common among those who experienced no angina on the treadmill, and these patients tended to have a lower Gensini coronary score, suggesting that the mass of myocardium at risk of ischaemia is likely to be smaller than in patients with angina on treadmill testing. In addition, patients with single vessel disease had a higher proportion of silent ischaemia on Holter monitoring, and this was also negatively correlated with the Gensini score.

Differences in the critical mass of ischaemic myocardium probably account for much of the variability between patients, but the data indicate that this mass effect may be modulated by the intensity of ischaemia (the product of severity and duration) which must reach a threshold level before angina is perceived by the patient. The smaller the mass of ischaemic myocardium the greater the intensity of ischaemia required to reach the critical threshold. Anginal latency may provide a crude functional measure of this, the tendency for patients with single vessel disease to have longer anginal latency reflecting not only a mass effect but also the extra time it takes for ischaemia within a relatively small mass of myocardium to intensify to the threshold at which angina is experienced by the patient.

Differences in the ischaemic stimulus are unlikely to explain all the variability between patients because neither mass nor intensity effects can account for the fact that different patients have different perceptual thresholds for experiencing cardiac pain. It is well established, for example, that thresholds are higher in elderly and diabetic patients[95,117] both of whom are more prone than the general population to asymptomatic myocardial infarction[10]. This threshold factor may have

influenced the findings in the present study, particularly as patients who experienced no angina on the treadmill not only had less severe coronary artery disease (mass effect) than the symptomatic group but also were older and had evidence of early autonomic dysfunction. Thus, the lying to standing heart rate ratio and rMSSD, representing parasympathetic function[148,149], and low frequency spectral peak, representing sympathetic activity[150], were significantly reduced in group B. The sensory innervation of the heart runs within the sympathetic and parasympathetic supply[109], and evidence of autonomic impairment in this group suggests that diffuse neuropathic mechanisms might have contributed to the absence of symptoms during treadmill stress testing, and to the higher proportion of silent ischaemia on Holter monitoring.

In an individual patient the ischaemic mass and the sensory threshold for perceiving angina are both likely to be fairly constant. Variations in the intensity of ischaemia, therefore, are best suited to account for the within-patient variability apparent on Holter monitoring whereby some ischaemic episodes provoked pain and others did not. The data support this by showing that in individual patients painful episodes were longer, occurred at a higher heart rate and were associated with a greater increase in heart rate than painless episodes, all of which would be expected to intensify the degree of ischaemia. To some extent this is reflected by the ST change which was more profound during painful episodes, a finding consistent with that of Cecchi et al[20]. Mulcahy et al[47] also reported that painful episodes were associated with more profound ST change on Holter monitoring than painless episodes, again suggesting that it is the intensity of ischaemia that

determines whether or not symptoms occur in an individual patient. In contrast to our own findings, however, and those of Deanfield et al[24], these investigators did not find that symptoms were related to the duration of ischaemia or heart rate[23].

Limitations of study. In this study, cautious interpretation of the data has been necessary because many of the major variables, particularly mass of ischaemic myocardium and intensity of ischaemia, are not amenable to direct measurement and have been inferred from treadmill, Holter and catheter laboratory findings. Nevertheless, the quality of the data was maximised by paying careful attention to methodology. Thus, only untreated patients with angiographically proven coronary artery disease and a normal resting electrocardiogram were included to avoid any ambiguity in the interpretation of ischaemic ST segment changes. During treadmill stress testing the patients were fitted with wax ear plugs and their only communication with the investigator was to indicate the onset of angina and the limit of exercise tolerance by pressing a buzzer. By these means, bias on the part of patient and investigator in detecting and recording (respectively) the onset of angina and exercise capacity was effectively excluded by minimising auditory and verbal distraction. Holter monitoring was continued for a full 48 hours to allow for random variation in the prevalence of ischaemia and before each study recordings were made in each of five positions to rule out any posture-induced ST segment or T wave changes.

Conclusion. This study has provided evidence for a unifying mechanism of angina that can account for much of the variability in the symptomatic expression of

myocardial ischaemia that exists between and within patients. The findings indicate that myocardial ischaemia will provoke symptoms if the magnitude of the ischaemic stimulus exceeds the sensory threshold for experiencing angina; if it does not, ischaemia will remain silent. It seems clear that the magnitude of the stimulus in an individual patient is determined both by the mass of ischaemic myocardium and the intensity of ischaemia. However, in certain patients the sensory threshold for experiencing angina may be increased, and this study suggests that a neuropathic mechanism may sometimes account for this.

CHAPTER 3

THE ROLE OF ENDOGENOUS OPIATES IN THE PERCEPTION OF ANGINA

3.1 INTRODUCTION

In the previous chapter evidence was put forward for a unifying mechanism of angina in which it was proposed that an ischaemic stimulus may provoke symptoms if its magnitude (defined by mass and intensity) exceeds the sensory threshold for experiencing angina. The integrity of the sensory innervation of the heart was identified as one possible variable that might affect this sensory threshold. However, endogenous opiates also have the potential to influence pain perception by increasing sensory thresholds but their role in the modulation of anginal perception has been controversial[124-131].

Data presented in part to the British Diabetic Association, Harrogate 1992 and to the American College of Cardiology, Anaheim 1993

Droste and Roskamm[142] found that patients with silent ischaemia on treadmill testing have a tendency to raised somatic pain thresholds and tolerance and these findings were endorsed by Pederson et al[151]. Several studies have found differences in endogenous opiates in patients with silent ischaemia[108,124,127], but whether plasma levels of beta-endorphin and met-enkephalin reflect the activity of these substances within the central nervous system, is unknown.

In this chapter, the influence of endogenous beta-endorphin and met-enkephalin on anginal perception has been examined, using naloxone, a specific opiate receptor antagonist, as a tool.

3.2 METHODS

The experiment was conducted in combination with the study described in chapter 2. Thus, the study population is identical. It should be noted however, that 48 hour Holter recording was performed only once in each patient.

3.2.1 Patient Selection

See section 2.2.1.

3.2.2 Study Design

Anti-anginal medication was withdrawn 5 days before the study with the exception of short acting nitrates which were disallowed only on the day of the study. No

medication was taken on the morning of the study. All studies took place at the same time of day (09.00 hours) with the patient fasted. Studies were conducted in a double blind randomised crossover fashion between naloxone and placebo. An intravenous cannula was inserted at the beginning of the study in the left arm and a 6mg bolus of naloxone (or 6ml of normal saline) was given, followed by an infusion at a rate of 0.1mg/minute (0.5ml/minute), which continued throughout the study. Patients first underwent an electrical somatic pain test, followed by a 45 minute rest period, and then an exercise treadmill test. In a subgroup of 17 consecutive patients, a second cannula was inserted in the right arm at the beginning of the study and blood was taken for assay of plasma beta-endorphin, met-enkephalin, catecholamines and cortisol as detailed below. The study was repeated with the crossover drug within 1 week.

3.2.3 Somatic Pain Test

Somatic pain was assessed using electrical pain stimulation[152]. A constant current stimulator was used in order to compensate for varying resistance with sweating, and a square wave stimulus at a frequency of 50Hz with an impulse duration of 5 milliseconds was applied. Electrodes were attached to the right forefinger, 20mm apart, and an increasing current was applied. All patients were given standard instructions. The patient indicated the threshold of pain and the limit of tolerance by pressing the buzzer. Studies were conducted in an environment free from disturbance, and the patients wore ear plugs to eliminate any background noise.

3.2.4 Exercise Treadmill Test

This was performed as described in section 2.2.3.

3.2.5 Blood Samples

Uncuffed blood samples were taken from the intravenous cannula for assay of beta-endorphin, met-enkephalin, adrenaline, noradrenaline and cortisol. The patients rested after pain testing and samples were drawn after 30 minutes of rest and 15 minutes later, immediately before exercise treadmill testing. The mean of these two results was considered the baseline. Further samples were taken at peak exercise, and 15 and 60 minutes after peak exercise, during a further period of rest. Following centrifugation, plasma was frozen in liquid nitrogen within 15 minutes, and stored at -20°C until assayed.

3.2.6 Assay of Beta-Endorphin and Met-Enkephalin

Plasma beta-endorphin[153] and met-enkephalin[154,155] were measured by radioimmunoassay. The lowest detection limit of the assays was 10pg.ml^{-1} and 1pg.ml^{-1}, respectively. The intra-and inter-assay coefficients of variation were 5.9 and 8.9% for beta-endorphin and 7.9 and 9.8% for met-enkephalin, respectively.

3.2.7 Assay of Catecholamines and Cortisol

Plasma adrenaline and noradrenaline were measured by liquid chromatography and electrochemical detection[156]. The lowest detection limit for each assay was 0.05nmol.l^{-1}. The intra- and inter-assay coefficients of variation were 5.1 and 7.5% for adrenaline and 3.7 and 6.6% for noradrenaline, respectively. Serum cortisol was

measured by radioimmunoassay[157]. The lowest detection limit of the assay was 50nmol.l^{-1}. The intra-and inter-assay coefficients of variation were 6.9 and 8.0%, respectively.

3.2.8 48 Hour Ambulatory Holter Monitoring

This was performed as described in section 2.2.4.

3.2.9 Coronary Angiography and Ventriculography

This was performed as described in section 2.2.7.

3.2.10 Statistical Analysis

All averaged results are expressed as mean values with standard error of the mean in parentheses. The significance of differences between groups A and B were obtained by the unpaired t-test for normally distributed variables, and by the Mann-Whitney U test for variables with a skew distribution (exercise times, adrenaline and met-enkephalin levels). The significance of differences between naloxone and placebo were obtained by the paired t-test for variables with a normal distribution and Wilcoxon rank sum test for those with a skew distribution. The distribution of diabetic patients, gender and presence of multi-vessel coronary disease was measured using the χ^2 test with Yates correction where appropriate.

3.2.11 Ethical Approval

The study was approved by the Newham Health District Ethics Committee, and written informed consent was given by all patients.

3.3 RESULTS

3.3.1 Patient Characteristics

Of the 43 patients included in the study, 31 experienced angina during both the placebo and the naloxone treadmill stress tests (group A). The remaining 12 patients (group B) experienced angina on only one test (n=3) or on neither test (n=9). The groups were similar as regards age (60 (2) versus 65 (2) years, p=0.17), sex distribution (25 versus 9 male, p=1.0) and prevalence of diabetes (8 versus 5, p=0.31).

3.3.2 Holter ST Monitoring

Ischaemic ST depression was recorded in 35 patients during 48 hour monitoring, 28 in group A and seven in group B. Group B had a significantly higher proportion of silent ischaemia during the monitoring period than group A (0.65 (0.06) versus 0.98 (0.01), p=0.001).

3.3.3 Somatic Pain Threshold (Figure 1)

Naloxone infusion caused reductions in electrical pain threshold (1.09 (0.11) versus 1.33 (0.18) mA, p=0.14) and pain tolerance (1.40 (0.10) versus 1.72 (0.19) mA, p=0.04) compared with placebo, suggesting effective opiate receptor blockade in the 43 patients studied. There were no significant differences between groups A and B either in the placebo measurements or in the response to naloxone.

3.3.4 Treadmill Stress Testing - Haemodynamic Response (Table 4)

Exertional increases in heart rate and blood pressure provoked ischaemic ST depression in every patient. During placebo infusion, group A developed ischaemia at an earlier stage than group B (180 (18) versus 276 (32) seconds, $p=0.01$) and stopped exercising earlier (307 (21) versus 464 (47) seconds, $p=0.009$). The times to ischaemia and total exercise duration were unaffected by naloxone. Although the blood pressure and rate pressure product at peak exercise were slightly lower on naloxone, there were no significant differences at the onset of ischaemia.

Figure 1: Effect of naloxone on electrical pain threshold and tolerance in symptomatic (group A) and asymptomatic (group B) patients.

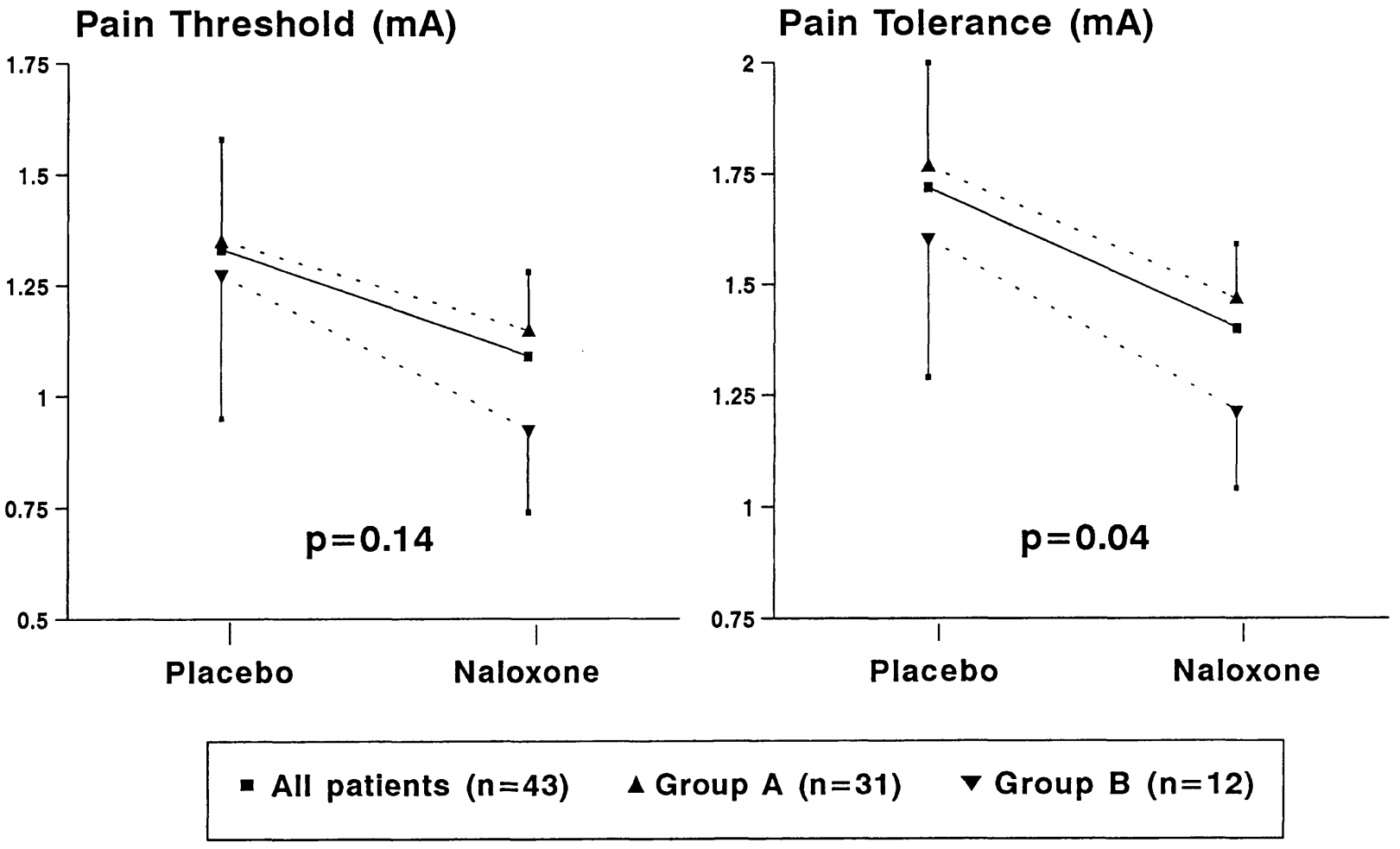


Table 4: Haemodynamic, ischaemic and symptomatic responses to exercise treadmill testing: symptomatic (group A) versus silent (group B) patients and naloxone versus placebo.

	PLACEBO			NALOXONE		
	GROUP A n=31	GROUP B n=12	p VALUE	GROUP A n=31	GROUP B n=12	p VALUE
Heart rate (beats/minute)						
Rest	82 (3)	77 (4)	0.27	81 (2)	77 (5)	0.47
Onset of ischaemia	117 (3)	123 (6)	0.31	116 (2)	120 (6)	0.57
Peak	131 (3)	142 (6)	0.11	132 (3)	139 (7)	0.33
Systolic blood pressure (mmHg)						
Rest	139 (5)	145 (7)	0.48	133 (5)	147 (6)	0.11
Onset of ischaemia	150 (4)	156 (6)	0.44	146 (4)	157 (6)	0.17
Peak	164 (5)	172 (7)	0.34	155 (4)**	170 (7)	0.07
Rate pressure product (mmHg.beats/minute.10^3)						
Rest	11.6 (0.5)	11.1 (0.8)	0.58	10.9 (0.5)*	11.3 (0.9)	0.63
Onset of ischaemia	17.5 (0.7)	19.3 (1.4)	0.21	17.0 (0.6)	18.9 (1.4)	0.15
Peak	19.7 (0.8)	21.7 (1.6)	0.22	18.8 (8.5)*	22.1 (1.5)	0.05
Time to ischaemia (s)	180 (18)	276 (32)	0.03	200 (16)	270 (36)	0.08
Exercise time (s)	307 (20)	464 (47)	0.009	325 (21)	464 (47)	0.01

Naloxone versus placebo; *$p<0.05$, **$p<0.005$

Despite effective opiate receptor blockade, naloxone did not affect symptomatic responses to exertional ischaemia. Thus the time to onset of angina in group A did not shorten (260 (20) versus 248 (20) seconds, p=0.72), and none of the group B patients in whom ischaemia was silent on placebo experienced angina during naloxone infusion. Exercise duration was also unaffected by naloxone (364 (22) versus 351 (22) seconds, p=16).

3.3.5 Treadmill Stress Testing - Neurohumoral Responses

a) Beta-endorphin (figure 2). Exercise produced a small rise in plasma levels of beta-endorphin, but this was not statistically significant. During placebo infusion, plasma levels were higher in group A than group B, both at rest (28.7 (2.8) versus 18.9 (2.2) ng/l, p=0.03) and at peak exercise (30.9 (3.0) versus 20.2 (4.5) ng/l, p=0.06). Naloxone infusion increased plasma levels in both groups, indicating effective opiate receptor blockade. There were no differences between the groups in the magnitude of their responses to naloxone.

b) Met-enkephalin (figure 2). Plasma levels of met-enkephalin were similar in groups A and B and were unaffected by exercise or naloxone infusion.

c) Catecholamines (figure 3). Plasma levels of noradrenaline increased significantly (p=0.01) during exercise in groups A and B. Responses were quantitatively similar in both groups and were unaffected by naloxone. Plasma adrenaline showed no change during exercise and was unaffected by naloxone.

d) Cortisol (figure 4). Plasma cortisol levels were markedly increased during naloxone infusion, and showed a small rise following exercise which did not reach significance. Responses were similar in groups A and B.

Figure 2: Response of beta-endorphin and met-enkephalin to exercise on naloxone and placebo in symptomatic (group A) and asymptomatic (group B) patients.

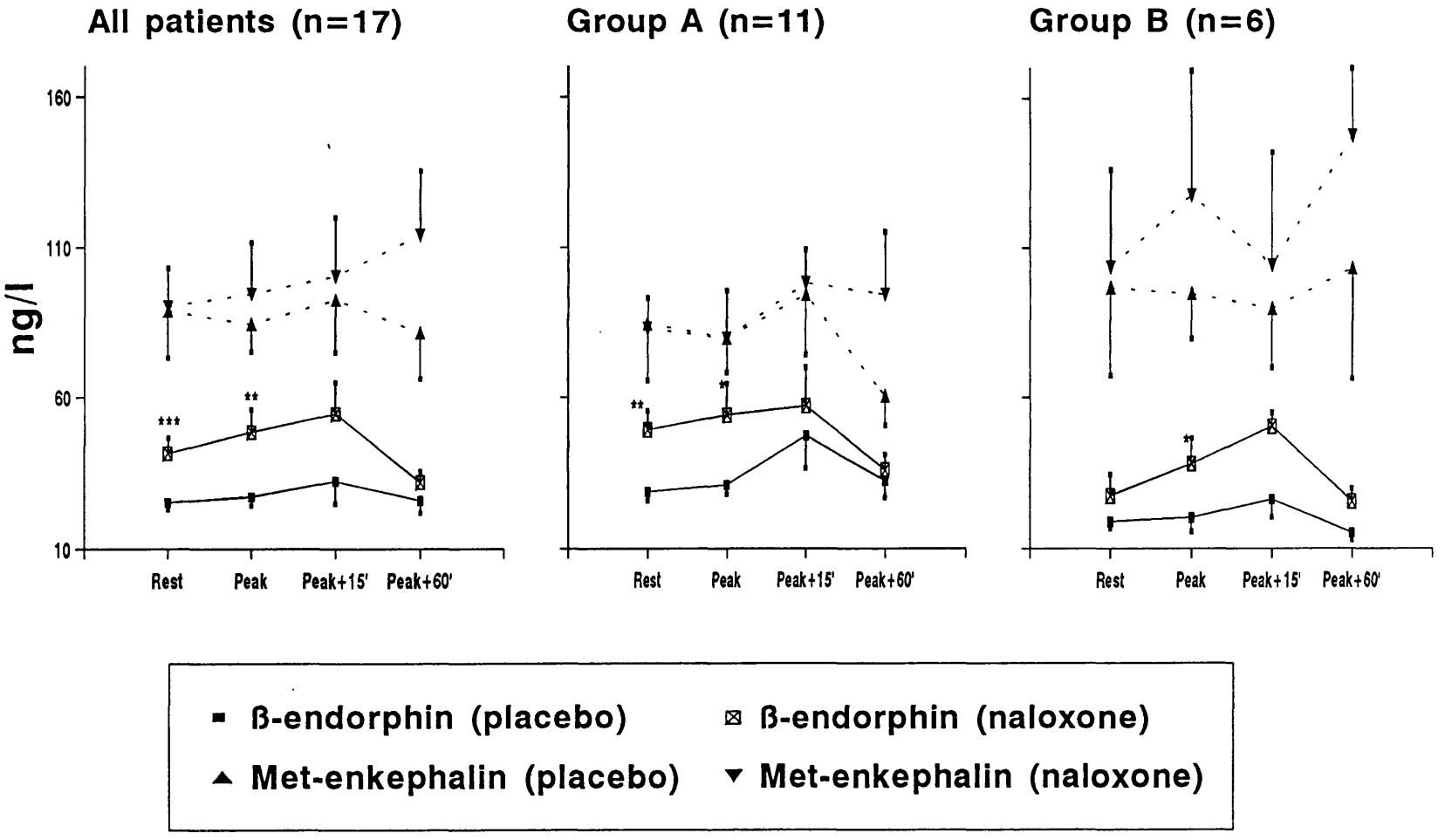


Figure 3: Response of plasma adrenaline and noradrenaline to exercise on naloxone and placebo in 17 patients.

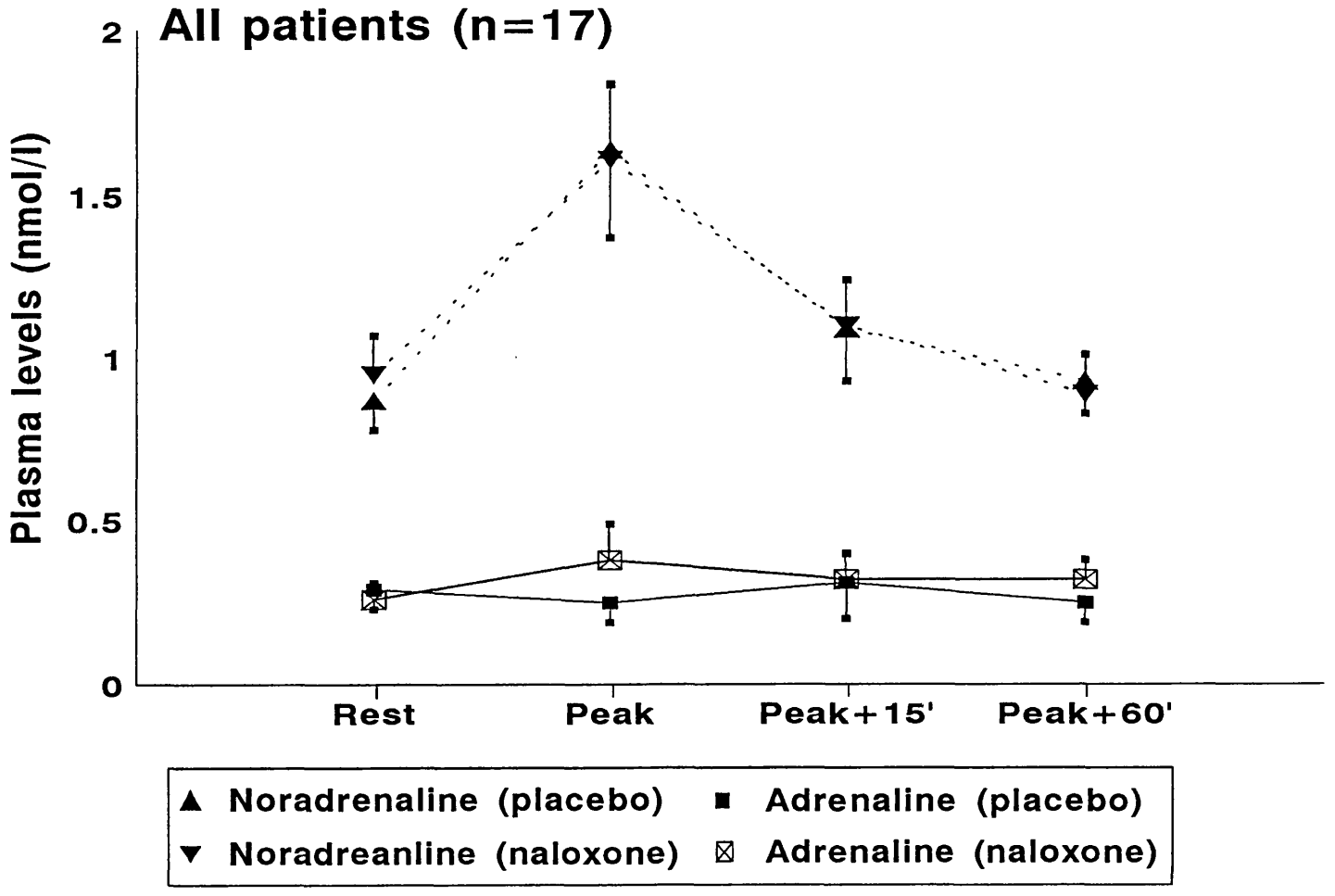
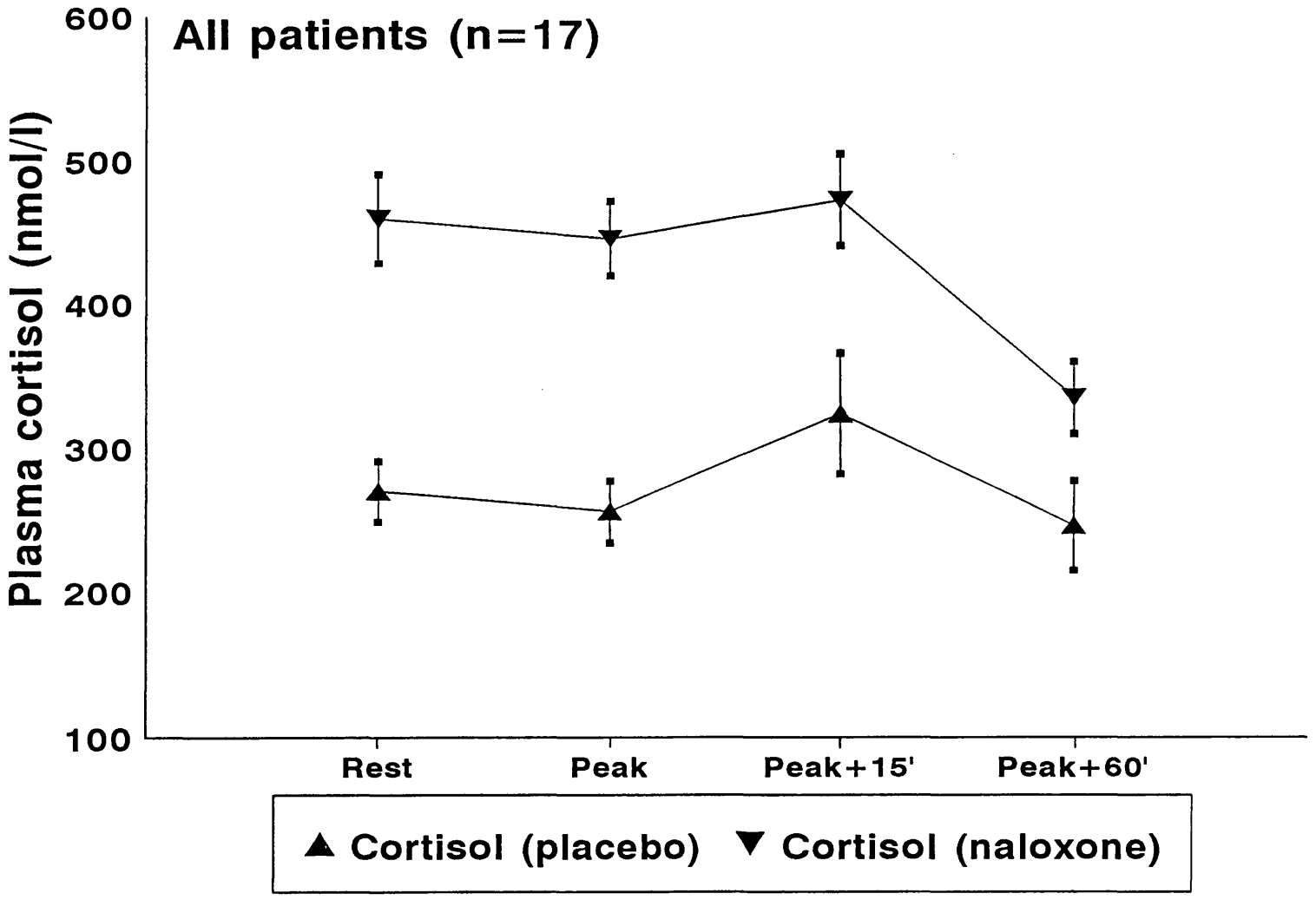


Figure 4: Response of plasma cortisol to exercise on naloxone and placebo in 17 patients.



3.4 DISCUSSION

In this study two groups of patients with angiographically proven coronary artery disease have been compared in order to investigate the role of endogenous opiates (particularly beta-endorphin and met-enkephalin) in modulating the perception of myocardial ischaemia. In one group exertional ischaemia during treadmill testing consistently provoked angina while in the other it was commonly silent. The predisposition of the latter group to silent ischaemia was confirmed by Holter ST monitoring but, despite this, plasma levels of beta-endorphin were lower than in the symptomatic group and showed no tendency to rise more acutely during exercise. The data suggest, therefore, that endogenous opiates do not contribute significantly to the pathogenesis of silent ischaemia.

The potential role of endogenous opiates in modulating symptomatic responses to myocardial ischaemia has been examined in previous studies but the findings have been conflicting[125-128,130]. Thus, Heller et al[125] found no difference in beta-endorphin levels either before, during or after exercise when comparing patients with silent and symptomatic ischaemia on treadmill testing. These authors concluded that endogenous opiates were unlikely to play an important role. However, other investigators have reported higher resting levels of beta-endorphin[128], or a larger rise during exercise[127], in patients with silent ischaemia on treadmill testing, leading Droste et al[127] to conclude that these substances may indeed play a major role in modulating symptomatic responses to myocardial ischaemia.

One possible explanation for these conflicting findings is that plasma concentrations of endogenous opiates do not accurately reflect their concentrations within the central nervous system[158] and may not, therefore, provide an accurate guide to their pain modulating activity. To obtain additional information about the central effects of endogenous opiates on the perception of exertional myocardial ischaemia, the effects of naloxone infusion on the haemodynamic, ischaemic and symptomatic responses to treadmill exercise have been measured. Naloxone is a specific opiate receptor antagonist with variable dose-related effects on different opiate receptors: μ-receptors are sensitive to low doses of naloxone but adequate blockade of the k- and ∂-receptors requires substantially higher doses[159]. For this reason a 6mg bolus dose of naloxone was used followed by an infusion of the drug at 0.1mg/min to ensure that full opiate receptor blockade was maintained throughout the exercise test and the early recovery period. The high dose of naloxone did not influence haemodynamic or ischaemic responses to exercise as reflected by rate pressure product or time to onset of ischaemia. Nor did it affect the stress response as judged by plasma catecholamine levels. However, the significant rise in plasma beta-endorphin suggested that the naloxone dosage was effective in blocking central opiate receptors, a suggestion confirmed by the measurements of somatic pain tolerance, which fell significantly.

Despite effective blockade of central opiate receptors during naloxone infusion, the symptomatic responses to treadmill exercise in both groups lend further support to the major conclusion that endogenous opiates do not contribute significantly to the pathophysiology of silent ischaemia. Thus, naloxone infusion did not cause

angina to occur earlier in group A, and failed to induce angina in any of those group B patients who had a silent stress test on placebo. These findings with naloxone are in broad agreement with those of Ellestad and Kuan[126], who failed to induce angina in ten asymptomatic patients, and also with Weidinger et al[131] who did not observe any difference in the onset of symptoms in ten patients. However, both these studies used relatively small doses of naloxone (2mg and 1.2mg by intravenous bolus, respectively) and it is possible that effective opiate receptor blockade was not achieved. Only Droste et al[127] have used a 6mg bolus dose of naloxone (albeit without continuing naloxone infusion) but, despite this, their findings conflict with the present study in a way that cannot be readily explained. Thus, even though naloxone caused no reduction in electrical pain threshold (a finding at variance with that of other investigators[160]), angina was induced in two of nine asymptomatic patients and occurred earlier in seven of eight symptomatic patients.

Although the findings presented in this chapter are different from those of Droste et al[127] in not supporting a role for endogenous opiates in the pathophysiology of silent ischaemia, the findings of both studies are entirely consistent with the known involvement of endogenous opiates in the normal stress response. Met-enkephalin is secreted from the adrenal medulla where it is stored in the same vesicles as adrenaline and noradrenaline[161]. Thus, it rises dramatically during an insulin stress[162,163] test, but not in response to the sympathetic stimulation that occurs during exercise[164]. Beta-endorphin, on the other hand, is secreted by the anterior pituitary gland (together with adrenocorticotrophin hormone) in response to

stimulation by corticotrophin releasing hormone[165]. This tends to occur shortly after stress, accounting for the peak in plasma beta-endorphin 15 minutes after exercise[166]. Negative feedback by endogenous opiates on the release of adrenocorticotrophin hormone was inhibited by naloxone, leading to markedly increased levels of cortisol, which demonstrated a similar pattern to beta-endorphin.

Limitations of study. In studies of this type there is inevitably a subjective element to the interpretation of ischaemic and symptomatic end-points which may account in part for the conflicting findings of different investigators and for the continuing uncertainties about the mechanisms of silent ischaemia. For this reason, particular care was taken to maximise the quality of the data by paying careful attention to methodology. Thus, conditions during the two studies were kept as similar as possible and a randomised double blind protocol was used to eliminate investigator and subject bias. The patient used a buzzer to indicate the onset and limits of tolerance of angina and somatic pain, in an attempt to restrict communication between subject and investigator to this single action.

Conclusion. The patients in this study with silent exertional ischaemia did not have raised plasma levels of endogenous opiates compared with symptomatic controls. Moreover, despite effective central blockade of opiate receptors with naloxone, exertional angina was not induced in these patients, nor was the time to angina shortened in the symptomatic controls. The data, therefore, provide no support for the hypothesis that variations in the central modulation of pain by endogenous

opiates account for variations in the perception of angina seen in patients with silent and symptomatic exertional ischaemia. The increase in β-endorphin with exercise which coincided with a rise in plasma cortisol, is most likely due to its release from the anterior pituitary gland as part of the physiological stress response.

CHAPTER 4

ANGINAL PERCEPTION IN DIABETIC PATIENTS WITH STABLE ANGINA

4.1 INTRODUCTION

Diabetic patients provide a particularly interesting group for studying the influence of perceptual variables on the clinical expression of myocardial ischaemia. As discussed in section 1.6.1, these patients are prone to silent myocardial infarction[98,167] which has been attributed to autonomic neuropathy affecting the sensory innervation of the heart[99,100]. Whether silent ischaemia is also more prevalent in diabetes remains uncertain[97,101-103,116], and this doubt is heightened by controversy about the potential mechanisms, particularly as regards the role of autonomic neuropathy. Thus, Langer et al[168], in a study of diabetic patients, found that silent ischaemia on thallium-201 myocardial scintigraphy occurred in eight of 21 patients with autonomic dysfunction, compared with two of 37 patients with

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Data presented in part to the British Diabetic Association, Harrogate 1992, and accepted for publication by the Journal of the American College of Cardiology

normal autonomic function. Ambepityia et al[117] also reported involvement of autonomic neuropathy in their finding that diabetic patients who experience angina during treadmill stress testing take almost twice as long to develop symptoms after the onset of ST depression than non-diabetic controls. In contrast to these investigators, however, Hume et al[115] found a similar prevalence of ST segment depression during exercise testing in diabetic patients with and without neuropathy and Koistinen et al[118] demonstrated similar autonomic function in diabetic patients with silent and painful ischaemia.

Questions concerning the prevalence and mechanisms of silent ischaemia in diabetes are important because diabetic patients are at increased risk of myocardial infarction and sudden cardiac death[169] and if premonitory symptoms are reduced or absent, specific prophylaxis becomes difficult to apply.

Chapter 2 described how the interaction of ischaemic and perceptual variables may affect the symptomatic expression of myocardial ischaemia. In that chapter it was also observed that patients with silent ischaemia showed a tendency towards subclinical neuropathy and it was postulated that this may increase the sensory threshold for perception of angina. Although the distribution of diabetic patients between the silent and painful groups was not statistically different, there was a small excess of diabetic patients in the silent group. In the present study, therefore, autonomic function in diabetic and non-diabetic patients has been compared with particular emphasis on measures of heart rate variability, which are specially

sensitive to subclinical neuropathic changes that occur in patients with diabetes[170-172].

4.2 METHODS

4.2.1 Patient Selection

Patients described in section 2.2.1 were included in this study, augmented by the addition of nine further patients with type II diabetes mellitus. These were recruited from patients attending a diabetic clinic with a history of angina. Entry criteria were identical to those described in chapter 2, with the exception of the resting ECG, which was not required to be normal. The study group comprised 52 patients, 41 men and 11 women, with a mean age of 60 (1) years (range 37 - 77).

4.2.2 Study Design

Anti-anginal medication was withdrawn 5 days before the study with the exception of short acting nitrates which were disallowed only on the day of the study. No medication was taken on the morning of the study. Patients underwent an exercise treadmill test, autonomic function tests and 24 hour ambulatory Holter monitoring for assessment of heart rate variability.

4.2.3 Exercise Treadmill Test

This was performed as described in section 2.2.3.

4.2.4 Autonomic Function Tests

These were performed as described in section 2.2.5.

4.2.5 Heart Rate Variability

This was measured as described in section 2.2.6 based on 24 hour ambulatory recordings acquired as described in section 2.2.4.

4.2.6 Coronary Angiography and Ventriculography

This was performed as described in section 2.2.7.

4.2.7 Statistical analysis

All averaged results are expressed as mean values with standard error of the mean in parentheses. Groups A and B, and diabetic and non-diabetic patients were compared using the unpaired t-test for normally distributed variables, and by the Mann-Whitney U test for other variables (left ventricular ejection fraction, blood pressure measurements during treadmill testing, exercise time on treadmill, all measures of heart rate variability, Valsalva ratio and lying to standing blood pressure). The distribution of multi-vessel coronary disease and diabetic patients were compared using the χ^2 test. Two-sided p values were considered significant at the 5% level.

4.2.8 Ethical Approval

The study was approved by the Newham Health District Ethics Committee, and written informed consent was given by all patients.

4.3 RESULTS

4.3.1 Diabetic Versus Non-diabetic Patients (Table 5)

Of the 52 patients included in the study, 22 (42%) were diabetic. There were no differences between the diabetic and non-diabetic patients as regards age, left ventricular function, and severity of coronary artery disease. However, clinical tests of parasympathetic function were reduced in the diabetic patients, and measures of heart rate variability tended to be lower.

Table 5: Comparison of patient characteristics, exercise parameters and autonomic function between non-diabetic and diabetic patients.

	NON-DIABETIC n=30	DIABETIC n=22	p VALUE
Age (years)	61 (2)	59 (1)	0.56
Gender (number of males)	23	18	0.92
Single/multi-vessel disease	8/22	8/14	0.66
Left ventricular ejection fraction (%)	57 (1)	56 (2)	0.74
Fasting glucose ($mmol.l^{-1}$)	5.1 (0.1)	10.8 (0.9)	<0.001
Glycosylated haemoglobin (%)	3.6 (0.1)	7.4 (0.7)	<0.001
Time to ischaemia (s)	207 (20)	244 (23)	0.24
Exercise duration (s)	383 (33)	355 (22)	0.97
Autonomic function; clinical tests			
Valsalva ratio	1.60 (0.06)	1.38 (0.07)	0.007
Lying-standing heart rate ratio	1.15 (0.02)	1.08 (0.02)	0.02
HR variation; deep breathing ($beats\ minute^{-1}$)	17.4 (1.5)	12.1 (1.5)	0.02
Fall in systolic BP; lying-standing (mmHg)	8 (2)	8 (2)	0.98
Increase in diastolic BP; handgrip (mmHg)	25 (1)	21 (2)	0.15
Autonomic function; heart rate variability			
High frequency peak (ms)	10.0 (1.0)	10.0 (0.8)	0.45
Low frequency peak (ms)	23.9 (2.1)	21.8 (1.7)	0.85
SDANN (ms)	130 (7)	106 (5)	0.06
rMSSD (ms)	26.4 (3.5)	24.8 (1.8)	0.56
pNN50 (%)	7.0 (2.0)	5.4 (1.0)	0.63
SD (ms)	53.4 (3.5)	48.9 (2.6)	0.50
SDRR (ms)	143 (7)	121 (5)	0.01

HR = heart rate; BP = blood pressure; SDANN = standard deviation of 5-minute mean R-R intervals; rMSSD = root-mean square of difference of successive R-R intervals; pNN50 = proportion of adjacent R-R intervals more than 50 milliseconds different; SD = mean of all 5-minute standard deviations of R-R intervals; SDRR = standard deviation of all R-R intervals from the mean.

4.3.2 Stress Testing (Table 6)

Although all the patients exhibited ischaemic ST depression during treadmill stress testing, only 36 (69%) experienced angina (group A); in the remainder, exertional ischaemia was silent (group B). Group B contained relatively more diabetic patients than group A (33 versus 63%, $p=0.05$) but there were no differences between the groups as regards age, left ventricular function, and severity of coronary artery disease. However, time to onset of 0.1mV ST depression, exercise duration and peak heart rate were all significantly greater in group A.

4.3.3 Autonomic Function Testing (Tables 7 and 8)

The patients who experienced no angina during treadmill stress testing (group B) showed significant parasympathetic impairment compared with group A, as reflected by reductions in the Valsalva and lying to standing heart rate ratios. In group B, this was associated with a consistent trend towards reduced heart rate variability on Holter monitoring. Subgroup analysis (table 8) showed that these differences in autonomic function between groups A and B were largely confined to the diabetic patients; in the non-diabetic patients there were no significant differences between the groups.

Table 6: **Comparison of patient characteristics and exercise parameters between symptomatic (group A) patients and asymptomatic (group B) patients.**

	GROUP A n=36	GROUP B n=16	p VALUE
Age (years)	60 (2)	60 (2)	0.90
Number of diabetic patients	12	10	0.05
Single/multi-vessel disease	10/26	6/10	0.71
Left ventricular ejection fraction (%)	57 (1)	56 (2)	0.59
Heart rate (beats minute^{-1})			
Rest	81 (3)	82 (3)	0.76
Onset of ischaemia	118 (3)	125 (4)	0.14
Peak exercise	132 (3)	145 (5)	0.03
Systolic blood pressure (mmHg)			
Rest	139 (4)	136 (6)	0.67
Onset of ischaemia	151 (4)	152 (6)	0.89
Peak exercise	167 (4)	169 (7)	0.77
Time to ischaemia (s)	200 (20)	271 (20)	0.03
Exercise duration (s)	329 (22)	466 (38)	0.003
Sum ST segment depression (mV)	0.80 (0.08)	0.90 (0.23)	0.69

Table 7: Comparison of autonomic function between symptomatic (group A) patients and asymptomatic (group B) patients.

	GROUP A n=36	GROUP B n=16	p VALUE
Autonomic function; clinical tests			
Valsalva ratio	1.56 (0.05)	1.40 (0.09)	0.08
Lying-standing heart rate ratio	1.15 (0.02)	1.05 (0.02)	0.002
HR variation; deep breathing (beats minute^{-1})	15.9 (1.2)	13.6 (2.4)	0.30
Fall in systolic BP; lying-standing (mmHg)	8.6 (1.3)	7.6 (2.6)	0.70
Increase in diastolic BP; handgrip (mmHg)	24.7 (1.3)	21.9 (1.8)	0.32
Autonomic function; heart rate variability			
High frequency peak (ms)	10.4 (0.8)	9.4 (1.2)	0.43
Low frequency peak (ms)	24.3 (1.8)	19.9 (1.7)	0.23
SDANN (ms)	123 (6)	111 (8)	0.23
rMSSD (ms)	27.2 (2.7)	22.2 (2.6)	0.12
pNN50 (%)	7.0 (1.5)	4.8 (1.9)	0.10
SD (ms)	53.4 (2.9)	46.6 (2.9)	0.24
SDRR (ms)	137 (5)	122 (8)	0.09

HR = heart rate; BP = blood pressure; SDANN = standard deviation of 5-minute mean R-R intervals; rMSSD = root-mean square of the difference of successive R-R intervals; pNN50 = proportion of adjacent R-R intervals more than 50 milliseconds different; SD = mean of all 5-minute standard deviations of R-R intervals; SDRR = standard deviation of all R-R intervals from the mean.

Table 8. **Autonomic function in symptomatic (group A) patients and asymptomatic (group B) patients; a subgroup comparison in diabetic and non-diabetic patients.**

	DIABETIC PATIENTS			NON-DIABETIC PATIENTS		
	GROUP A n=12	GROUP B n=10	P VALUE	GROUP A n=24	GROUP B n=6	p VALUE
Age	59 (2)	60 (2)	0.62	61 (2)	60 (5)	0.76
Autonomic function; clinical tests						
Valsalva ratio	1.47 (0.08)	1.28 (0.11)	0.11	1.60 (0.07)	1.61 (0.12)	0.90
Lying-standing heart rate ratio	1.14 (0.03)	1.01 (0.02)	0.003	1.16 (0.02)	1.13 (0.02)	0.28
Heart rate variation; deep breathing (beats/minute)	13.8 (2.0)	10.1 (2.3)	0.23	16.9 (1.5)	19.5 (4.3)	0.48
Fall in systolic pressure; lying-standing (mmHg)	6.9 (1.8)	10.2 (3.4)	0.38	9.5 (1.7)	3.3 (3.5)	0.13
Increase in diastolic pressure; handgrip (mmHg)	22.5 (2.9)	19.1 (3.4)	0.50	25.2 (1.5)	23.9 (1.6)	0.71
Autonomic function; heart rate variability						
High frequency peak (ms)	11.5 (1.2)	8.4 (0.8)	0.06	9.8 (1.0)	11.4 (3.3)	0.65
Low frequency peak (ms)	24.6 (2.5)	18.4 (1.9)	0.11	24.1 (2.5)	22.8 (3.4)	1.00
SDANN (ms)	110 (4)	102 (10)	0.15	130 (8)	130 (14)	0.77
rMSSD (ms)	28.7 (2.6)	20.1 (1.9)	0.01	26.4 (4.0)	26.5 (6.8)	0.95
pNN50 (%)	7.48 (1.36)	3.01 (0.97)	0.01	6.65 (2.19)	8.24 (5.21)	1.00
SD (ms)	52.6 (3.8)	44.0 (3.2)	0.14	53.9 (3.2)	51.3 (5.3)	0.96
SDRR (ms)	126 (5)	114 (9)	0.07	144 (8)	138 (13)	0.82

SDANN = standard deviation of 5-minute mean R-R intervals; rMSSD = root-mean square of difference of successive R-R intervals; pNN50 = proportion of adjacent R-R intervals more than 50 milliseconds different; SD = mean of all 5-minute standard deviations of R-R intervals; SDRR = standard deviation of all R-R intervals from the mean.

4.4 DISCUSSION

In this study of exertional myocardial ischaemia, diabetic and non-diabetic patients have been examined, all of whom had stable angina. Care was taken not to include diabetic patients with clinical evidence of micro-vascular complications, particularly retinopathy, proteinuria, impaired renal function and peripheral neuropathy. There was an excess of diabetic patients among the group that experienced no angina during treadmill stress testing, but because this study was not designed to examine the prevalence of silent ischaemia, patient selection bias may account for this difference. The severity of coronary artery disease, however, was no less severe in diabetic compared with non-diabetic patients, or in silent compared with symptomatic patients. Indeed, in the diabetic patients, ST segment depression tended to occur earlier during treadmill stress testing, suggesting that ischaemia in this group may be more severe than in the non-diabetics. It is unlikely, therefore, that any propensity to silent ischaemia in the patients with diabetes was due to a smaller mass of ischaemic myocardium.

If silent ischaemia in diabetes cannot be explained by the theory of ischaemic mass, perceptual abnormalities provide a likely alternative. Patients with diabetes frequently have impaired nerve conduction due to micro-vascular disease, and post-mortem studies have associated silent myocardial infarction with neuropathic changes in intracardiac sympathetic and parasympathetic afferent fibres[100]. However, clinical evidence for an association between silent myocardial ischaemia and neuropathy has been conflicting. Langer et al[168] studied 58 patients with

diabetes and no clinical evidence of cardiac disease, and found that myocardial perfusion defects on thallium scintigraphy were more common in those with impaired autonomic function. In contrast to these findings, however, Nesto et al[101], while confirming a high prevalence of silent exertional ischaemia in diabetic patients with abnormal thallium scintigrams, could find no difference in micro-vascular complications between silent and symptomatic subgroups.

In the present study, evaluation of autonomic function utilised not only bedside techniques, but also 24 hour Holter recordings for measurements of heart rate variability which are particularly sensitive to early neuropathy in diabetes[171,173]. There were significant abnormalities of autonomic function in the patients who experienced no chest pain during treadmill testing as reflected by reductions in the Valsalva and lying to standing heart rate ratios, both of which point to a parasympathetic defect. In addition, there was a consistent trend towards reduced heart rate variability on Holter monitoring. However, the data in table 8 show clearly that the autonomic abnormality in the patients with silent ischaemia was largely confined to the diabetic subgroup, among whom the parasympathetic defect on standard bedside testing was associated with significant reductions of sympathetic and parasympathetic indices of heart rate variability (low frequency spectral peak, root-mean square of difference of successive R-R intervals and the proportion of adjacent R-R intervals more than 50 ms different) in comparison with the symptomatic patients. In the non-diabetic subgroup, on the other hand, autonomic function was generally better preserved and showed no tendency towards impairment in those who experienced no symptoms.

Limitations of study. In this study patients with abnormal resting ECG's were included, adding a potential source of error in interpretation of ST segment changes where the baseline may be abnormal and repolarisation changes may exist. However, Holter tapes were not used in the assessment of ischaemia in this study, and the only factor which relies on interpretation of the ST segment is the onset of ischaemia during treadmill testing.

Conclusion. This study has shown that, despite the absence of overt micro-vascular complications, diabetic patients with silent exertional ischaemia have evidence of significant autonomic impairment compared with symptomatic patients. This difference is not seen in non-diabetic patients, and indicates that subclinical neuropathy is an important cause of silent ischaemia in patients with diabetes.

CHAPTER 5

INFLUENCE OF COLD EXPOSURE ON THE PERCEPTION OF ANGINA

5.1 INTRODUCTION

In exploring mechanisms affecting the symptomatic expression of myocardial ischaemia an investigation was undertaken of the effects of cold exposure. Patients with angina frequently complain that their symptoms are more easily provoked in the cold, particularly on a windy day. Several investigators have studied patients with a history of cold intolerance and confirmed that cold exposure induces angina earlier and reduces exercise tolerance[174-177]. However, Juneau et al[178] studied unselected patients and found that such changes were not seen in all patients with angina, but were restricted to those with a history of cold intolerance. Thus there

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Preliminary data presented to the Physiological Society, London 1992 and British Cardiac Society, London 1993

may be two populations of patients with angina who exhibit differing symptomatic responses to cold exposure. The mechanism for this difference has not been investigated.

Coronary vasoconstriction may occur in the cold leading to a decrease in myocardial oxygen supply and providing a possible explanation for cold intolerance. Although this may be important in patients who experience angina on immediate exposure to cold[179], cold induced coronary vasoconstriction is abolished by exercise[180], and seems unlikely to account for differences observed in exertional angina.

Cold exposure has been consistently shown to produce a rise in systemic blood pressure both in normal subjects[181] and patients with angina[174,176,178,182-186]. Heart rate responses, however, have been variable and while some investigators have reported a higher rate in the cold[182,184,186,187], others have found either no difference or a lower rate[178,183,185]. This variable rate response may provide an explanation for differences in cold tolerance between patients. Thus, cold-induced sympathetic activation may cause a tachycardia as a result of β_1 receptor stimulation. Alternatively, it may cause a bradycardia if the baroreceptor response to α_2 receptor mediated vasoconstriction is normal. It has been suggested that absence of this bradycardia, perhaps due to dysfunction of the baroreceptor reflex, may provide an explanation for cold intolerance[188] but this has not been investigated.

We have, therefore, studied an unselected population with angina in order to compare haemodynamic responses in cold and warm environments, between patients with and without a history of cold intolerance, with particular emphasis on the sympathetic nervous system and baroreceptor function.

5.2 METHODS

5.2.1 Patient Selection

Patients were recruited consecutively from men undergoing exercise treadmill testing for the assessment of angina. Patients aged ≤70 years with a normal resting ECG who developed ≥0.1mV of planar or down-sloping ST segment depression on routine exercise treadmill testing were eligible. Patients underwent coronary angiography to confirm significant coronary artery disease (defined as at least one stenosis of >50% in one or more major coronary arteries). Patients with diabetes, peripheral neuropathy or any other neurological disease were excluded. Normal renal and liver function, and normal haemoglobin, were confirmed in all cases. Patients were asked about a history of cold intolerance before the study. Fourteen patients were studied, mean age 57 (3) years (range 41 - 70).

5.2.2 Study Design

Anti-anginal medication was withdrawn 5 days before the study with the exception of short acting nitrates which were disallowed only on the study day. No medication was taken on the morning of the study. An intravenous cannula was

placed in the right forearm before starting the study to enable blood to be taken for assay of catecholamines. Patients underwent two exercise treadmill tests: one in the cold (6°C) and one at room temperature (25°C), in random order on the same day. Studies were performed in a specially designed chamber which could be set and maintained at any temperature. Patients were instructed to take a light breakfast 2 hours before the study, and were given a standard light snack after the first test. The second test was performed after a 2 hour break. Patients wore standardised clothing for both tests: light trousers and no upper garments. Patients spent 15 minutes in the chamber before beginning each test. During the treadmill test in the cold, a fan blowing at 2 metres/second was directed at the face and upper chest.

5.2.3 Baroreceptor Function

Baroreceptor function was assessed at room temperature by measuring the fall in systolic blood pressure 1 minute after standing from the supine position.

5.2.4 Blood Samples

Uncuffed blood samples were taken from the intravenous cannula for assay of adrenaline and noradrenaline. Two samples were drawn 5 minutes apart before entering the temperature chamber (room temperature) and a mean of these two samples were taken as the baseline. Further samples were taken 15 minutes after entering the chamber, immediately before exercise treadmill testing and a final sample was taken at peak exercise. Following centrifugation, plasma was frozen within 15 minutes, and stored at -80°C until assayed.

5.2.5 Assay of Catecholamines

Plasma adrenaline and noradrenaline were measured as described in section 3.2.7.

5.2.6 Exercise Treadmill Test

A symptom limited treadmill test was performed according to the Bruce protocol, using a Marquette treadmill. A three channel ECG was monitored continuously and ECGs were recorded at baseline and every 60 seconds throughout the study. Brachial artery blood flow was measured at baseline (two measurements), at each stage, and at peak exercise, using a duplex Doppler probe to measure blood velocity and brachial artery diameter. Brachial vascular resistance was calculated by dividing the mean arterial pressure (measured by sphygmomanometry in the contra-lateral arm) by brachial artery flow.

In order to obtain objective measurement of the onset of angina, no communication was made with the patient during the test, and the patient indicated the onset of chest discomfort by pressing a buzzer. Exercise was stopped when the patient pressed the buzzer for the second time, or if any of the following occurred: a fall in systolic blood pressure >10mmHg, significant ventricular arrhythmias, or >0.5mV ST segment depression. One patient developed ventricular premature beats during the study at 25°C and was excluded.

5.2.7 Statistical Analysis

All averaged results are expressed as mean values with standard error of the mean in parentheses. All variables were normally distributed and parametric statistics are

used throughout. Measurements in the cold and room temperature were compared using a paired t-test. Groups A and B were compared using an unpaired t-test. Two-sided p values were considered significant at the 5% level.

5.2.8 Ethical Approval

The study was approved by the North East Thames Ethics Committee, and written informed consent was given by all patients.

5.3 RESULTS

5.3.1 Exercise Responses - All Patients (Table 9)

a) Haemodynamic responses. Heart rate was not significantly affected by environmental temperature and in both the cold and the warm, the peak rate response was the same. Systolic blood pressure, however, was consistently higher in the cold, both at rest and during exercise, although at peak exercise the difference was not significant. Brachial vascular resistance, like blood pressure, was higher in the cold but the difference was only significant at peak exercise.

b) Ischaemic and symptomatic responses. The time to onset of ischaemic ST depression was unaffected by the environmental temperature and although angina tended to occur earlier in the cold the difference was not significant. The peak exercise time was not significantly affected by environmental temperature.

Table 9: Comparison of exercise parameters in the cold and warm.

	COLD n=14	WARM n=14	P VALUE
Room temperature (°C)	6.5 (0.2)	24.9 (0.6)	0.0001
Skin temperature (°C)	22.8 (0.6)	33.0 (0.2)	0.0001
Pre-exercise			
Heart rate (beats.minute^{-1})	89 (4)	90 (4)	0.92
Systolic blood pressure (mmHg)	155 (6)	140 (5)	0.007
Brachial vascular resistance (mmHg.litre^{-1}.minute)	2.56 (0.23)	2.10 (0.22)	0.09
Rate pressure product (mmHg.beats.minute^{-1}x10^{3})	14.4 (0.7)	12.5 (0.6)	0.007
Onset of ischaemia			
Time (s)	204 (35)	223 (29)	0.21
Heart rate (beats.minute^{-1})	112 (4)	120 (4)	0.17
Systolic blood pressure (mmHg)	183 (10)	161 (8)	0.007
Rate pressure product (mmHg.beats.minute^{-1}x10^{3})	20.5 (1.2)	19.1 (0.9)	0.29
Onset of angina			
Time (s)	310 (48)	342 (45)	0.27
Heart rate (beats.minute^{-1})	119 (5)	122 (5)	0.53
Systolic blood pressure (mmHg)	191 (8)	170 (7)	0.005
Rate pressure product (mmHg.beats.minute^{-1}x10^{3})	22.5 (1.0)	20.8 (1.0)	0.17
Peak exercise			
Time (s)	406 (54)	431 (46)	0.28
Heart rate (beats.minute^{-1})	151 (9)	150 (7)	0.75
Systolic blood pressure (mmHg)	192 (8)	181 (6)	0.06
Brachial vascular resistance (mmHg.litre^{-1}.minute)	1.50 (0.12)	1.19 (0.16)	0.007
Rate pressure product (mmHg.beats.minute^{-1}x10^{3})	25.9 (3.0)	23.9 (2.0)	0.22

5.3.2 Cold-Intolerant versus Cold-Tolerant Patients (Table 10, Figures 5 and 6)

Seven patients gave a history of cold intolerance (group A); the remainder reported no effect of environmental temperature on the severity of their angina (group B). The ages of patients in groups A and B were similar (54 (4) versus 59 (3) years). However, baroreceptor function, measured by the fall in systolic blood pressure on standing from the supine position, was diminished in group A compared with group B (19 (7) versus 0 (4) mmHg, $p=0.04$).

a) Haemodynamic responses. Environmental temperature did not significantly affect the heart rate response to exercise in either group. Nevertheless, in group A the rate response tended to be more pronounced in the cold, a difference not seen in group B. Blood pressure was higher in the cold in both groups. Thus, in group A, cold exposure caused the relation between rate pressure product and exercise duration to tend towards the left. In group B, on the other hand, cold exposure had little effect on this relation.

b) Ischaemic and symptomatic responses. In both groups, the onset of ischaemia, the onset of angina and peak exercise occurred at relatively fixed rate pressure products. Thus, in group A, the cold-induced leftward shift of the rate pressure product to exercise time relation resulted in the earlier onset of ischaemia and angina which led in turn to a significant reduction in peak exercise time. In group B, on the other hand, cold exposure had less effect on rate pressure product

during exercise and, accordingly, neither ischaemia nor angina occurred any earlier and peak exercise time was unaffected.

5.3.3 Response of Catecholamines to Cold and Exercise (Figure 7)

Adrenaline levels increased with exercise, but there was no difference between the warm and cold environments. In contrast, noradrenaline levels increased more than two-fold at rest in the cold environment, and more than doubled again with exercise. There was no difference in adrenaline or noradrenaline levels between cold-intolerant and cold-tolerant patients at baseline, pre-exercise or at peak exercise.

Table 10: **Comparison of haemodynamic responses to exercise in cold-intolerant (group A) and cold-tolerant (group B) patients.**

	GROUP A (n=7)			GROUP B (n=7)		
	COLD	WARM	P VALUE	COLD	WARM	P VALUE
Differences pre-exercise						
Heart rate (beats.minute^{-1})	90 (4)	92 (6)	0.61	89 (8)	87 (6)	0.72
Systolic blood pressure (mmHg)	155 (9)	133 (7)	0.009	156 (7)	146 (8)	0.25
Brachial vascular resistance	2.76 (0.38)	1.96 (0.31)	0.03	2.36 (0.27)	2.23 (0.31)	0.76
Rate pressure product	14.5 (0.8)	12.4 (1.0)	0.04	14.3 (1.2)	12.6 (0.8)	0.11
Differences at onset of ischaemia						
Time (s)	201 (58)	242 (50)	0.05	206 (43)	203 (31)	0.91
Heart rate (beats.minute^{-1})	112 (5)	120 (5)	0.39	112 (6)	120 (6)	0.32
Systolic blood pressure (mmHg)	178 (14)	165 (14)	0.16	188 (14)	157 (9)	0.03
Rate pressure product	20.1 (2.1)	19.4 (1.3)	0.70	20.8 (1.4)	18.8 (1.2)	0.30
Differences at onset of angina						
Time (s)	348 (87)	449 (60)	0.04	272 (44)	236 (38)	0.13
Heart rate (beats.minute^{-1})	121 (5)	125 (7)	0.67	117 (8)	120 (7)	0.68
Systolic blood pressure (mmHg)	189 (11)	180 (10)	0.07	191 (11)	161 (8)	0.02
Rate pressure product	22.9 (1.8)	22.2 (1.4)	0.70	22.1 (1.3)	19.3 (1.3)	0.14
Differences at peak exercise						
Time (s)	411 (83)	484 (61)	0.07	401 (77)	379 (68)	0.24
Heart rate (beats.minute^{-1})	155 (18)	152 (12)	0.78	147 (7)	146 (8)	0.92
Systolic blood pressure (mmHg)	186 (12)	183 (7)	0.64	197 (11)	179 (6)	0.04
Brachial vascular resistance	1.65 (0.16)	1.37 (0.27)	0.09	1.34 (0.15)	1.00 (0.16)	0.06
Rate pressure product	27.5 (5.2)	26.1 (3.2)	0.65	24.4 (3.5)	21.7 (2.3)	0.10

Figure 5: Effects of environmental temperature on haemodynamic variables during stress testing in cold-intolerant (group A) and cold-tolerant patients (group B).

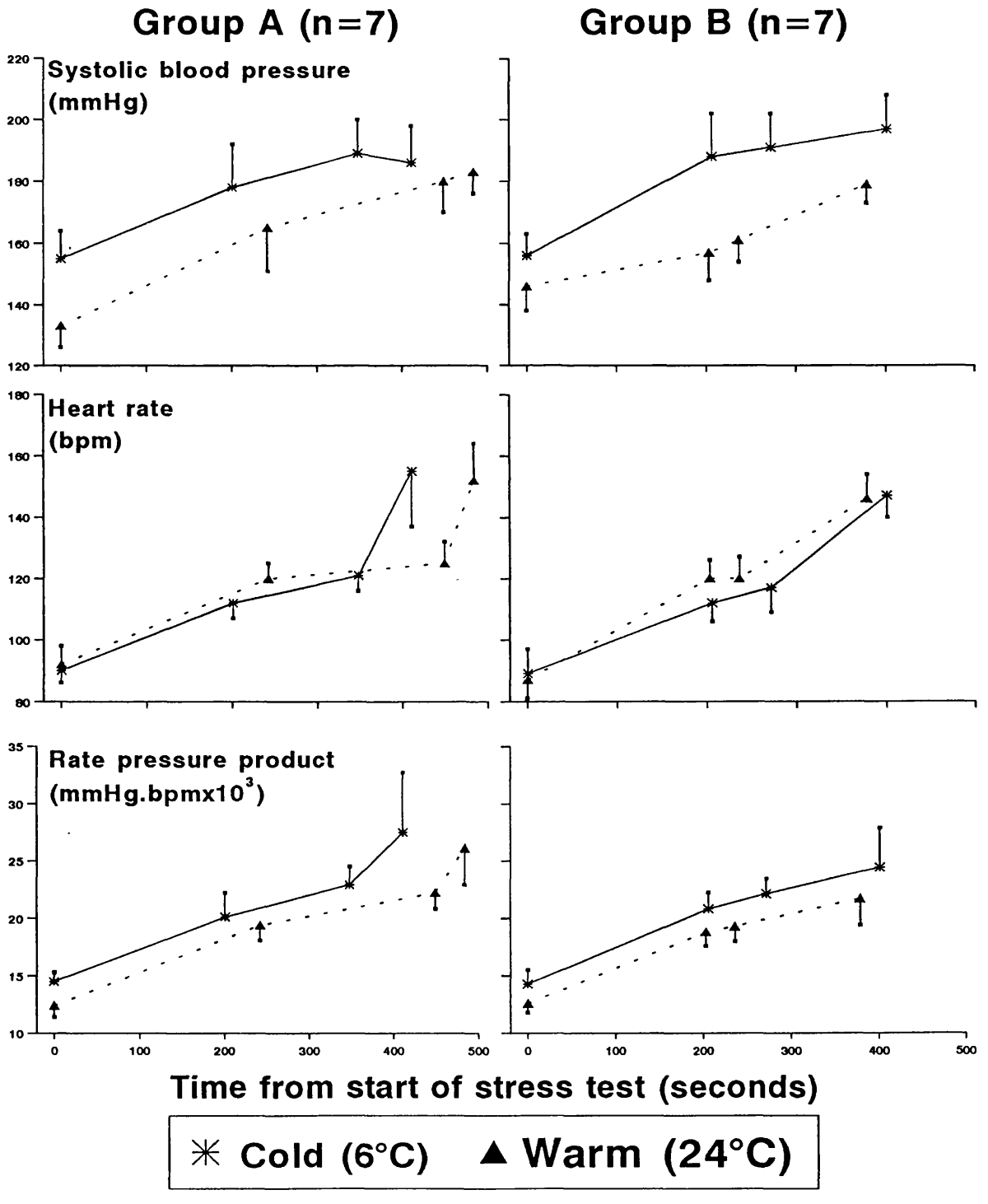


Figure 6: Comparison of lying to standing blood pressure response between cold intolerant (group A) and cold tolerant patients (group B).

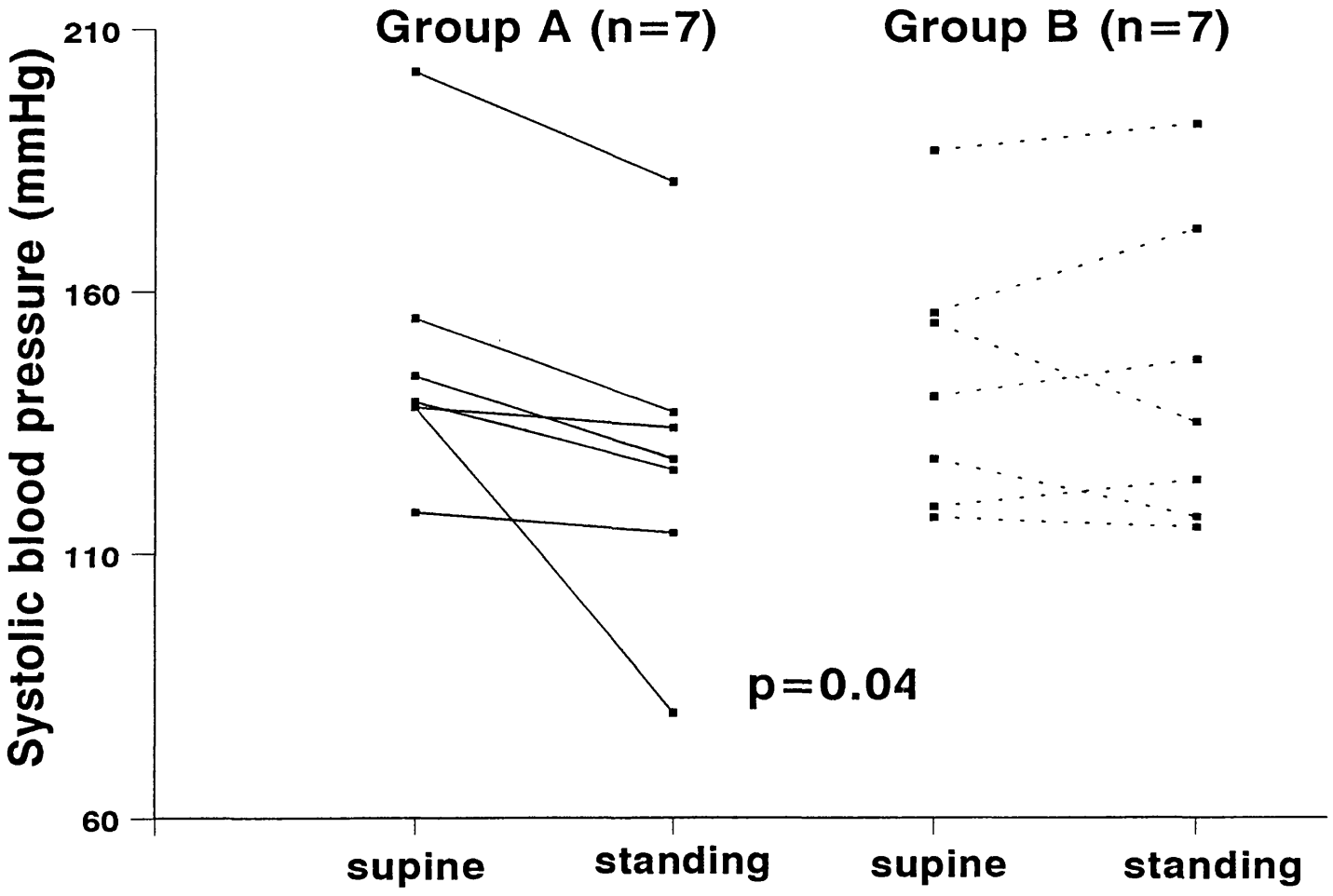
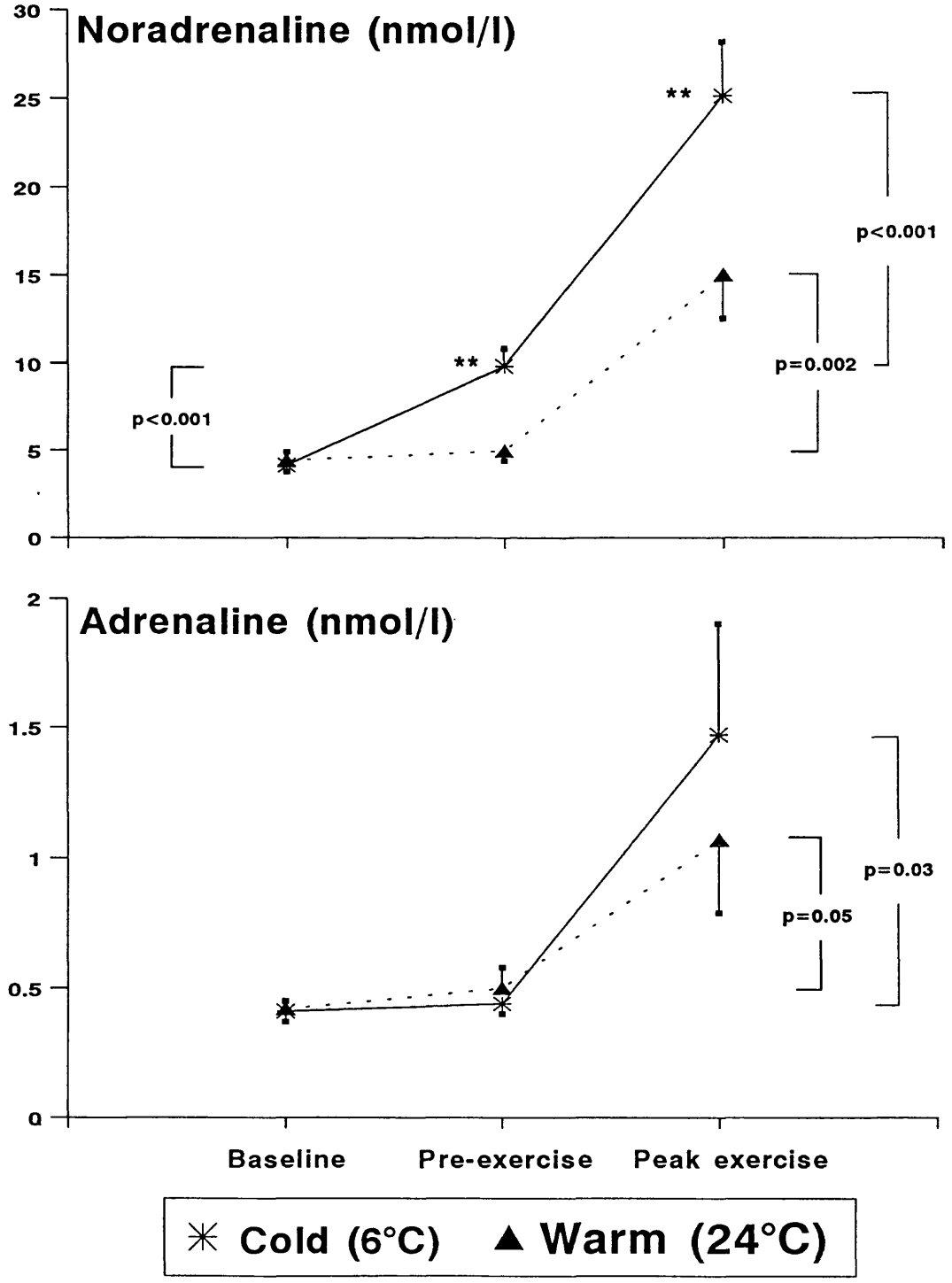


Figure 7: **Effects of environmental temperature and exercise on plasma adrenaline and noradrenaline.**

Difference between cold and warm environments: **p<0.001.



5.4 DISCUSSION

This study has examined haemodynamic, ischaemic and symptomatic responses to exercise in patients with angina. Exercise tests were performed in random sequence, at room temperature and at 6°C, in order to evaluate the effects of cold exposure. The cold stimulus was less severe than that used in previous studies[174-176,178,182,184-186] but was exaggerated by blowing air into the patients' faces, in order to simulate the conditions of a windy winter's day in London. Another important feature of this study was the patient population which included cold-intolerant and cold-tolerant patients. This contrasts with most previous studies which have included only patients with a history of cold intolerance[174-176,182,184-186].

The easily derived product of heart rate and systolic blood pressure correlates closely with myocardial oxygen demand[189]. Because exercise causes both these variables to increase, it commonly provokes angina in patients with coronary artery disease. Cold exposure may also provoke angina but it has been difficult to identify a unifying mechanism that accounts satisfactorily for this observation. It has usually been attributed to increased myocardial oxygen demand caused by peripheral vasoconstriction but this does not provide an explanation for differences between patients. Some investigators, therefore, have suggested that reduced myocardial oxygen delivery caused by coronary vasoconstriction may be the dominant mechanism[178,179]. In support of this Juneau et al[178] reported that rate pressure product at the onset of electrocardiographic ischaemia was significantly lower during exercise in the cold in cold-sensitive patients, implying that ischaemia was

occurring at a lower myocardial oxygen consumption. More commonly in studies of this type, however, the rate pressure product at which ischaemia develops has been shown to be independent of environmental temperature, and one group of investigators found that it increased significantly in the cold[185]. These conflicting findings appear to indicate important variability in the haemodynamic responses to cold which may in part explain why clinical responses are equally variable. Thus not all investigators have been able to demonstrate that cold exposure in patients with coronary artery disease produces significant reductions in exercise capacity, even in patients with a history of cold intolerance[184].

Reasons for the variable haemodynamic and clinical responses to cold reported in different angina studies are not clear but may relate, at least in part, to heterogeneity within and between the study populations. Thus, when the exercise tests at room temperature were compared with those at 6°C for the group as a whole, it was found that, despite rises in brachial vascular resistance and systolic blood pressure during cold exposure, the times to ischaemia and angina remained fairly constant and exercise tolerance was unaffected. Ischaemia in the two tests occurred at relatively fixed rate pressure products suggesting that it was caused by myocardial oxygen demand exceeding a temperature-independent threshold, not by cold-induced coronary vasoconstriction. When the same comparison was applied to subgroups with and without a history of cold intolerance some interesting differences emerged. At 6°C, patients with a history of cold intolerance tended towards a leftward shift in the relationship between rate pressure product and exercise duration ensuring that the ischaemic threshold was exceeded at a

lower workload such that angina developed earlier and exercise tolerance was reduced. In patients with no history of cold intolerance, on the other hand, this leftward shift did not occur and consequently there was no tendency for ischaemia to develop earlier during cold exposure.

The data, therefore, are consistent with the view that cold intolerance in patients with exertional angina is the result of exaggerated myocardial oxygen demand, reflected by the changes in rate pressure product. Cold-induced increases in peripheral resistance and blood pressure probably make the major contribution to this, mediated by increased levels of noradrenaline on exercise which are particularly marked in the cold. However, this does not provide the full explanation, since similar increases in catecholamines and rate pressure product were observed in the subgroup which was not cold-intolerant. In this subgroup, however, the rate of the rise in heart rate was similar during exercise in the cold and the warm. In the cold-intolerant group, on the other hand, increases in exertional blood pressure during cold exposure were accompanied by a tendency towards a steeper heart rate response. Accordingly, rate pressure product at a given workload increased.

Mechanisms responsible for the different rate responses in the cold-tolerant and intolerant groups are not clear but it is possible to speculate that the baroreceptor reflex plays a role. This was normal in the cold-tolerant group (judged by blood pressure changes from lying to standing) and the diminished heart rate response during cold-induced increases in exertional blood pressure could therefore be regarded as physiological. In the cold-intolerant group, on the other hand,

baroreceptor function was impaired and the heart rate response to exercise showed no tendency to diminish despite cold-induced increases in blood pressure.

Conclusion. This study has shown that cold exposure in patients with exertional angina causes peripheral vasoconstriction and an increase in blood pressure, particularly at sub-maximal exercise. However, associated increases in myocardial oxygen demand may be offset by reductions in heart rate if baroreceptor function is normal. If baroreceptor function is abnormal, on the other hand, reductions in heart rate may not occur in response to cold-induced increases in blood pressure. Rate pressure product therefore increases and its relation with exercise duration shifts to the left with the result that the ischaemic threshold is exceeded at a lower workload. This mechanism may account for some of the variability in tolerance to cold exposure that affects patients with exertional angina.

SECTION 2

MYOCARDIAL INFARCTION

CHAPTER 6

THE EFFECT OF COLD ON THE PATHOGENESIS OF ACUTE MYOCARDIAL INFARCTION

6.1 INTRODUCTION

In the previous chapter, it has been observed that myocardial ischaemia and angina can be provoked more easily during exercise in the cold, probably mediated by stimulation of the sympathetic nervous system. In section 2 of the thesis, attention is directed towards acute myocardial infarction, and this chapter examines the influence of cold on the pathogenesis of myocardial infarction.

Circadian and seasonal rhythms are recognised in many physiological systems. Catecholamines, for example, have a circadian rhythm, with a morning peak and nocturnal trough[190], while mood is known to vary with season[191].

Data presented to the British Cardiac Society, Harrogate 1992 and the American College of Cardiology, Anaheim 1993, and accepted for publication by the British Heart Journal

Over recent years, similar patterns have been sought and established in ischaemic heart disease. Several studies have shown that a circadian rhythm occurs in myocardial infarction[192-197] as well as in myocardial ischaemia[23,198,199] and sudden cardiac death[200-203], although the mechanisms are unclear. Some evidence also exists for seasonal rhythms in ischaemic heart disease, but because this is based on often unreliable death registration data, cautious interpretation is necessary[204]. Thus a winter peak in cardiac mortality has been reported in both the United Kingdom and in Canada[205,206], and there are more cardiac deaths on colder days in Auckland[207], Brisbane[208] and Montreal[209]. Although these mortality studies suggest seasonal variations in cardiac deaths, there is little information on seasonal variation in the incidence of acute myocardial infarction and conflicting data on the role of environmental temperature. Thus, more infarcts occur on colder days in the subarctic climate of Northern Finland[210], but temperature does not appear to influence the onset of acute myocardial infarction during the cold Scandinavian winter[211] or in Tasmania[212], which experiences a limited temperature range throughout the year.

In the present study, therefore, the seasonal variation of acute myocardial infarction in a London borough has been analysed, with particular reference to the influence of environmental temperature.

6.2 METHODS

6.2.1 Study Group

The study group comprised 633 consecutive patients with acute myocardial infarction admitted to the coronary care unit of Newham General Hospital over a 4 year period from 1st January 1988 to 31st December 1991. Newham General Hospital serves a population of approximately 220,000 and hospital policy at the time of the study was to admit all patients with suspected acute myocardial infarction to the coronary care unit regardless of age. The mean age of the patients was 62 years (range: 26 - 94) and 462 were male. The diagnosis of acute myocardial infarction was based on any two of the following three criteria: 1) cardiac chest pain lasting at least 30 minutes; 2) ECG changes of myocardial infarction with ≥0.1mV ST segment elevation in two or more contiguous limb leads or ≥0.2mV ST segment elevation in two or more contiguous chest leads; 3) diagnostic rise in creatine kinase (≥400iu/l).

6.2.2 Environmental Temperature

The date and time of onset of chest pain were recorded at the time of admission. Weather conditions for each day over the 4-year study period were obtained from the London Weather Centre. To determine the influence of environmental temperature, the minimum temperature on the day of infarction for each of the 633 patients was noted, as well as the minimum temperature on each day during the 4 year study period. The minimum temperature for each day was defined as the minimum temperature during the 12 hours before 09.00 hours.

6.2.3 Control Group

For assessment of seasonal changes in the magnitude of the local population, a separate analysis was undertaken of the incidence of acute appendicitis over the same period. Data were obtained from the operating theatre surgical register.

6.2.4 Statistical Analysis

Circadian variation was examined by calculating the number of patients whose pain started in each of 12 2-hour periods throughout the day. For seasonal and temperature variation, admission rates to the hospital were calculated by month and temperature band. Tests of heterogeneity and linear trend were applied[213] and 95% confidence intervals were derived from tabulations of the Poisson distribution.

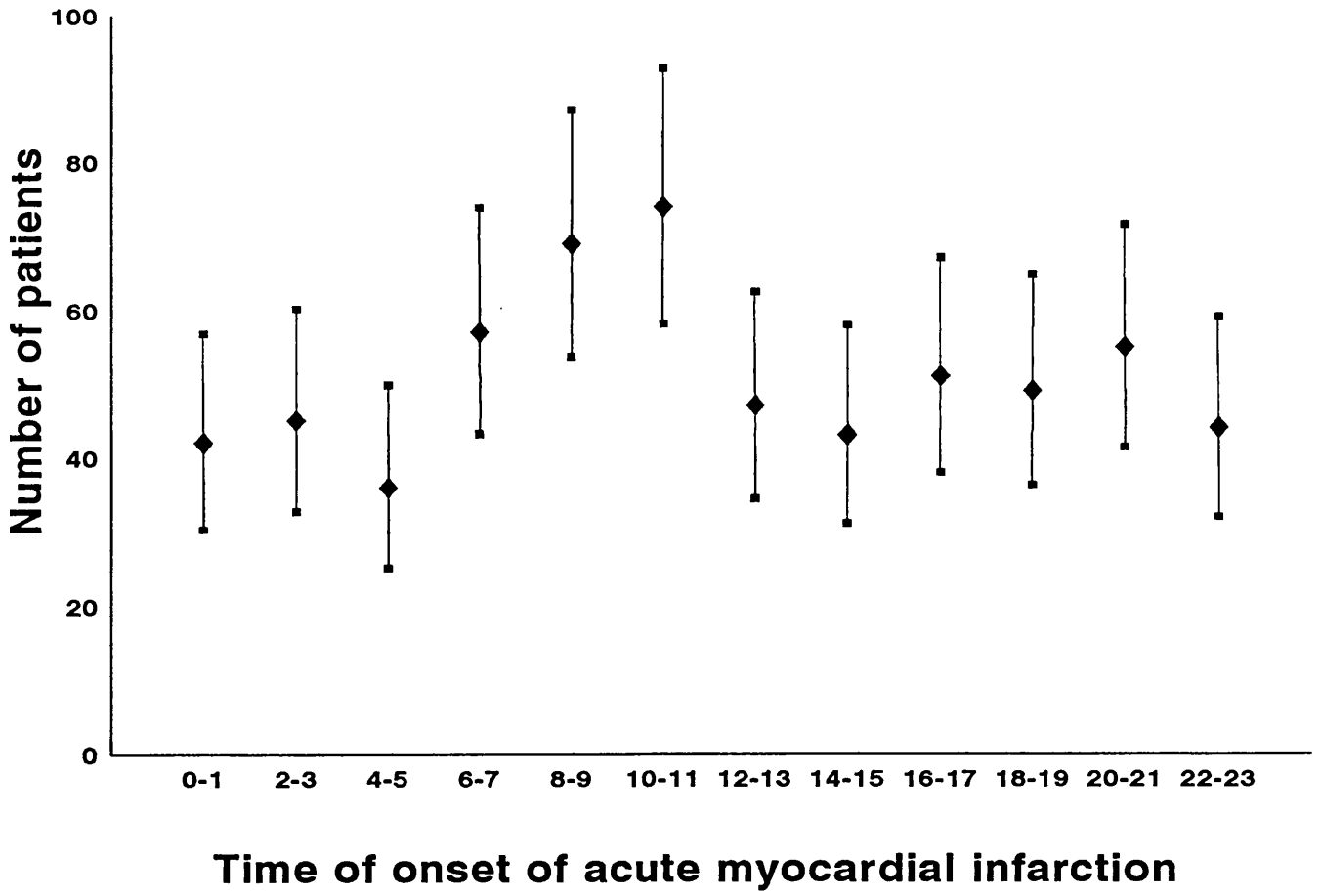
6.3 RESULTS

6.3.1 Circadian Variation (Figure 8)

The time of onset of pain was known in 612 patients and is shown in figure 8. There was significant variation in onset of infarction throughout the day (test for heterogeneity: χ^2 = 25.9 on 11 degrees of freedom, p = 0.007). The main peak occurred in the second quarter of the day (06.00 - 11.59 hours), during which 31.6% of the group experienced the onset of symptoms.

Figure 8: **Distribution of time of symptom onset of acute myocardial infarction (n=612) by 12 two-hour periods with 95% confidence intervals.**

Test for heterogeneity: χ^2 = 25.9 on 11 df, p = 0.007.



6.3.2 Seasonal Variation (Figure 9)

The hospital admission rate also showed significant seasonal variation with more admissions during winter than summer months. Thus 30.5% of the total study group presented in the 3 months from December to February. In contrast, acute appendicitis did not show seasonal variation (test for heterogeneity: χ^2 = 15.6 on 11 degrees of freedom, p = 0.2) and as many patients were admitted between April and September (212) as between October and March (209) (Figure 10).

6.3.3 Temperature Variation (Table 11)

The admission rate from myocardial infarction was inversely related to the minimum daily temperature. The admission rate on days when the minimum temperature fell below 3°C was nearly double that observed on days with a minimum temperature of 15°C or more.

6.3.4 Temperature versus Seasonal Variation (Table 12)

To determine if the excess of infarction on colder days reflected a seasonal rather than a temperature effect, the winter months (October to March) and the summer months (April to September) were considered separately. There were only a small number of days in the upper two temperature bands in the winter, and the lower two temperature bands in the summer. The two bands in each season were, therefore, combined for presentation and statistical analysis. The higher rate of infarction on colder days was apparent for both summer and winter months but the trend was only statistically significant in summer.

Figure 9: **Distribution of month of occurrence of acute myocardial infarction (n=633) with 95% confidence intervals.**

Test for heterogeneity: χ^2 = 26.0 on 11 df, p = 0.006.

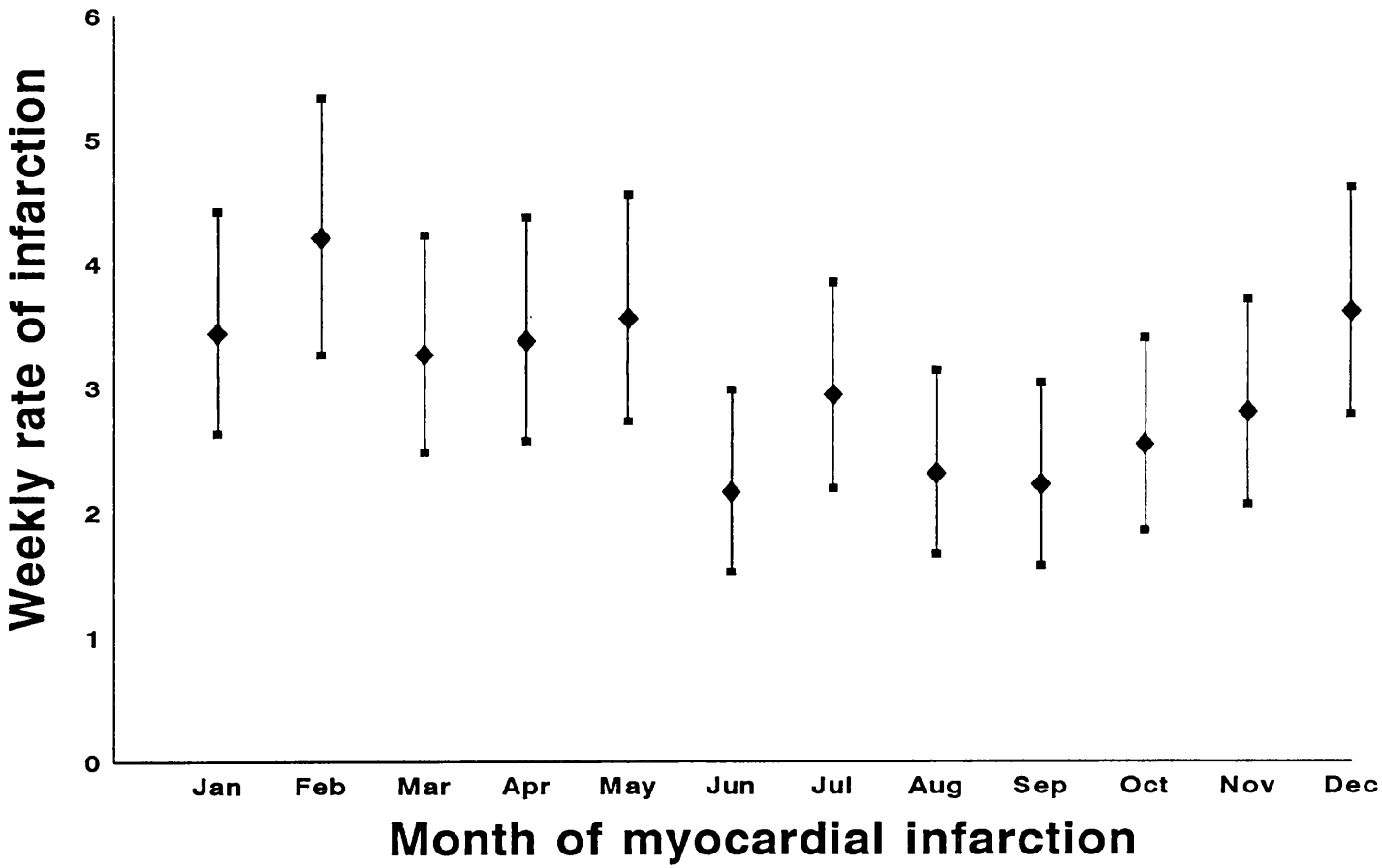


Figure 10: **Distribution of month of occurrence of appendicectomy (n=421) with 95% confidence intervals.**

Test for heterogeneity: χ^2 = 15.6 on 11 df, p = 0.2.

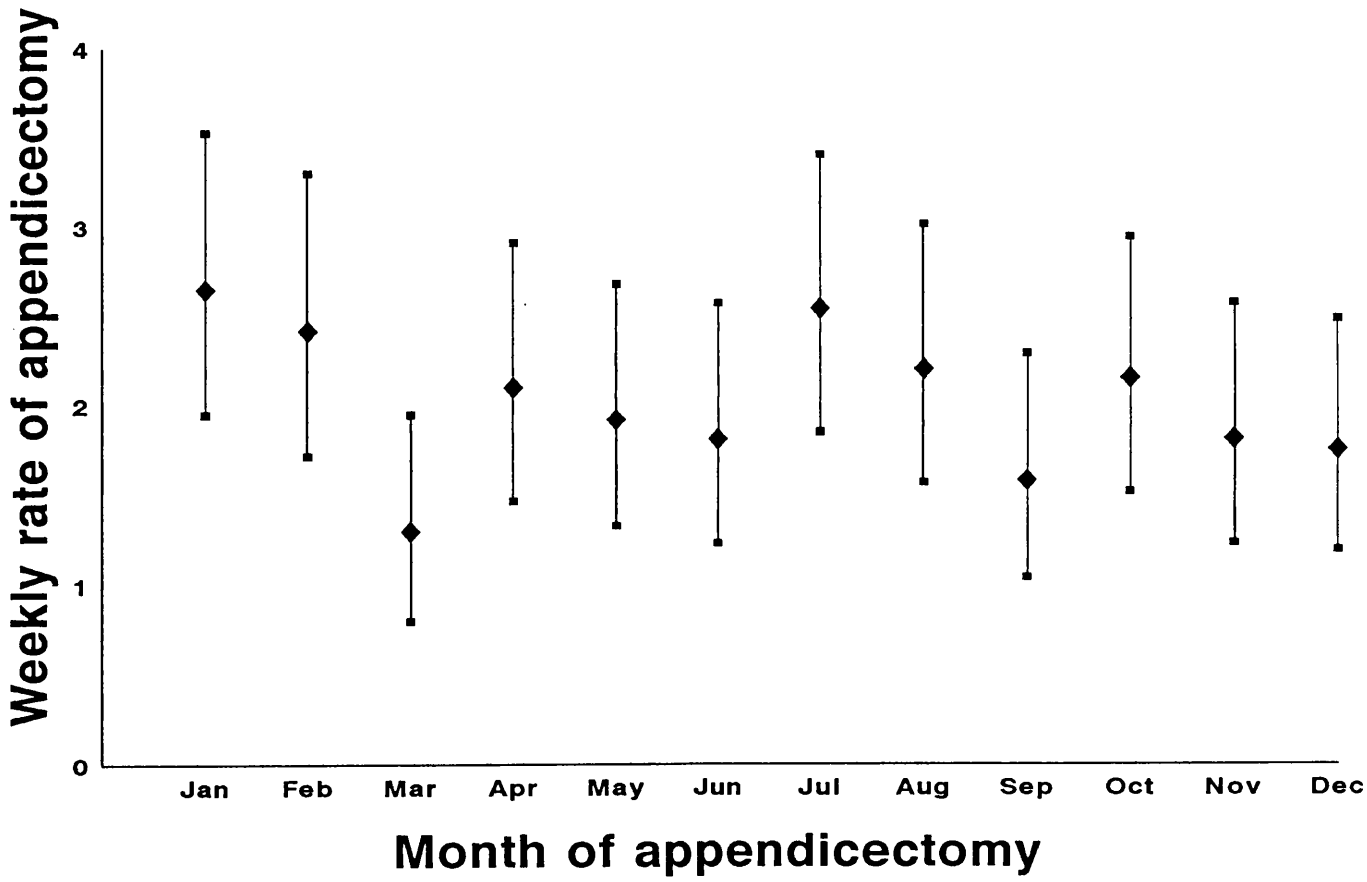


Table 11: **Number of days and acute myocardial infarctions in six temperature bands with weekly rate of myocardial infarction.**

TEMPERATURE GROUP (°C)	DAYS	MYOCARDIAL INFARCTIONS	RATE/WEEK	95% CI
< 3.0	99	65	4.60	3.55 - 5.86
3.0 - 5.9	239	110	3.22	2.65 - 3.88
6.0 - 8.9	285	137	3.36	2.83 - 3.98
9.0 - 11.9	322	131	2.85	2.38 - 3.38
12.0 - 14.9	288	113	2.75	2.26 - 3.30
≥ 15.0	228	77	2.36	1.87 - 2.95

Test for heterogeneity: $\chi^2 = 18.5$ on 5 df, $p = 0.002$

Test for linear trend: $\chi^2 = 15.4$ on 1 df, $p < 0.001$

95% CI = 95% confidence intervals

Table 12: **Number of days and acute myocardial infarctions in five temperature bands with weekly rate of myocardial infarction; shown separately for winter and summer months.**

TEMPERATURE GROUP (^{O}C)	DAYS	MYOCARDIAL INFARCTION	RATE/WEEK	95% CI
Winter 6 months[*]				
< 3.0	89	57	4.48	3.40 - 5.81
3.0 - 5.9	193	91	3.30	2.66 - 4.05
6.0 - 8.9	210	94	3.13	2.53 - 3.83
9.0 - 11.9	163	59	2.53	1.93 - 5.63
≥ 12.0	72	43	4.18	3.03 - 5.63
Summer 6 months[**]				
< 6.0	56	27	3.38	2.22 - 4.91
6.0 - 8.9	75	43	4.01	2.90 - 5.41
9.0 - 11.9	159	72	3.17	2.48 - 3.99
12.0 - 15.0	222	72	2.27	1.78 - 2.86
≥ 15.0	220	75	2.39	1.88 - 2.99

[*]Test for heterogeneity χ^2 = 11.8 on 4df, p = 0.02

[*]Test for linear trend: χ^2 = 1.88 on 1df, p = 0.17

[**]Test for heterogeneity: χ^2 = 12.3 on 4df, p = 0.015

[**]Test for linear trend: χ^2 = 8.76 on 1df, p = 0.003

95% CI = 95% confidence intervals

6.4 DISCUSSION

This study suggests a morning peak in the onset of acute myocardial infarction as has been demonstrated previously[192-197], and a seasonal variation, with more infarcts in the winter months. The mechanism of this seasonal variation is unknown, but it appears to be dependent on climatic variables. In the sub-tropical climate of New Orleans, for example, the incidence of acute myocardial infarction peaks during the summer[214], a finding consistent with those from other hot climates[215,216]. This contrasts to the winter peak observed in temperate[206] and cold climates[210]. However, it has not been established whether the variation between winter and summer is truly seasonal, or whether it depends upon environmental temperature.

The temperature data demonstrated an excess of infarcts on colder days, but this does not reliably distinguish between the effects of season and environmental temperature. However, by considering the summer and winter months separately, in order to control for season, it was possible to analyse the independent influence of temperature on the onset of acute myocardial infarction. The analysis confirmed a higher rate of infarction on colder days in both winter and summer, suggesting that under conditions of reduced environmental temperature the risk of acute myocardial infarction increases independently of the time of year.

Mechanisms relating environmental temperature to the onset of acute myocardial infarction must remain speculative. Sympathetic tone may be important because it increases in the cold, with several consequences[181]. Blood pressure tends to rise,

increasing the myocardial oxygen demand. Haematological variables are also affected as reflected by increases in beta-thromboglobulin and platelet factor 4 which in turn enhance platelet aggregation[217]. However, these adverse haematological effects of sympathetic stimulation may to some extent be countered by changes in blood viscosity and haematocrit which tend to be higher in patients presenting with acute myocardial infarction in the summer, compared with the winter[218].

The analysis has assumed that the population at risk of infarction remains constant throughout the year. This assumption may not be accurate because of seasonal changes caused, in particular, by annual holidays which are usually taken in the summer months. By choosing acute appendicitis, it was possible to obtain accurate data based on the operating theatre surgical register, and did not have to depend on Hospital Activity Analysis data, which are notoriously unreliable[219]. The incidence of acute appendicitis showed no seasonal changes and, importantly, there was no palpable reduction in the summer months, even though the population at risk is younger and probably more mobile than those at risk of acute myocardial infarction. Thus any effect of seasonal population changes is likely to have been small.

Conclusion. This study suggests a seasonal variation in the incidence of acute myocardial infarction which is at least partly dependent on the environmental temperature. Myocardial infarction occurs more commonly on colder days,

regardless of the time of year, indicating that environmental temperature may be an important variable in the pathogenesis of acute myocardial infarction.

CHAPTER 7

ANGINAL PERCEPTION IN THE EARLY POST-INFARCTION PERIOD

7.1 INTRODUCTION

As discussed in 1.3.3, ischaemia is common and frequently asymptomatic following acute myocardial infarction[14,15,51]. Despite this, investigation of mechanisms affecting the symptomatic expression the pathophysiology of silent ischaemia has been largely confined to patients with stable angina and much less is known about patients with acute myocardial infarction.

In chapter 2, the interaction of ischaemic and perceptual variables on the symptomatic expression of myocardial ischaemia was examined in patients with stable angina. In acute myocardial infarction, there is, inevitably, less myocardium with the potential for ischaemia; this smaller mass may provide a possible explanation for the relatively high prevalence of silent myocardial ischaemia. Autonomic dysfunction is also common early after myocardial infarction, possibly because of destruction of neuro-receptors and neural pathways within and around the infarcted territory[220]. However, whether this creates zones of denervated

myocardium, that are insulated from the central pain centres, remains speculative[221].

The purpose of the present study was to evaluate Holter recordings, treadmill responses, coronary arteriography and heart rate variability in patients with recent myocardial infarction in order to elucidate the mechanisms of ischaemia in these patients. Particular attention has been given to defining the relative contributions of ischaemic and neuropathic factors in order to account for the variable association between myocardial ischaemia and the provocation of symptoms.

7.2 METHODS

7.2.1 Patient Selection

These were consecutive patients from three district general hospitals who received thrombolytic therapy for acute myocardial infarction diagnosed when at least two of the following criteria were fulfilled: 1) typical chest pain lasting >30 minutes; 2) ≥0.1mV ST elevation in at least one standard or two precordial leads on the ECG; 3) rise in serum creatine kinase to >400iu/l. Only patients with a stable in-hospital course were considered for inclusion, and patients with repolarisation abnormalities caused by left bundle branch block, paced rhythms or concurrent digoxin therapy were excluded. There were 256 such patients, but 184 were taking beta blocking drugs or calcium antagonists at the time of the study and were also excluded. The

remaining 72 patients (65 male) underwent exercise treadmill tests and Holter monitoring.

7.2.2 Study Design

All patients underwent ambulatory Holter monitoring during the in-hospital period, exercise treadmill tests, at or around the time of discharge, and a subset of patients underwent cardiac catheterisation after hospital discharge.

7.2.3 48 Hour Ambulatory Holter Monitoring

Seventy one patients underwent 48 hour ambulatory Holter monitoring of ST segments. Recordings were made at a median of 76 hours (range 48 - 235) after the onset of infarction when the patients were mobile. Leads CMV_5 and modified lead 2 were used. Recordings were made and analysed as described in section 2.2.4. Of these recordings 69 were of adequate quality for analysis.

7.2.4 Exercise Treadmill Test

This was performed according to the modified Bruce protocol at a median of 15 days post-infarction (range 7 - 35). A 12 channel ECG was monitored continuously and ECGs were recorded at the onset of ischaemia (0.1mV of planar or down-sloping ST segment depression, measured at 80 milliseconds after the J point) and at peak exercise. Heart rate was monitored throughout the test and blood pressure was recorded at baseline, at the onset of ischaemia, and at peak exercise. Exercise was stopped when the patient developed limiting symptoms, or if any of the following criteria were fulfilled: a fall in systolic blood pressure >10mmHg,

significant ventricular arrhythmias, or >0.5mV ST depression. None of these criteria occurred in the patients included in the study. The workload at peak exercise was recorded.

7.2.5 Heart Rate Variability

The first 24 hours of Holter recordings were analysed for heart rate variability as described in section 2.2.6.

7.2.6 Coronary Angiography and Ventriculography

Twenty one patients from two centres underwent routine coronary angiography regardless of symptoms and treadmill findings (excluding those who were >70 years), in accordance with the current policy of the units. This was performed 2 to 6 weeks after infarction. Coronary disease and left ventricular function was quantified as described in section 2.2.7.

7.2.7 Statistical analysis

All averaged results are expressed as mean values with standard error of the mean in parentheses. Groups A and B were compared using the unpaired t-test for normally distributed variables, and by the Mann-Whitney U test for other variables (number and duration of episodes of ischaemia on Holter monitoring and measures of heart rate variability). Severity of coronary disease and the distribution of diabetic patients in groups A and B were compared using the χ^2 test. Two-sided p values were considered significant at the 5% level.

7.2.8 Ethical Approval

The study was approved by the Newham Health District Ethics Committee, and written informed consent was given by all patients.

7.3 RESULTS

7.3.1 Treadmill Stress Testing and Coronary Angiography (Table 13)

Of the 72 patients who underwent treadmill stress testing, 16 (group A) experienced angina which was associated with ≥0.1mV ischaemic ST segment depression in 14 cases. The remaining 56 patients (group B) experienced no angina, although 23 of them developed ischaemic ST segment depression. Thus a total of 37 patients had ischaemic exercise ECGs. The number of diabetic patients in group A and B was not significantly different (4 versus 7, $\chi^2=0.692$; $p=0.41$).

Comparison of the 14 group A and 23 group B patients with ischaemic exercise ECGs showed that the patients from group A had more extensive coronary artery disease, developed ST segment depression earlier during the stress test, and had a significantly lower exercise tolerance than those from group B.

7.3.2 48 Hour Holter ST Monitoring (Table 14)

Sixty nine patients had analysable Holter recordings of whom 23 had one or more episodes of ischaemic ST segment depression. A total of 122 episodes of ST

segment depression were recorded, which were silent in all but two cases. Of the 23 patients with ischaemic Holter recordings, ten had experienced angina on the treadmill (group A) and 13 had not (group B).

Comparison of the ten group A and 13 group B patients with ischaemic Holter recordings showed that the patients in group A, despite their smaller numbers, had more ischaemic episodes (63 versus 51, $p=0.003$) and a greater cumulative duration of ischaemia (1398 versus 860 minutes, $p=0.001$) during the 48 hour monitoring period. However, the characteristics of the ischaemic episodes showed no differences between the two groups.

7.3.3 Heart Rate Variability (Table 15)

This was measured in 68 patients, 13 from group A and 55 from group B. There were no significant differences in spectral or non-spectral indices between the patients who experienced angina during treadmill testing (group A) and those who did not (group B).

Table 13: Comparison of angiographic and exercise variables between symptomatic (group A) and asymptomatic (group B) patients.

	GROUP A n=14	GROUP B n=23	P VALUE
Age (years)	65 (2)	59 (2)	0.13
Cardiac catheter data (n=21)			
Single/multi-vessel disease	0/6	7/10	0.06
Left ventricular ejection fraction (%)	29 (8)	40 (4)	0.16
Heart rate (beats minute^{-1})			
Rest	92 (3)	91 (3)	0.80
Peak	137 (3)	142 (4)	0.32
Systolic blood pressure (mmHg)			
Rest	118 (3)	120 (4)	0.66
Peak	143 (7)	152 (7)	0.34
Time to 0.1 mV ST depression (s)	194 (25)	359 (39)	0.001
Maximum ST depression (0.1 mV)	0.21 (0.3)	0.18 (0.2)	0.34
Maximum workload (METS)	5.5 (0.5)	7.8 (0.6)	0.02

METS = metabolic equivalents.

Table 14: Comparison of ischaemic episodes on Holter between symptomatic (group A) and asymptomatic (group B) patients.

	GROUP A n=10	GROUP B n=13	P VALUE
Mean duration of episodes (minutes)	20 (5)	28 (9)	0.71
Maximum ST depression (mV)	0.19 (0.3)	0.15 (0.2)	0.25
Heart rate pre-episode (beats.minute^{-1})	83 (5)	83 (6)	0.97
Heart rate at peak ST depression (beats.minute^{-1})	85 (6)	82(5)	0.70
Increase in heart rate at peak ST depression (%)	2.1 (3.7)	-0.05 (4.6)	0.72

Table 15: Comparison of heart rate variability between symptomatic (group A) and asymptomatic (group B) patients.

	GROUP A n=13	GROUP B n=55	P VALUE
High frequency peak (ms)	7.1 (0.9)	8.2 (0.7)	0.70
Low frequency peak (ms)	14.8 (2.5)	15.1 (1.2)	0.98
SDANN (ms)	76 (7)	68 (3)	0.29
rMSSD (ms)	19 (2)	23 (2)	0.31
pNN50 (%)	2.9 (0.9)	5.3 (1.0)	0.25
SD (ms)	37 (5)	42 (3)	0.57
SDRR (ms)	85 (8)	81 (4)	0.58

SDANN = standard deviation of 5-minute mean R-R intervals. rMSSD = root-mean square of the difference of successive R-R intervals. pNN50 = proportion of adjacent R-R intervals more than 50 ms different. SD = mean of all 5-minute standard deviations of R-Rs. SDRR = the standard deviation about the mean.

7.4 DISCUSSION

In this study mechanisms of angina in patients with recent myocardial infarction have been examined, with particular emphasis on the interaction of ischaemic and neuropathic factors. Data obtained during treadmill testing, Holter monitoring and coronary arteriography indicate that while a neuropathic defect may be evident in the early post-infarction period, the severity of myocardial ischaemia, as defined by mass and intensity, is the major determinant of whether or not symptoms are experienced by the patient.

Although treadmill stress testing produced electrocardiographic ischaemia in just over half the patients included in the study, this was symptomatically silent in 62% of them, confirming the observations of previous investigators that silent ischaemia is common early after acute myocardial infarction[14,15,51]. The propensity of these patients to silent ischaemia has been attributed to ischaemic damage affecting the sensory innervation of the heart[220], although in our study, left ventricular function tended to be better preserved in the silent group. However, the validity of this mechanism remains unproven because studies examining the relation between autonomic function and the symptomatic expression of myocardial ischaemia in patients with recent myocardial infarction have not been reported previously.

Heart rate variability is a sensitive marker of autonomic function, particularly its parasympathetic component[172], and is known to be impaired in the early post-infarction period with gradual improvement over the ensuing weeks and

months[222]. The data confirm early reductions of both spectral and non-spectral measures of heart rate variability, compared with published data on normal controls[146], presumably reflecting damage to the sensory innervation of the heart. This may certainly have increased perceptual thresholds and contributed to the high prevalence of silent ischaemia in the patients in this study, but it does not provide the complete explanation since no differences in heart rate variability could be demonstrated by comparing patients who did (group A) and those who did not (group B) experience angina during treadmill stress testing.

If neuropathic mechanisms increase perceptual thresholds early after myocardial infarction, the severity of ischaemia - as reflected by ischaemic mass and intensity - is likely to be a major determinant of whether or not angina is experienced by the patient. The data provide some support for this hypothesis by showing that patients with inducible ischaemia, who experienced no angina during treadmill testing, not only had less extensive coronary artery disease (and, by inference, a smaller ischaemic mass), but also took nearly twice as long to develop ischaemic ST segment depression compared with the symptomatic group. It may be because the silent patients were less ischaemic that they achieved a significantly higher workload on the treadmill. The important role of the severity of ischaemia in determining whether these patients with increased perceptual thresholds experience angina is also reflected in the Holter data which showed that the patients with silent ST segment depression had significantly fewer ischaemic episodes and a lesser cumulative duration of ischaemia.

Limitations of study. This study has relied on indirect measures to assess the mass of ischaemic myocardium. Thus the magnitude of ST segment depression and its duration have been used as a measure of intensity of ischaemia, and simple categorising of the extent of coronary disease may give a limited indication of the potential severity of ischaemia. In addition, the patients in this study inevitably had Q waves and repolarisation abnormalities on their resting ECG's, potentially interfering with interpretation of ST segment changes.

Conclusion. The data confirm a high prevalence of silent ischaemia in the early post-infarction period. Analysis of heart rate variability indicates that this may be the result of an increased perceptual threshold caused by damage to the sensory innervation of the heart. However, because myocardial ischaemia will only provoke angina if the stimulus is sufficient to exceed the perceptual threshold, it is the severity of ischaemia which determines whether or not symptoms are experienced by the individual patient.

CHAPTER 8

ANGINAL PERCEPTION EARLY AFTER ACUTE MYOCARDIAL INFARCTION: A COMPARISON WITH STABLE ANGINA

8.1 INTRODUCTION

Chapters 2 and 7 have shown that the intensity of ischaemia and the integrity of the sensory nerve supply of the heart are important factors in determining the symptomatic expression of myocardial ischaemia in stable angina and the post-infarction period. In the present study, patients with stable angina and myocardial infarction have been compared in order to identify any differences in the relative importance of ischaemic and perceptual variables between these groups.

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8.2 METHODS

8.2.1 Patient Selection: Stable Angina (Group 1)

Patients were selected as described in section 2.2.1. Of 43 eligible patients, 35 had ischaemic episodes during Holter monitoring (defined as ≥ 0.1mV of planar or down-sloping ST segment depression) and were included in this study. Anti-anginal medication was withdrawn 5 days prior to the study with the exception of short acting nitrates which were disallowed only during the study.

8.2.2 Patient Selection: Acute Myocardial Infarction (Group 2)

Patients were recruited from the 256 with acute myocardial infarction described in section 7.2.1. Of the 256 patients, 102 had ischaemic episodes during Holter monitoring and 92 had ischaemic changes on the exercise ECG. In order to provide an appropriate comparison with group 1, only patients with ischaemia on both tests were included. There were 40 such patients, and these comprised group 2.

8.2.3 Study Design

A prospective study of ischaemia on exercise treadmill testing and 48 hour ambulatory Holter monitoring and 24 hour heart rate variability comparing patients with stable angina (group 1) and acute myocardial infarction (group 2).

8.2.4 Exercise Treadmill Test

This was performed as described in section 7.2.4 except that the Bruce protocol was used in group 1. In group 2 the modified Bruce protocol was used and was performed at a median of 18 days post-infarction (range 7 - 34).

8.2.5 48 Hour Ambulatory Holter Monitoring

All patients underwent 48 hour ambulatory Holter monitoring of ST segments. Recordings were made in group 2 at 96 hours (range 48 -174) after the onset of infarction when the patients were mobile. Recordings were made and analysed as described in section 2.2.4.

8.2.6 Heart Rate Variability

The first 24 hours of Holter recordings were analysed for heart rate variability as described in section 2.2.6.

8.2.7 Statistical Analysis

All averaged results are expressed as mean values with standard error of the mean in parentheses. Groups 1 and 2, and exercise and Holter data are compared using the unpaired t-test for normally distributed variables, and by the Mann-Whitney U test for other variables (duration of ischaemia and pNN50). The number of diabetic patients, gender distribution and the presence of angina on treadmill testing in groups 1 and 2 were compared using the χ^2 test. Two-sided p values were considered significant at the 5% level.

8.2.8 Ethical Approval

The study was approved by the Newham Health District Ethics Committee, and written informed consent was given by all patients.

8.3 RESULTS

8.3.1 Patient Characteristics

The two groups comprised 35 patients with stable angina (group 1) and 40 patients with recent myocardial infarction (group 2). There were no significant differences between the groups as regards age (62 (2) versus 60 (1) years), gender distribution (77 versus 98% male), and prevalence of diabetes (26 versus 18%). Although none of the patients in group 1 was on anti-anginal treatment at the time of the study, some of the patients in group 2 were on treatment with a beta-blocker during Holter monitoring (n=16) and exercise treadmill testing (n=13).

Table 16: Comparison of exercise treadmill testing variables between patients with stable angina (group 1) and myocardial infarction (group 2). Group 2[i] comprises the subset of patients with acute myocardial infarction not taking beta-blockers at the time of treadmill testing.

	GROUP 1 n=35	GROUP 2 n=40	GROUP 2[i] n=27
Heart rate (beats minute^{-1})			
Rest	81 (3)	83 (3)	89 (3)
Onset of 0.1mV ST depression	117 (3)	120 (3)	123 (3)
Peak exercise	133 (3)	135 (3)	139 (4)
Systolic blood pressure (mmHg)			
Onset of 0.1mV ST depression	149 (4)	134 (5)*	141 (7)
Peak exercise	163 (4)	145 (5)**	150 (6)
Rate pressure product (x10^3)			
Peak exercise	21.9 (0.8)	19.7 (0.8)	20.8 (0.9)
METS			
Onset of 0.1mV ST depression	4.2 (0.3)	5.1 (0.4)	4.6 (0.5)
Peak exercise	6.3 (0.4)	7.4 (0.5)	7.1 (0.6)

METS = metabolic equivalents

Significance of differences between groups 2 (and 2[i]) with respect to group 1:

*$p<0.05$, **$p<0.005$.

Table 17: **Comparison of Holter variables between patients with stable angina (group 1) and myocardial infarction (group 2). Group 2[i] comprises the subset of patients with acute myocardial infarction not taking beta-blockers at the time of treadmill testing.**

	GROUP 1 n=35	GROUP 2 n=40	GROUP 2[i] n=24
Heart rate (beats min^{-1})			
Pre-episode	79 (2)	77 (2)	83 (3)
Peak ST depression	92 (4)	80 (3)*	84 (3)
Percentage increase in heart rate	18.2 (3.0)	3.7 (1.6)**	1.7 (2.1)**

Significance of differences between groups 2 (and 2[i]) with respect to group 1:

*$p<0.05$, **$p<0.005$.

8.3.2 Exercise Treadmill Testing (Table 16)

Haemodynamic determinants of exertional ischaemia and the symptomatic responses were compared between groups 1 and 2. In both groups exercise produced a normal increase in heart rate and led to ischaemic ST depression at comparable work-loads. There was no significant difference in the rate-pressure product at peak exercise. However, exertional ischaemia was associated with angina in 80% of group 1 compared with only 40% of group 2 ($p<0.005$). This difference between the groups persisted when analysis of the responses in group 2 was confined to those 27 patients not on beta-blockers (group 2[i]).

8.3.3 48 Hour Ambulatory Holter Monitoring

a) Relation between ST depression and angina. In group 1, ischaemic ST depression was associated with angina in 23 patients (66%), 19 of whom also had episodes of silent ischaemia. The remaining 12 patients in group 1 had only silent ischaemia. In group 2, on the other hand, ischaemic ST depression was associated with angina in only two patients (5%), both of whom also had silent ischaemic episodes. The remaining 38 patients in group 2 had only silent ischaemia. Consequently, although ischaemic episodes were shorter in group 1 (11 (1) versus 23 (4) minutes, $p<0.005$), the cumulative duration of painful ischaemia was much greater than in group 2 (993 versus 59 minutes).

b) Relation between ST depression and heart rate changes (table 17). Immediately before episodes of ST depression average heart rates were similar in groups 1 and 2. However, ST depression was associated with a significantly greater increase in heart rate in group 1 than in group 2.

These differences between the Holter findings in groups 1 and 2 persisted when analysis of the group 2 data was confined to those 24 patients not on beta-blockers (group 2[i]).

8.3.4 Heart Rate Variability

Spectral and non-spectral measures of heart rate variability were significantly reduced in group 2 compared with group 1, irrespective of beta-blocker therapy (table 18). Analysis according to the symptomatic response to treadmill exercise (table 19) showed that, in group 1, patients who experienced no chest pain had significantly lower spectral and non-spectral measures of heart rate variability than patients who experienced angina. In group 2, on the other hand, patients with silent ischaemia on the treadmill had no reduction in heart rate variability compared with the symptomatic group, irrespective of beta-blocker therapy. Two recordings in group 1 and six recordings in group 2 were of inadequate quality for heart rate variability analysis.

8.3.5 Exercise Treadmill Testing versus Ambulatory Holter Monitoring (Table 20)

The resting heart rates for both tests were similar and showed no significant differences between groups 1 and 2. During exercise testing, ischaemic ST depression was associated with a sharp rate increase in both groups but during Holter monitoring it was associated with a much smaller rate increase, particularly in group 2 (see above). Consequently, in both groups the heart rate at peak ST depression was significantly higher during exercise testing than Holter monitoring.

This difference persisted when analysis of the responses in group 2 was confined to those patients not on beta-blockers.

Table 18: **Comparison of heart rate variability between patients with stable angina (group 1) and myocardial infarction (group 2). Group 2[i] comprises the subset of patients with acute myocardial infarction not taking beta-blockers at the time of treadmill testing.**

	GROUP 1 n=33	**GROUP 2** n=38	**GROUP 2[i]** n=22
Low frequency peak (ms)	23 (2)	15 (1)**	14 (2)**
High frequency peak (ms)	10 9(1)	8 (1)*	7 (1)*
SDANN (ms)	126 (6)	74 (4)**	72 (5)**
rMSSD (ms)	26 (3)	21 (1)	20 (2)
pNN50 (%)	6.1 (1.5)	4.0 (0.7)	3.8 (0.9)
SD (ms)	53 (3)	38 (2)**	35 (3)**
SDRR (ms)	139 (6)	86 (4)**	83 (6)**

Significance of differences between groups 2 and 2[i] with respect to group 1:

*$p<0.05$, 2**$p<0.005$.

Table 19: Comparison of heart rate variability in patients with stable angina (group 1) and myocardial infarction (group 2) between patients with and without angina on treadmill testing. Group 2[i] comprises the subset of patients with acute myocardial infarction not taking beta-blockers at the time of treadmill testing.

	GROUP 1		GROUP 2		GROUP 2[i]	
	ANGINA ON ETT n=26	NO ANGINA ON ETT n=7	ANGINA ON ETT n=13	NO ANGINA ON ETT n=21	ANGINA ON ETT n=9	NO ANGINA ON ETT n=11
Low frequency peak (ms)	25 (2)	17 (1)**	13 (2)	15 (2)	12 (2)	15 (3)
High frequency peak (ms)	11 (1)	8 (1)*	7 (1)	8 (1)	6 (1)	8 (1)
SDANN (ms)	130 (7)	112 (10)	70 (5)	75 (6)	64 (6)	76 (9)
rMSSD (ms)	28 (3)	19 (2)*	20 (2)	23 (2)	19 (2)	22 (3)
pNN50 (%)	7.1 (1.8)	2.6 (0.9)*	2.9 (0.8)	4.8 (1.1)	2.9 (1.2)	4.8 (1.6)
SD (ms)	55 (4)	44 (3)*	36 (4)	38 (3)	32 (5)	37 (4)
SDRR (ms)	143 (7)	124 (11)	82 (6)	86 (7)	74 (7)	87 (10)

ETT = exercise treadmill testing. Significance of differences in heart rate variability in patients without angina on treadmill testing compared with patients with angina on treadmill testing in each group; *$p<0.05$, **$p<0.005$.

Table 20: Comparison of heart rates before and at maximum ischaemia between exercise treadmill testing and Holter monitoring in patients with stable angina (group 1) and myocardial infarction (group 2). Group 2[i] comprises the subset of patients with acute myocardial infarction not taking beta-blockers at the time of treadmill testing.

	GROUP 1 n=35		**GROUP 2** n=40		**GROUP 2[i]** n=23	
	Heart rate at rest (bpm)	**Heart rate at peak STD** (bpm)	**Heart rate at rest** (bpm)	**Heart rate at peak STD** (bpm)	**Heart rate at rest** (bpm)	**Heart rate at peak STD** (bpm)
Exercise test	81 (3)	133 (3)	83 (3)	135 (3)	92 (4)	143 (4)
Holter	79 (2)	92 (4)**	77 (2)	80 (3)**	85 (3)	86 (3)**

STD = ST segment depression; bpm = beats per minute.

Significance of heart rate on Holter with respect to heart rate on exercise testing; **$p<0.005$

8.4 DISCUSSION

This study of myocardial ischaemia has provided a direct comparison between patients with stable angina and patients with recent myocardial infarction. The data point to important differences between the mechanisms of ischaemia and its symptomatic expression in the two groups. Nevertheless, it is clear from the treadmill data that in both groups demand-driven myocardial ischaemia can be provoked. Thus, exercise produced similar increments in heart rate and blood pressure until the inability of oxygen supply in the diseased coronary arteries to keep pace with increasing demand led to ischaemic changes on the ECG. The ST changes occurred at almost identical average workloads and rate-pressure products, confirming that during treadmill testing increased oxygen demand was the principle mechanism of ischaemia.

Periodic increments in oxygen demand may also have contributed to ischaemia during Holter monitoring, particularly in the patients with stable angina (group 1), in whom ST change was associated with a significant increase in heart rate. However, this is unlikely to be the only mechanism because the increase in heart rate was considerably lower than that which provoked ST depression during treadmill stress testing, suggesting that reductions in myocardial oxygen delivery contributed significantly to ischaemia during Holter monitoring. The data do not permit firm conclusions about the cause of these inappropriate reductions in oxygen delivery (presumably they relate to alterations in coronary vasomotor tone) but the finding that patients with stable angina are susceptible to both

demand-driven and supply-driven ischaemia during Holter monitoring is consistent with reports from other investigators[223].

In contrast to the patients with stable angina, the patients studied early after myocardial infarction (group 2) showed ST depression during Holter monitoring with almost no increase in heart rate. Clearly, these ischaemic episodes cannot readily be explained by alterations in oxygen demand, unlike those recorded during treadmill stress testing. Periodic reductions in oxygen delivery, therefore, are likely to be the dominant mechanism of ischaemia in this group, a conclusion supported by the findings of Currie et al[224]. These investigators showed that increments in heart rate during Holter ischaemia in the early post-infarction period (6 days) were less pronounced compared with later recordings (38 days) when demand-driven ischaemia is likely to become more prominent. Again, our data do not permit firm conclusions about the mechanism of supply-driven ischaemia early after infarction, but it is possible to speculate that it relates to continuing instability of the coronary plaque in the infarct-related artery after successful thrombolytic therapy, with intermittent platelet aggregation and thrombus formation leading to variable luminal obstruction and reductions in oxygen delivery. This is analogous to the mechanism that explains the increased risk of re-infarction early after thrombolytic therapy.

Ischaemic episodes were more commonly silent in the patients with recent infarction (group 2) than in the patients with stable angina (group 1). It has been suggested that the propensity of patients with recent infarction to silent ischaemia reflects damage to the sensory innervation of the heart[81]. Certainly the heart-rate

variability data in the present study point to significant autonomic dysfunction in the group with recent infarction and, because myocardial sensory afferents are thought to reside in the autonomic supply, this may have contributed to the heightened susceptibility to silent ischaemia during treadmill testing and Holter monitoring. Nevertheless, this is unlikely to provide the full explanation because in the subgroup analysis presented in table 19 there was no evidence of exaggerated autonomic dysfunction in those group 2 patients with silent exertional ischaemia, suggesting that other mechanisms apart from neuropathy must also be involved in reducing ischaemic pain perception early after myocardial infarction.

Limitations of study. Interpretation of the findings in this study must take account of the differences between the groups. Thus the patients with stable angina were selected because of the history of angina and this no doubt accounts in part for their higher prevalence of symptomatic ischaemia. However, it cannot account for the very low prevalence of symptomatic ischaemia in the group with recent infarction, nor for other differences in responses to treadmill stress testing and Holter monitoring that were observed between the groups. A further difference is that patients in group 1 were selected on the basis of a normal resting ECG to optimise interpretation of ST changes, thus no patients in this group had previous Q-wave myocardial infarction, which is in contrast to patients in group 2, all of whom had recent myocardial infarction. Thus any conclusions concerning mechanisms of angina cannot necessarily be extended to patients who have had myocardial infarction in the more distant past.

As regards exercise protocols, a low-level test was felt appropriate and safe in the early post-infarction period, and the full Bruce protocol was chosen for patients with stable angina in order to increase the likelihood of an ischaemic result[58]. Had the Bruce protocol been used in the patients with recent infarction, a higher workload might have been achieved[58], but it is unlikely that this would have affected the major conclusions of this study.

An additional factor requiring consideration is beta-blocker therapy which was not withheld in patients with recent infarction. Because beta blockers can modify ischaemic and symptomatic responses during treadmill testing and Holter monitoring, a separate analysis was undertaken for the subgroup of patients not on treatment. The major differences between the groups persisted, confirming that they cannot be attributed to the effects of beta-blockers.

Conclusion. Myocardial ischaemia in both stable angina and recent infarction may be symptomatic or silent and may be demand-driven or supply-driven. However, this comparative study has confirmed that in stable angina painful, demand-driven ischaemia is relatively more common while in the early post-infarction period silent, supply-driven ischaemia predominates. The data indicate that the failure of myocardial ischaemia to provoke symptoms in some patients with acute myocardial infarction appears to be unrelated to the autonomic dysfunction which is observed in the post--infarction period. This is in contrast to the finding in chapter 2, that autonomic dysfunction plays an important role in the variable symptomatic expression of myocardial ischaemia in patients with stable angina. Thus, in acute

myocardial infarction, other mechanisms must account for variations in this symptomatic expression.

CHAPTER 9

CIRCADIAN VARIATION IN MYOCARDIAL ISCHAEMIA EARLY AFTER ACUTE MYOCARDIAL INFARCTION: A COMPARISON WITH STABLE ANGINA AND THE ROLE OF THE AUTONOMIC NERVOUS SYSTEM

9.1 INTRODUCTION

In this dissertation, the variable symptomatic expression of myocardial ischaemia has been amply demonstrated, both in patients with stable angina and those with recent myocardial infarction. This variability applies not only to the level of symptoms but also to their timing. Thus, in chapter 6, it was confirmed that acute myocardial infarction occurs more commonly in the second quarter of the day. Similar diurnal changes have been shown in other coronary syndromes[23,200,225], but

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Preliminary data presented to the American Heart Association, New Orleans 1992 and the British Cardiac Society, Harrogate 1992

the mechanisms are unknown. Diurnal fluctuation - both in sympathetic drive[226,227] and the balance of thrombotic/thrombolytic activity[228-230] - may play contributory roles, but the evidence is incomplete.

In stable angina, like myocardial infarction, symptoms appear to be more common in the second quarter of the day[198]. However, in the early post-infarction period, when myocardial ischaemia is common and usually silent[15,51,231], there are few data on diurnal variability[231]. This represents an important gap in our knowledge, because ischaemia during this period may indicate a poor prognosis[15] and its mechanism is therefore of potential therapeutic interest.

The data in chapter 7 and 8 show that autonomic function is severely deranged in the post-infarction period and this has also been found by other investigators[232]. Deranged autonomic function may be involved, not only in the pathogenesis of ischaemia after myocardial infarction but also in those processes that predispose to a poor prognosis. This study, therefore, has been designed to investigate further changes in autonomic function early after acute myocardial infarction with particular emphasis on diurnal rhythms in patients with acute myocardial infarction in comparison with the diurnal rhythm seen in patients with stable angina.

9.2 METHODS

9.2.1 Patient Selection: Stable Angina (Group 1; n=43)

Patients were selected as described in section 2.2.1. Forty three patients were eligible, and all were included in this study. Anti-anginal medication was withdrawn 5 days before the study with the exception of short acting nitrates which were disallowed only during the study.

9.2.2 Patient Selection: Acute Myocardial Infarction (Group 2; n=131)

Patients were recruited from the 256 with acute myocardial infarction as described in section 7.2.1. Of these, 125 were excluded either because they were taking beta-blockers or because of repolarisation abnormalities caused by left bundle branch block, paced rhythms and concurrent digoxin therapy.

9.2.3 48 Hour Ambulatory Holter Monitoring

All patients underwent 48 hour ambulatory Holter monitoring of ST segments. In group 2, recordings were made at a median of 76 hours (range 48 -235) after the onset of infarction when the patients were mobile. The recordings were made and analysed as described in section 2.2.4.

9.2.4 Heart Rate Variability

The first 24 hours of Holter recording were analysed for spectral and non-spectral measures of heart rate variability using Marquette heart rate variability software version 1 as described in section 2.2.6. In addition to 24 hour assessment of non-

spectral measures, the amplitude of low (0.04 - 0.15 Hz) and high (0.15 - 0.40 Hz) frequency spectral analysis was measured for each hour. Only patients with adequate quality recordings for the whole 24 hours were included in analysis of heart rate variability. There were 24 such patients in group 1 and 36 in group 2. Low frequency to high frequency amplitude ratios were calculated and plotted at hourly intervals.

9.2.5 Statistical Analysis

All averaged results are expressed as mean values with standard error of the mean in parentheses. Spectral and non-spectral measures of heart rate variability in the two groups were compared using the Mann-Whitney U test. Analyses of circadian rhythms in heart rate variability were carried out using repeated measures analysis of variance of the following variables: log high frequency amplitude, log low frequency amplitude and log of the ratio of low to high frequency ratio. 2-sided p values were considered significant at the 5% level.

9.2.6 Ethical Approval

The study was approved by the Newham Health District Ethics Committee, and informed consent was given by all patients.

9.3 RESULTS

9.3.1 Patient Characteristics

The study included 44 patients with stable angina (group 1) and 131 patients in the early post-infarction period (group 2). The two groups were similar as regards age (61.3 (1.4) versus 62.0 (0.9) years) and gender distribution (80 versus 84% males).

9.3.2 Ischaemic Episodes (Figure 11)

Analysis of the 48 hour Holter recordings identified 337 ischaemic episodes in 35 patients in group 1, and 370 ischaemic episodes in 65 patients in group 2. In group 1, 12 patients had only silent episodes, four had only painful episodes and 19 had both. In contrast, 63 patients in group 2 had only silent ischaemia and the remaining two had both silent and painful episodes ($\chi^2=47.7$, $p<0.0001$). The number and duration of ischaemic episodes occurring in each of 12 2-hour periods throughout the day and night are shown in figures 11. In group 1, ischaemic episodes showed a clear circadian rhythm, 218 episodes (65%) occurring between 06.00 and 18.00 hours compared with 119 episodes (35%) occurring during the night ($p<0.001$, Wilcoxon signed rank sum test). However, in group 2, this rhythm was abolished, with a tendency to more episodes during the night. Thus there were 157 episodes (42%) during the day, and 213 episodes (58%) during the night hours ($p=0.08$).

9.3.3 Heart Rate Variability (Figure 12)

Analysis of the first 24 hours of each Holter recording showed that spectral and non-spectral measures of heart rate variability were higher in group 1 than in group 2 (table 21). In the group as a whole, the high frequency spectral component of heart rate variability showed a clear circadian rhythm ($p=0.0001$). In group 1, there was a peak at night (18.00 - 06.00 hours) of 11.1 ms and a day-time (06.00 - 18.00 hours) trough of 9.1 ms. The pattern in group 2 was not significantly different ($p=0.12$), but appeared slightly attenuated with a peak of 7.2 ms and a trough of 6.6 ms. A similar circadian variation was seen in the low frequency range ($p=0.0001$) which, although it appeared attenuated in group 2, was not significantly different between the groups ($p=0.72$). Group 1 had a day-time peak of 22.7 ms and a night-time trough of 21.4 ms; in group 2 the amplitudes were 13.5 and 12.6 ms respectively.

9.3.4 Sympatho-vagal balance (Figure 13)

When the ratio of low to high frequency variability was analysed, to provide a measure of sympatho-vagal balance, the circadian rhythm changed. In the group as a whole, there was a significant circadian variation ($p<0.002$) which was different between the groups ($p=0.06$). In group 1, peak values occurred during the day with a trough at night (2.39 versus 2.18), but this was clearly abolished in group 2 (1.98 versus 1.95).

Figure 11: Circadian variation in the number and duration of ischaemic episodes over 12 two-hour periods in patients with stable angina (group 1) and myocardial infarction (group 2).

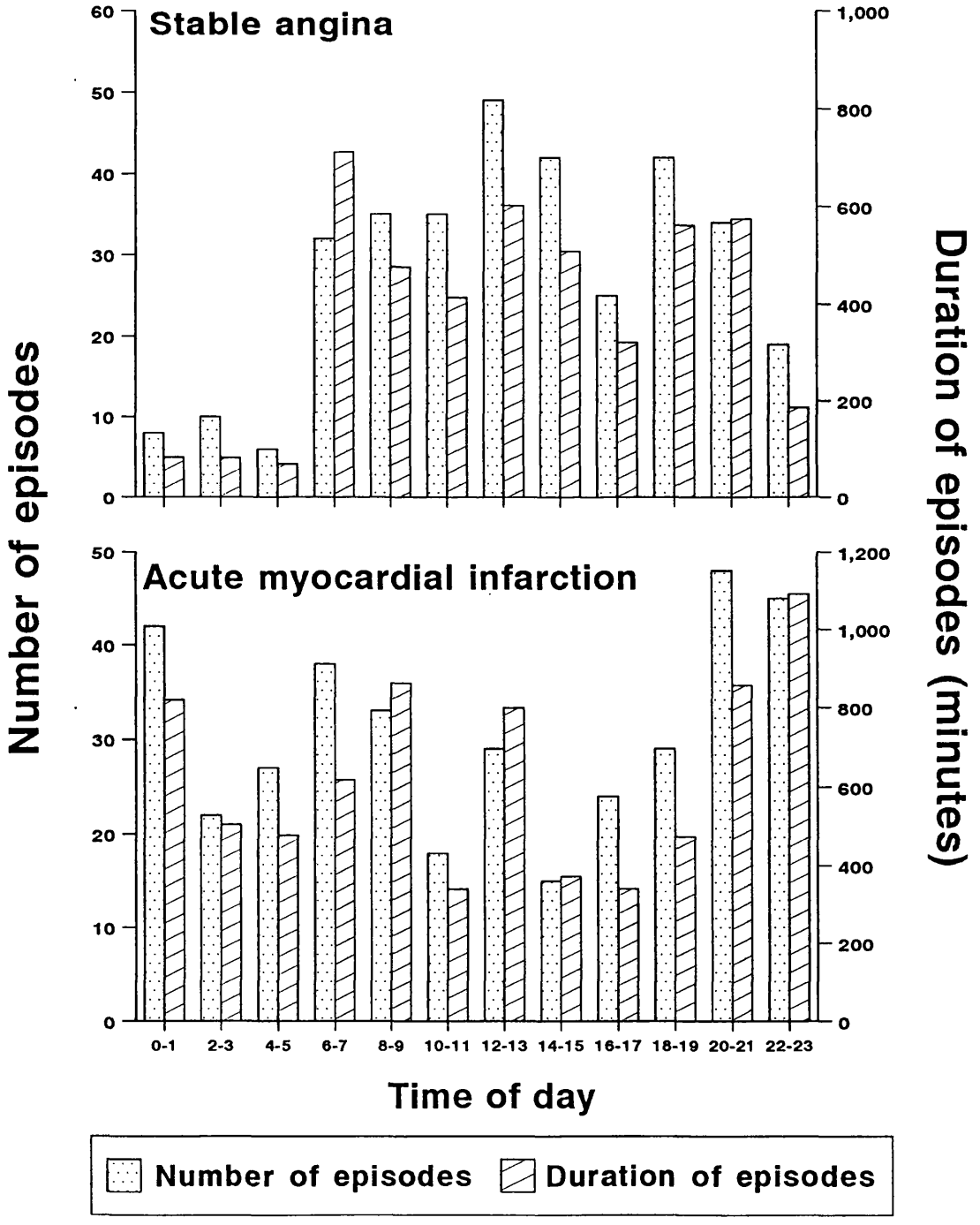

Figure 12: Circadian variation in low- and high-frequency spectral measures of heart rate variability over 24 one-hour periods in patients with stable angina (group 1) and myocardial infarction (group 2).

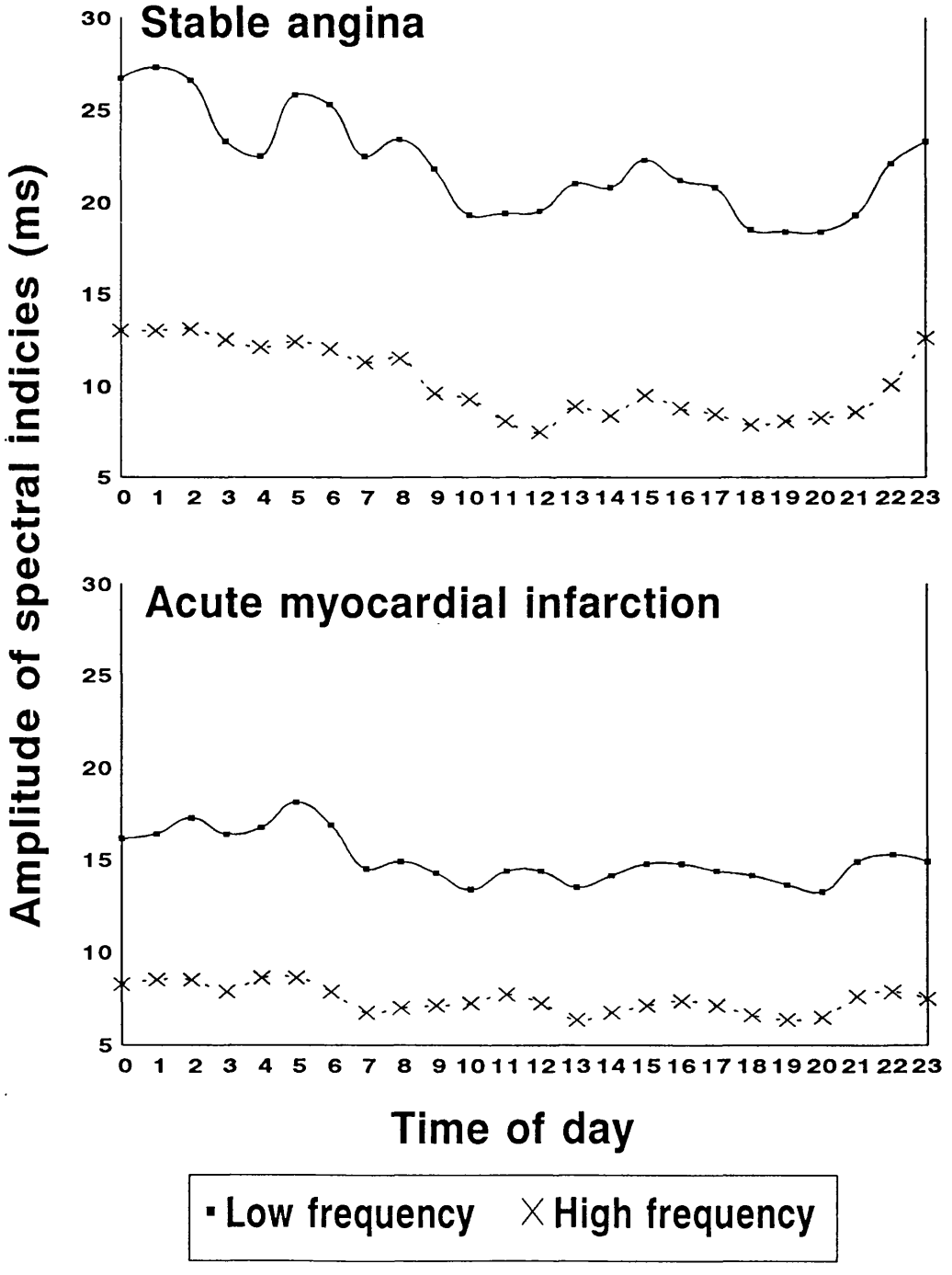

Figure 13: Circadian variation in ratio of low to high-frequency as a marker of sympatho-vagal balance over 24 one-hour periods in patients with stable angina (group 1) and myocardial infarction (group 2).

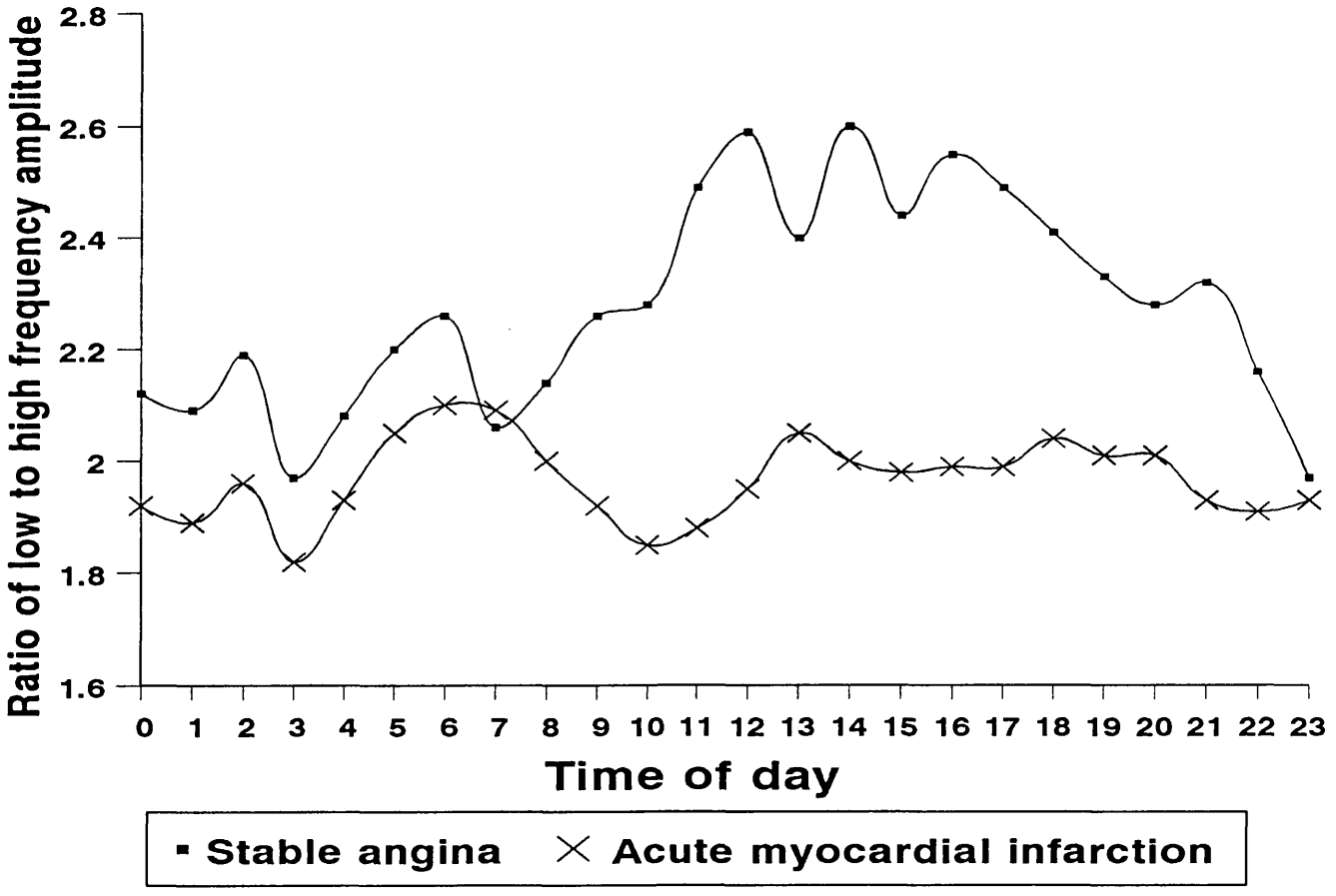

Table 21: Heart rate variability in patients with stable angina (group 1) and myocardial infarction (group 2).

	GROUP 1 n=24	GROUP 2 n=36	P VALUE
High frequency peak (ms)	10.7 (7-14)	6.7 (4-9)	0.0007
Low frequency peak (ms)	23.7 (16-28)	13.0 (8-15)	0.0001
SDANN (ms)	130 (106-144)	66 (53-78)	0.0001
SD (ms)	53 (41-60)	33 (23-40)	0.0001
rMSSD (ms)	25 (17-28)	20 (14-25)	0.02
pNN50 (%)	5.5 (1.7-6.5)	3.4 (0.4-5.3)	0.02
SDRR (ms)	143 (122-156)	78 (60-86)	0.0001

Values given are mean (inter-quartile range).

9.4 DISCUSSION

This study has confirmed important derangement of autonomic function early after acute myocardial infarction and loss of the circadian rhythm of ambulatory ischaemia which is seen in patients with stable angina. The data suggest that in patients with stable angina, circadian rhythms of autonomic and ambulatory ischaemia may be causally inter-related.

Mechanisms of ambulatory myocardial ischaemia remain uncertain. It appears to represent a complex process of oxygen supply-demand imbalance provoked partly by increases in heart rate[233] and blood pressure[35,234] and partly by increases in coronary vascular tone[35]. However, any mechanistic theory of ambulatory ischaemia must be able to account for its circadian rhythm which has been demonstrated in previous studies of patients with stable angina[23] and confirmed in the present study. Deedwania and Nelson[223] showed that the peak of ischaemic episodes in the second quarter of the day was associated with a simultaneous peak of heart rate and blood pressure and, since the minute-by-minute control of these haemodynamic variables is predominantly a function of the autonomic nervous system, they suggested that surges in sympathetic activity at this time of day might be responsible for their observations.

The present study, in which Holter monitoring permitted simultaneous analysis of ST segment changes and heart rate variability, provides further evidence implicating the autonomic nervous system as a major determinant of the circadian rhythm of

ambulatory myocardial ischaemia. Pagani et al[235] have suggested that spectral analysis of heart rate variability can provide information on the interaction between sympathetic and parasympathetic regulatory activities, the low-frequency component reflecting the level of sympathetic drive to the heart and the high-frequency component (which disappears after administration of atropine) reflecting vagal activity. Thus the low- to high-frequency ratio provides a convenient index of sympatho-vagal balance[236]. Spectral analysis of heart rate variability has been applied to the patients in this study and it has been shown that in stable angina, a circadian rhythm of sympatho-vagal balance exists, peaking during the day-time hours at the time when ambulatory myocardial ischaemia is also at its peak. Early after myocardial infarction, on the other hand, when autonomic function is known to be deranged, the circadian rhythm of sympatho-vagal balance was severely attenuated, due largely to loss of the morning sympathetic surge. Perhaps because of this, the morning peak of ambulatory ischaemia was also lost. Of course, early after myocardial infarction treated by thrombolysis, plaque instability and intra-coronary thrombotic debris can cause ongoing ischaemia[237], independently of autonomic influences, and this might obscure any relation that exists between these two variables. Nevertheless, the data provide circumstantial evidence supporting the hypothesis of Deedwania and Nelson[223] that in patients with stable angina the circadian rhythms of ambulatory ischaemia and sympatho-vagal activity may be causally inter-related.

The hypothesis that the circadian rhythm of ambulatory ischaemia in patients with stable angina is caused by fluctuations in sympathetic activity is attractive for three

reasons. It is consistent with the known circadian rhythms of blood catecholamine[190] and cortisol[238] levels which also peak in the second quarter of the day. It is also consistent with reports that beta blockers are effective in reducing the frequency and the circadian variation of ambulatory ischaemia[239]. Finally it is consistent with current concepts of the pathophysiology of ambulatory myocardial ischaemia which view it as the combined response to increases in oxygen demand and reductions in oxygen supply, in variable ratio[240]. Thus, sympathetically-driven increments in heart rate and blood pressure would be expected to provoke ischaemia through parallel increases in myocardial oxygen demand. However, patients with stable angina are often predisposed to exaggerated vasoconstriction due to the development of endothelial dysfunction in relation to atherosclerotic plaques[241] and, when this is the predominant response to a sympathetic stimulus, it can lead to supply-driven ischaemia without a major increase in myocardial oxygen demand. This is regarded as the most likely mechanism for those episodes of ambulatory ischaemia that occur without a preceding increase in heart rate or blood pressure[240].

The circadian rhythm of sympatho-vagal activity in patients with stable coronary artery disease may also account for previously described circadian rhythms of out-of-hospital sudden cardiac deaths[200] and onset of acute myocardial infarction[197]}, both of which peak in the second quarter of the day. Thus it is possible to speculate that the same sympathetic drive that provokes the morning peak in myocardial ischaemic episodes might also provoke cardiac arrhythmias or plaque events, either by direct effects on the myocardium or indirectly through

provocation of ischaemia and surges in blood pressure. This may have important implications for prophylactic treatment if effective suppression of the morning peak in sympathetic drive could be achieved by administration of beta-blockers.

Conclusion. This study has shown that circadian rhythms of sympatho-vagal balance and ambulatory myocardial ischaemia are diminished, or lost altogether, early after acute myocardial infarction. Whether the autonomic imbalance contributes to the propensity to arrhythmias during this period is an important question that merits further investigation. In stable angina, on the other hand, a clear circadian rhythm of sympatho-vagal balance was demonstrated, peaking during the day-time and dipping at night. Although causality cannot be proved, the data suggest that the circadian rhythm of sympatho-vagal balance may explain, at least in part. the parallel circadian rhythm of ambulatory ischaemia that characterises patients with stable angina.

CHAPTER 10

GENERAL DISCUSSION

10.1 SUMMARY OF FINDINGS

This thesis has studied mechanisms affecting the symptomatic expression of myocardial ischaemia in various groups of patients. Attention was first directed towards patients with stable angina. Most of the current literature on silent myocardial ischaemia has concentrated on such patients, yet there is still controversy over the relative contributions of ischaemic and perceptual mechanisms. Good evidence exists for the 'mass' theory but the literature suggests that neuropathic mechanisms also play a role, at least in certain subgroups. In chapter 2, both of these hypotheses have been tested in a single group of patients to determine the contributions of each, and to account for the variability in symptoms that exists between and within patients. The findings indicate that myocardial ischaemia will provoke symptoms if the magnitude of the ischaemic stimulus exceeds a sensory threshold for experiencing angina, the magnitude of the stimulus being determined both by the mass of ischaemic myocardium and the intensity of ischaemia. However, in certain patients the sensory threshold for

experiencing angina is increased, and this study confirmed that a neuropathic mechanism may sometimes account for this. At least half the patients included in this study were aged over 60 years and an appreciable number were diabetic. It seems likely that patients in these subgroups would be most susceptible to subclinical neuropathy and this hypothesis was tested for diabetic patients in the fourth chapter of the dissertation. The data show that subclinical neuropathy is indeed more common in diabetic patients with silent ischaemia, confirming that threshold effects can influence the symptomatic expression of myocardial ischaemia in patients of this type.

Endogenous opiates provide an alternative mechanism whereby sensory thresholds for the perception of angina may be modulated. Despite intensive investigation, however, no firm consensus about the importance of these peptides has emerged. The double blind, placebo controlled study described in chapter 3 has re-examined this issue. The data show clearly that patients with silent exertional ischaemia do not have raised plasma levels of endogenous opiates compared with symptomatic controls. Moreover, exertional angina is not induced by naloxone in these patients, nor is the time to angina shortened in the symptomatic controls. The data, therefore, provide no support for an influence of endogenous opiates in the perception of angina, but confirm their role as part of the physiological response to stress.

It is well established that many patients with angina experience an exacerbation of their symptoms during cold exposure. Thus, the opportunity was taken to examine

ischaemic and symptomatic responses to exercise in a cold environment in order to obtain further information about the factors that influence the symptomatic expression of myocardial ischaemia. Patients with a history of cold intolerance were compared with cold-tolerant patients. The data in chapter 5 show that cold exposure caused a sympathetically mediated increase in blood pressure that is quantitatively similar regardless of the history of cold tolerance. However, in cold-tolerant patients, baroreceptor function is normal and associated increments in myocardial oxygen demand may be offset by reductions in heart rate. In cold-intolerant patients, on the other hand, baroreceptor function is abnormal and the cold-induced increase in blood pressure does not produce a reduction in heart rate. Thus during cold exposure, rate pressure product at any given level of exercise increases in cold-intolerant patients ensuring the earlier onset of angina. This mechanism may account for some of the variability in tolerance to cold exposure that affects patients with exertional angina.

In the second part of the thesis, attention was directed towards acute myocardial infarction. Following the study of the influence of environmental temperature on angina, chapter 6 examined the influence of season and temperature on the incidence of acute myocardial infarction in a temperate climate. Interestingly, there are more infarcts on colder days in both summer and winter although the mechanisms remain speculative.

Chapters 7, 8 and 9 have examined possible mechanisms for the variable symptomatic expression of myocardial ischaemia in patients with acute myocardial

infarction. The data in chapter 7 confirm that myocardial ischaemia during the post-infarction period is common and frequently silent. These patients have marked autonomic dysfunction, as measured by 24 hour heart rate variability, and damage to the sensory innervation of the heart may account, at least in part, for the low level of symptoms in the group as a whole. However, autonomic function is similar in patients with painful and silent ischaemia, and the data show that the severity of myocardial ischaemia largely determines whether or not symptoms are experienced in individual patients.

To identify any differences in the relative importance of ischaemic and perceptual variables between patients with stable angina and those with acute myocardial infarction, the two groups have been compared in chapter 8. Supply driven, rather than demand driven ischaemia, is relatively more important in the post-infarction period, and this is likely to be associated with less intense ischaemia. In contrast to patients with stable angina, there is no difference in autonomic function, between post-infarction patients with and without silent myocardial ischaemia. Thus damage to the myocardial innervation is unlikely to be the major mechanism accounting for the between-patient variation in the symptomatic expression of myocardial ischaemia.

Further comparison of patients with acute myocardial infarction and stable angina has been made in chapter 9, with particular emphasis on circadian variation in myocardial ischaemia and autonomic function. In stable angina, the circadian rhythm of myocardial ischaemia, peaking during the day-time hours and dipping

at night, was associated with a similar circadian rhythm of sympatho-vagal balance, as assessed by spectral measures of heart rate variability. In contrast, in the early post-infarction period, both the ischaemic and sympatho-vagal rhythms are severely diminished or lost altogether. Although causality cannot be proven, the data suggest that circadian changes in sympatho-vagal tone may explain, at least in part, the circadian rhythm of ambulatory myocardial ischaemia in patients with stable angina.

10.2 STUDY LIMITATIONS

This thesis has dealt primarily with the perception of pain; patients have been asked to indicate the onset of angina, the limit of exercise tolerance as well as the threshold and tolerance of pain induced by electrical stimulation. In addition, during ambulatory Holter recording, patients have been asked to indicate any anginal episodes during the monitoring period. All of these measures are, by definition, subjective and are therefore susceptible to uncontrollable variations between and within individuals, as well as depending on the reliability of patients in reporting symptoms. These variations can be controlled to a certain extent, and the protocol has been optimised, wherever possible, by choosing a blinded crossover design and using standard instructions to all patients in each part of the study. However, such variation cannot be eliminated and care has been taken to minimise interpretation of results which are dependent on subjective factors, particularly when of borderline significance.

In this thesis, the mass of ischaemic myocardium has been shown to be an important factor in the variable symptomatic expression of myocardial ischaemia. However, there are no direct methods for measuring ischaemic mass, and indirect methods must be used. Two such methods have been used; the first is measurement of ST segment depression and the second is quantification of the severity of coronary artery disease. Although other methods exist, such as thallium myocardial scintigraphy, there is no evidence that these are superior to the techniques used in this study, as there is no gold standard for the quantification of myocardial ischaemia.

10.3 SUGGESTIONS FOR FURTHER STUDIES

Mechanisms of anginal perception. Neuropathic mechanisms may account for a lack of pain associated with myocardial ischaemia in diabetic patients and perhaps in the elderly with stable angina, but there are other factors which may account for individual variation which have not been addressed in the present thesis. The central processing of nociception is complex, and subject to influence at various levels. Baroreceptor reflexes have been postulated as important modulators of central pain regulation[242], but there has been little investigation of their role in modulating angina, and such studies may provide important information. Psychological factors may play an additional role in modulating the subjective experience of an objective phenomenon and warrant more investigation. There However, data are limited at present (as discussed in section 1.6.4) and due to the

nature of the variables to be measured, studies must be designed carefully. Uncertainty remains regarding the prevalence of silent ischaemia in patients with diabetes compared with non-diabetic patients, and a large definitive study to answer this long-standing question is overdue.

The variable influence of cold in patients with angina is still poorly understood. The data presented in chapter 5 provide preliminary evidence suggesting that baroreceptor dysfunction may be involved in the mechanisms of cold intolerance, but this was based on only one test of baroreceptor function and further studies, perhaps utilising the tilt test and application of lower body negative pressure, may aid the understanding of this phenomenon.

Intervention studies. At present there are few data about the importance of treating silent ischaemia. In patients who have a subclinical neuropathy and reduced anginal perception, it seems likely that painless myocardial ischaemia may be associated with severe coronary disease and a poor prognosis which may potentially be improved by revascularisation. In contrast, the patient who has silent ischaemia due to a small ischaemic stimulus may not benefit from revascularisation or even medical therapy. Hence, the mechanism of anginal perception is important in determining the potential benefits of treatment. However, no definite conclusions should be drawn without properly controlled trials of treatment to assess the benefits and risks of such intervention. There is a need for large multi-centre studies to answer this question, and it is hoped that investigations, such as the

current Asymptomatic Cardiac Ischemia Pilot (ACIP) study[90] described in section 1.5.3, will be helpful.

10.4 CONCLUSIONS

There are still many unanswered questions regarding the variable symptomatic expression of myocardial ischaemia, but several conclusions may be drawn from the data presented in this dissertation. Ischaemic mass is an important determinant of the presence of symptoms in patients with stable angina and in the early post-infarction period, and this factor probably accounts for much of the variation in symptoms which occurs within an individual. A subclinical neuropathy appears to be responsible for the lack of angina in patients with diabetes. It may also account for the increased prevalence of silent ischaemia early after myocardial infarction, but not for the between patient variation which occurs during this period. Beta-endorphin, which has been postulated as playing an important role in modulating symptoms associated with myocardial ischaemia, does not appear to be important.

The autonomic nervous system appears to play a role both in mediating myocardial ischaemia, and in modulating symptoms. Thus, circadian variations in sympatho-vagal balance match the variations in ambulatory ischaemia in patients with stable angina and acute myocardial infarction. In addition, differences in cold tolerance between patients may relate to baroreceptor function; thus patients who are cold-

intolerant appear to have impaired baroreceptor function and do not develop the bradycardia associated with cold-induced vasoconstriction in cold-tolerant patients.

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APPENDIX A

ILLUSTRATIONS OF ELECTROCARDIOGRAMS AND HOLTER RECORDINGS

Figure A1: **Electrocardiograms recorded before (next page) and at peak exercise (subsequent page) in a non-diabetic patient with three vessel coronary artery disease who developed angina during treadmill testing.**

10:21:24

25mm/s
10mm/mV
40Hz

ID: 139377
64yrs Ht: Wt:
Female Cauc

HR: 88bpm

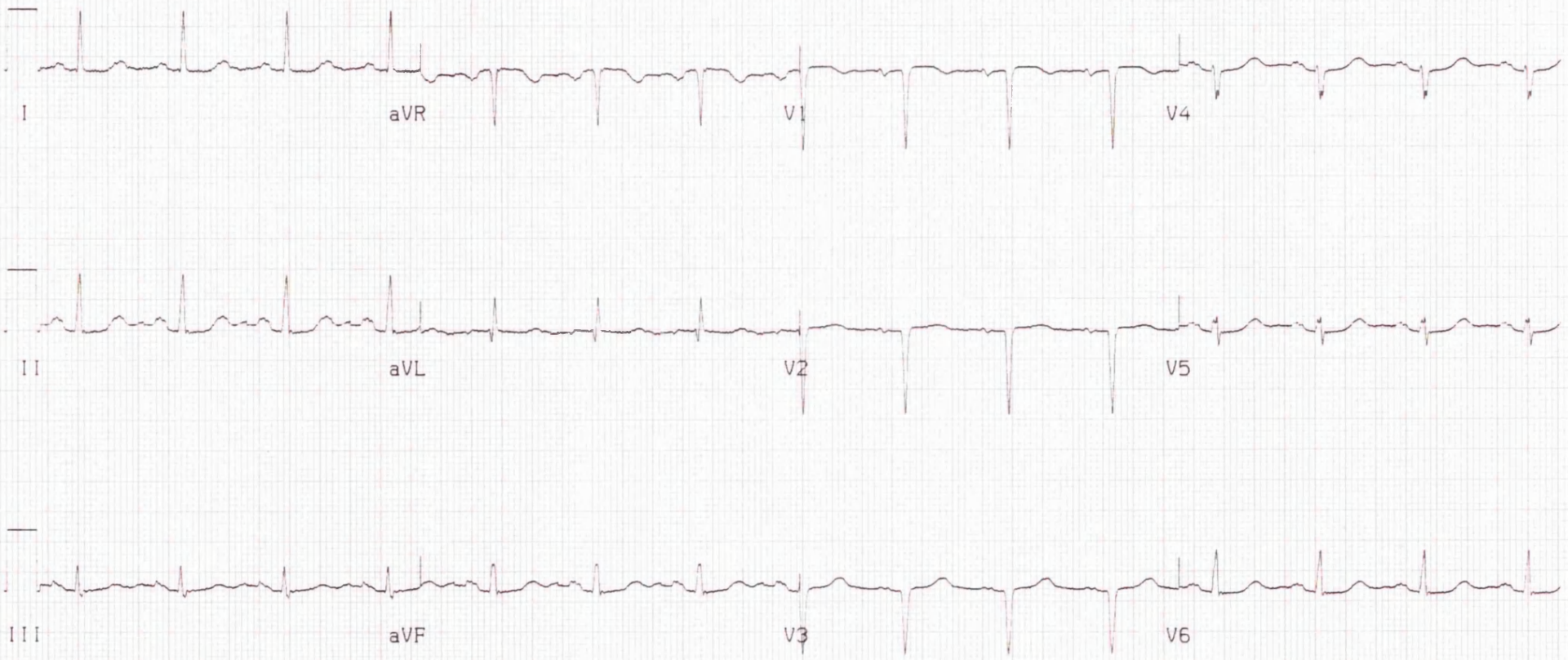
PAIN STUD
PRE-TEST

Clock 1: 00:00
Clock 2: 00:00

Speed: 0.0mph
Grade: 0.0%

Measured At 80ms post J (10mm/mV)
Auto Points

Lead	ST(mm)	Lead	ST(mm)
I	-0.4	V1	0.6
II	-0.2	V2	0.7
III	0.3	V3	0.6
aVR	0.4	V4	0.3
aVL	-0.2	V5	0.0
aVF	0.0	V6	-0.1



11:58:16

25mm/s
10mm/mV
40Hz

ID: 139377
64yrs Ht: Wt:
Female Cauc

HR: 107bpm

PAIN STUD
EXERCISE 2

Clock 1: 03:30
Clock 2: 00:30

Speed: 2.5mph
Grade: 12.0%

* Chest Pain *

Measured At 80ms post J (10mm/mV)
Auto Points

Lead	ST(mm)	Lead	ST(mm)
I	-0.6	V1	0.9
II	-0.9	V2	0.6
III	-0.2	V3	0.4
aVR	0.8	V4	0.0
aVL	-0.1	V5	-0.6
aVF	-0.5	V6	-1.1

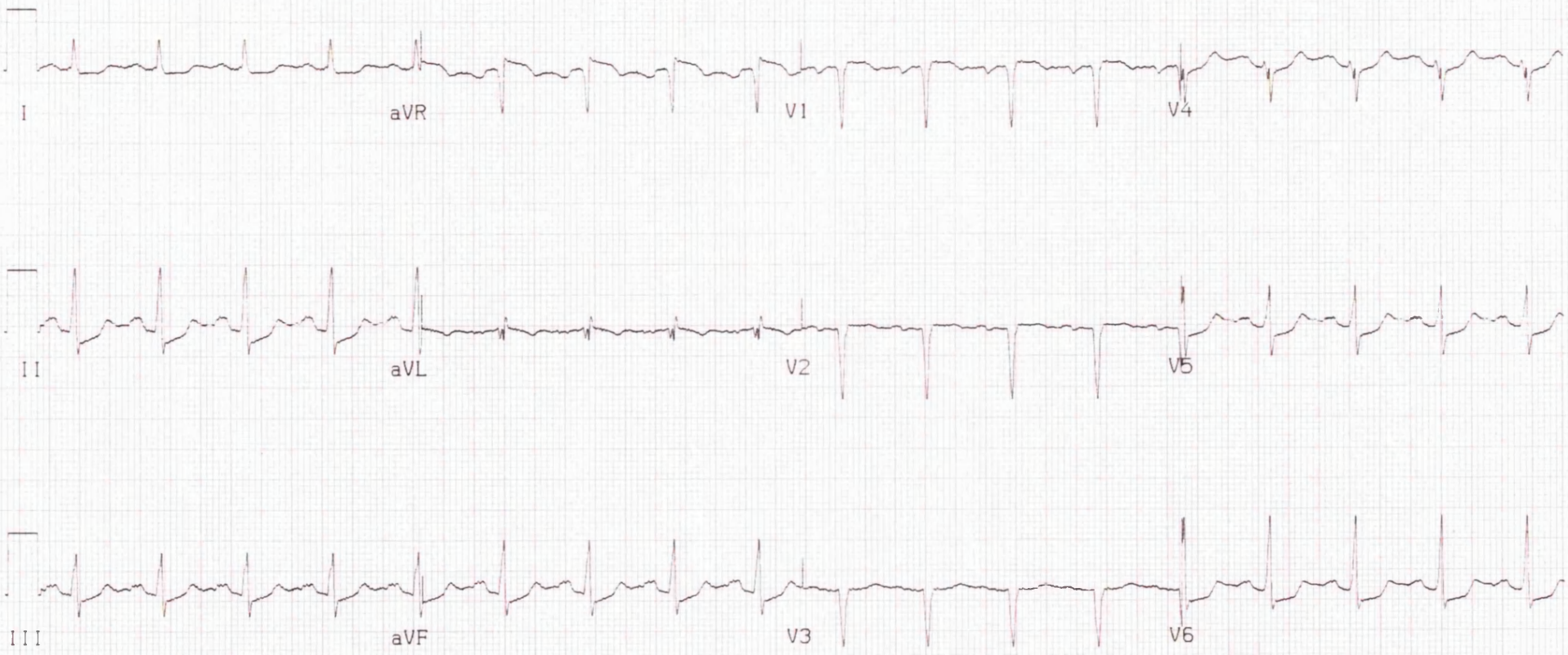


Figure A2: **Electrocardiograms recorded before (next page) and at peak exercise (subsequent page) in a non-diabetic patient with single vessel coronary artery disease who developed ischaemia, but no angina, during treadmill testing.**

11:45:16
25mm/s
10mm/mV
40Hz

ID: 334866
65yrs Ht: Wt:
Male Cauc

HR: 87bpm

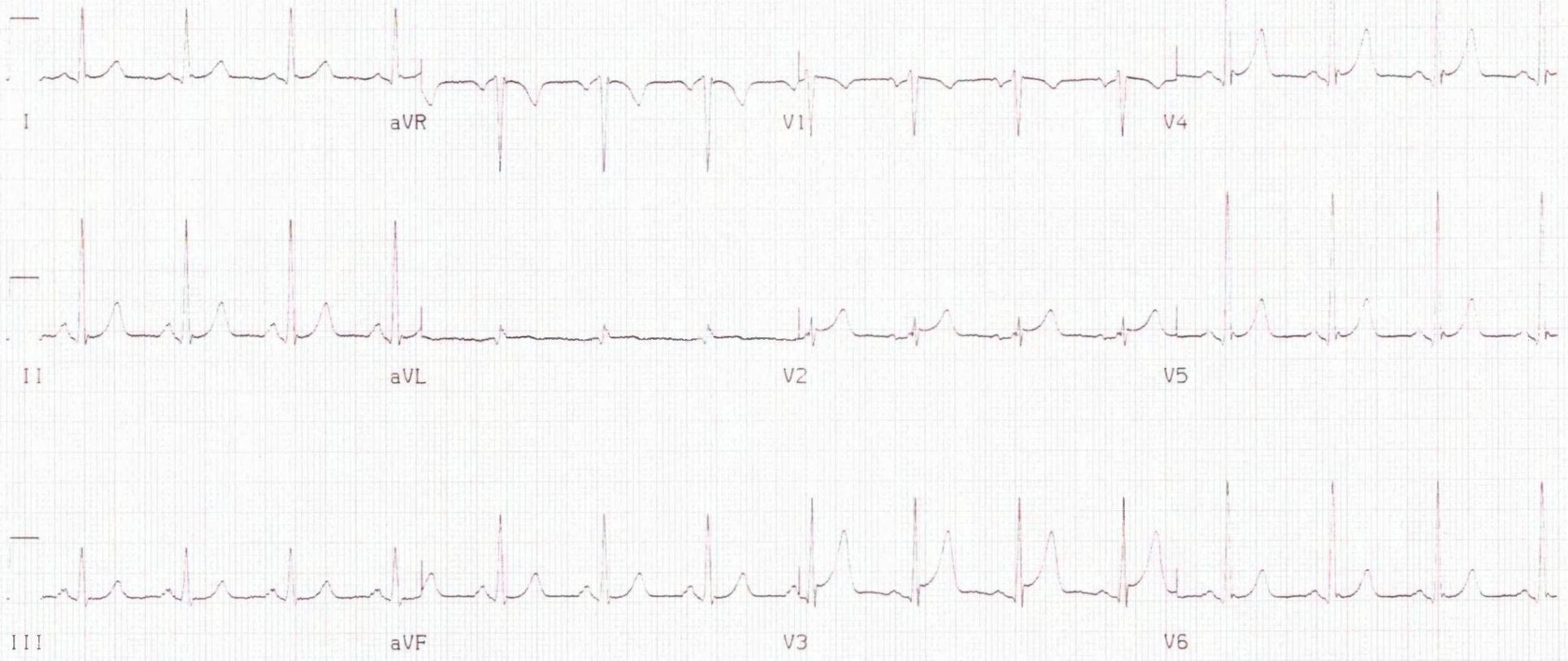
PAIN STUD
PRE-TEST

Clock 1: 00:00
Clock 2: 00:00

Speed: 0.0mph
Grade: 0.1%

Measured At 80ms post J (10mm/mV)
Auto Points

Lead	ST(mm)	Lead	ST(mm)
I	0.6	V1	0.2
II	0.7	V2	1.8
III	0.1	V3	3.5
aVR	-0.6	V4	1.8
aVL	0.2	V5	1.1
aVF	0.4	V6	0.7



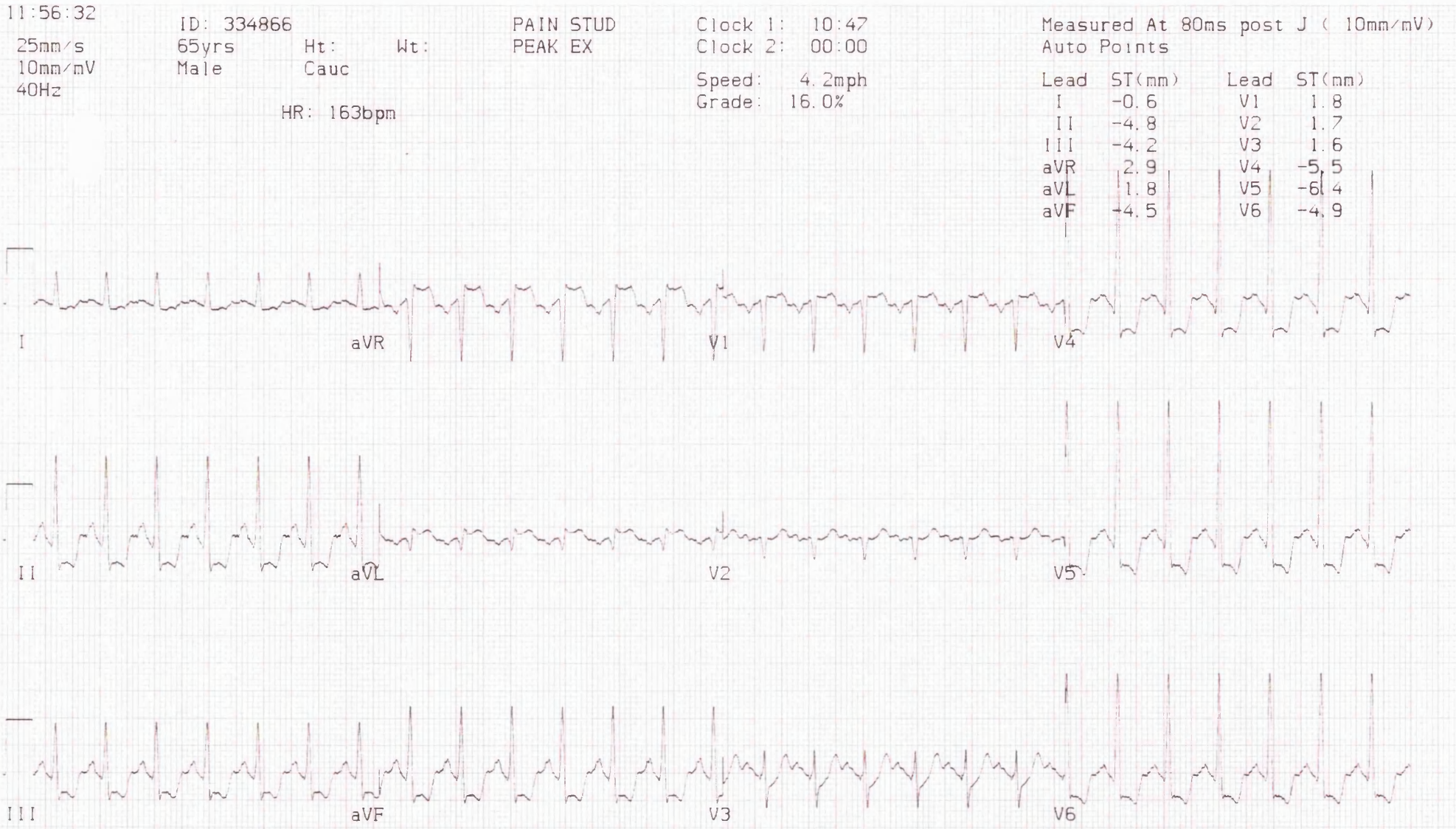

11:56:32
25mm/s
10mm/mV
40Hz
ID: 334866
65yrs Ht: Wt:
Male Cauc
HR: 163bpm
PAIN STUD
PEAK EX
Clock 1: 10:47
Clock 2: 00:00
Speed: 4.2mph
Grade: 16.0%
Measured At 80ms post J (10mm/mV)
Auto Points
Lead ST(mm) Lead ST(mm)
I -0.6 V1 1.8
II -4.8 V2 1.7
III -4.2 V3 1.6
aVR 2.9 V4 -5.5
aVL 1.8 V5 -6.4
aVF -4.5 V6 -4.9
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6

Figure A3: **An episode of ST segment depression on Holter monitoring which was associated with angina in the patient featured in figure A1.**

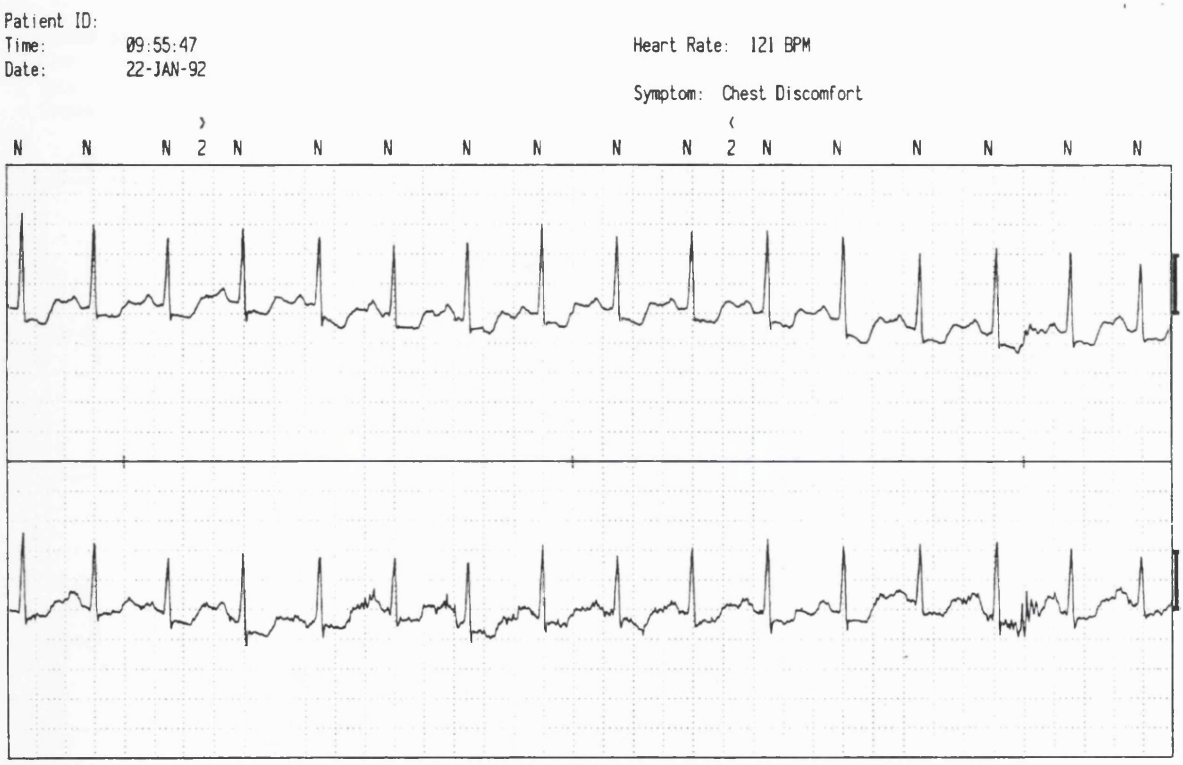
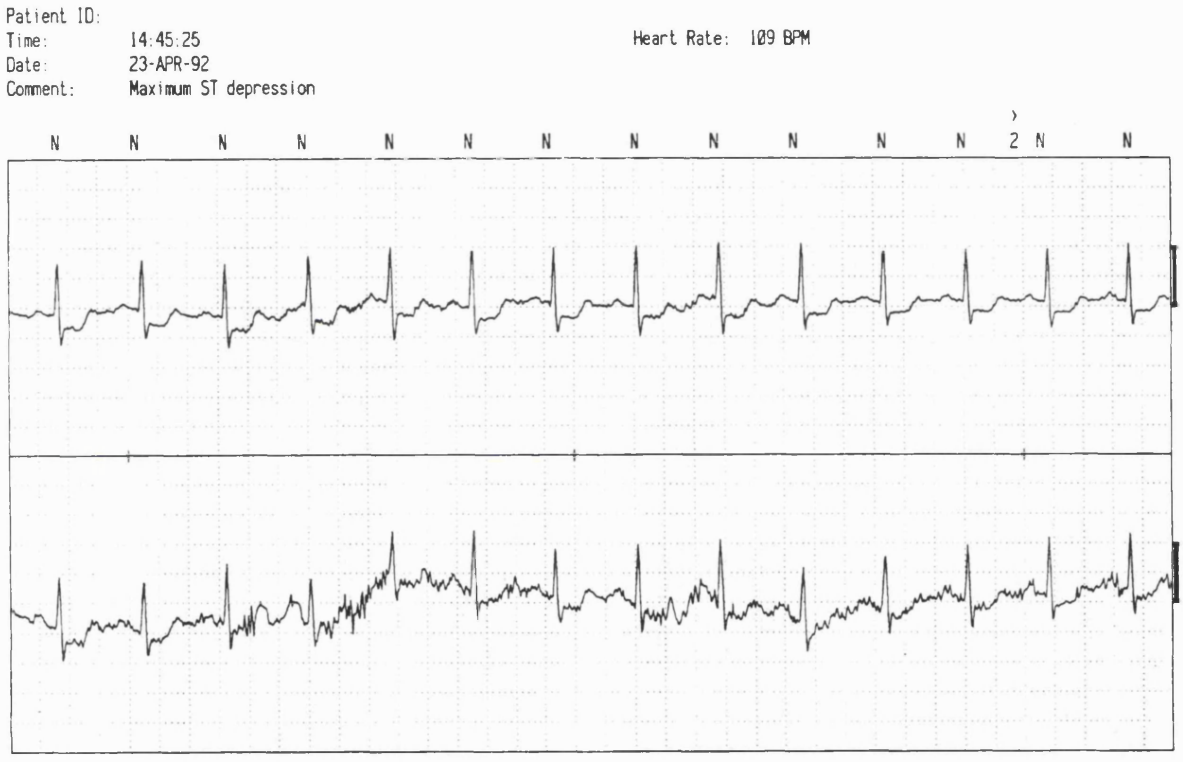


Figure A4: **An episode of ST segment depression on Holter monitoring not associated with angina and classified as myocardial ischaemia in a patient with angina on exercise treadmill testing.**



APPENDIX B

AN INTRODUCTION TO HEART RATE VARIABILITY

APPENDIX B

AN INTRODUCTION TO HEART RATE VARIABILITY

Heart rate variability has been used extensively in this thesis as a measure of autonomic function. Over the last decade, there has been much research relating to the measurement and interpretation of heart rate variability and it has become a valuable technique for the assessment of autonomic function, particularly in diabetic patients and following acute myocardial infarction. In addition, considerable data have been accumulated on the prognostic significance of reduced heart rate variability in patients following myocardial infarction and in patients with malignant ventricular arrhythmias.

DEFINITION

In sinus rhythm, the heart rate is subject to various factors which may influence the beat-to-beat variation in R-R interval. The sympathetic nervous system tends to cause an increase in heart rate, while parasympathetic activity will cause a decrease in heart rate. Other factors such as respiration, the baroreceptor reflex and the renin-angiotensin system also have an important influence on beat-to-

beat variation in heart rate. Measurement of this variation in heart rate may be used to assess the competence and activity of these physiological systems, particularly the integrity of the sympathetic and parasympathetic nervous systems. There are two broad techniques used in the quantification of heart rate variability; spectral analysis (or frequency domain) and non-spectral analysis (or time domain).

SPECTRAL ANALYSIS

Each influence on heart rate is characterised by a particular rhythm or cycle length. For example, respiration at a rate of 15 breaths per minute (1 breath per 4 seconds) will have a cycle length of 0.25 Hz. The parasympathetic nervous system can respond over a wide frequency range, but the sympathetic nervous system only responds at low frequencies (below 0.1 Hz). The various rhythms are superimposed on each other, leading to an apparent lack of pattern, but they may be separated out using mathematical techniques such as Fast Fourier Transformation. If a patient, breaths in a controlled fashion at 15 beats per minute, there will be a peak at 0.25 Hz and its amplitude compared with other peaks will reflect the relative contribution of respiratory variation on overall heart rate variability.

Pomeranz et al[150] have characterised the pattern of heart rate variability attributable to the sympathetic and parasympathetic nervous system using pharmacological blockade. By using atropine and propranolol (separately, and in combination) in normal subjects breathing at a constant rate, they demonstrated that sympathetic blockade reduced the low frequency peak only

(0.04 - 0.12 Hz), whereas atropine reduced the low frequency peak and virtually abolished the high frequency peak.

NON-SPECTRAL ANALYSIS

The change in R-R interval over a given time period may also be defined by more simple statistical methods using variance, standard deviation and proportions. In order to interpret these measures, investigators have studied normal populations as well as patients (with diabetes, following myocardial infarction, and after cardiac transplantation) and compared non-spectral with spectral measures.

The SD and the SDANN are calculated in two stages. First, the mean and standard deviation for all sinus R-R intervals within a five minute period are calculated for each of 288 periods over 24 hours. The SD is calculated as the mean of these standard deviations, and is sensitive to the higher frequency components of heart rate variability, rather than the lower frequency changes which occur with sympathetic and baroreceptor activity. Takase et al[243] have shown that SD is reduced in patients with non-insulin dependant diabetes mellitus, particularly those with clinical evidence of an autonomic neuropathy. The SDANN is calculated as the standard deviation of the 288 mean R-R intervals, and reflects activity in the lower frequency range. This measure has not previously been used in patients with diabetes. The normal ranges for SD and SDANN are >30 ms and 100 ms respectively*.

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*Marquette Electronics, Heart Rate Variability Physician's Guide

The SDRR is the square root of the mean of the squared deviation of each R-R interval from the mean over the 24 hour period. It is sensitive to variation in both the high and low frequency range, and is reduced in patients with an increased mortality following myocardial infarction[244]. The normal range for SDRR is >100 ms*.

The pNN50 and rMSSD are calculated from the two R-R intervals relating to three consecutive sinus beats. These groups of three beats may overlap, so that each R-R interval is compared to both the one preceding and the one succeeding it. The pNN50 is calculated as the proportion of successive R-R intervals which differ by more than 50 milliseconds. The rMSSD is calculated by squaring and summing the difference between each pair of adjacent R-R intervals and dividing this sum by the number of differences. The square root of this sum is the rMSSD. Both of these measures are sensitive to the high frequency component of heart rate variability, representing parasympathetic activity. The normal ranges for pNN50 and rMSSD are > 15% and >25 ms* respectively.

METHOD OF MEASUREMENT

The sinus node is innervated by both the sympathetic and parasympathetic nervous systems, but the onset of P waves is difficult to detect accurately. It is more convenient to detect the R wave and assume that the PR interval is constant, and it is this method which is usually employed. Analysis of recordings

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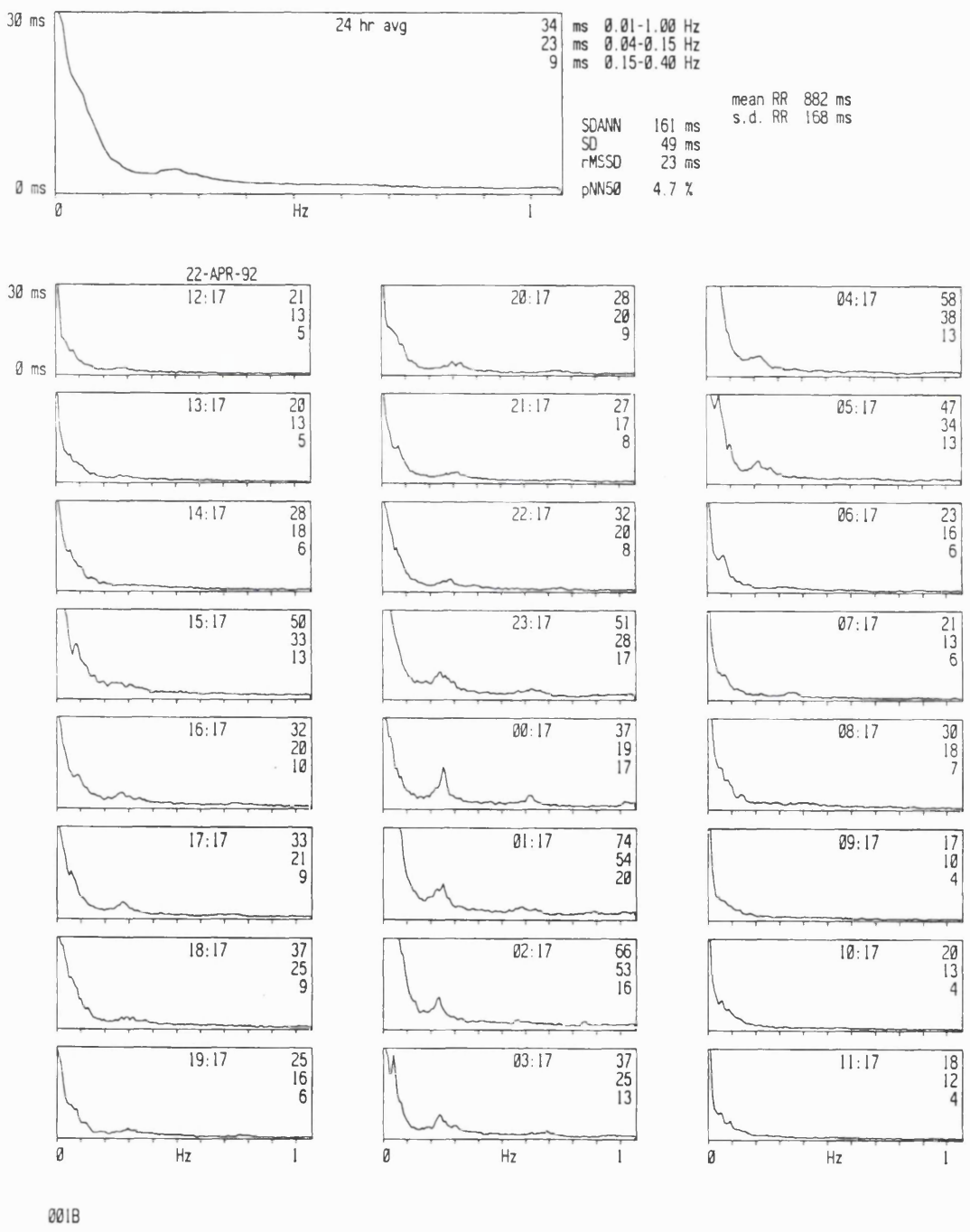
*Marquette Electronics, Heart Rate Variability Physician's Guide

requires careful attention to the correct labelling of QRS complexes; it is essential that all ectopic beats are correctly identified to avoid false calculation of a normal R-R interval.

Heart rate variability can be measured over any time interval. When it is necessary to control for factors such as respiration or posture, it is helpful to consider a limited time frame, perhaps measured in minutes. However, there is considerable circadian variation which must be taken into consideration when a limited period is studied. The measurement of 24 hour heart rate variability can now be performed using standard ambulatory ECG equipment with commercially available software and allows a more complete assessment of heart rate variability. Each software programme has its own algorithm to deal with ectopic beats and artifact. Marquette software only uses sinus-to-sinus R-R intervals in its calculations, replacing any excluded interval with the coupling interval values of the next sinus-to-sinus coupling interval. Intervals which differ by more than 25% from the previous interval are also disregarded. An example of the printout from the Marquette system used in this thesis is shown in Figure B1 (page 223).

Figure B1: 24 hour heart rate variability in a non-diabetic patient with angina on treadmill testing. Spectral analyses for each hour are shown below with a 24 hour average at the top. Amplitude in each frequency band is shown at the right of each graph. Non-spectral measures for the 24 hour period are shown at the top.



FACTORS AFFECTING HEART RATE VARIABILITY

In addition to pathology relating to the autonomic nervous system, other factors may effect heart rate variability. Ziegler et al[96] have shown that spectral and non-spectral measures have a weak negative correlation with age over the range 15 - 67 years. This is unlikely to be an important factor in the patients studied in this thesis, where there was less spread in age. The same study found no difference between male and female subjects and these findings are consistent with other investigators[245].

There are marked circadian changes in heart rate variability[145,245-248] with the sympathetic nervous system playing a relatively more important role during the day, and the parasympathetic nervous system being more important at night. This variation appears to be independent of posture[245].

Although it is well established that heart rate variability is reduced following myocardial infarction[222,249-251] there are few data relating to the importance of the site of infarction. Piplis et al[252] found a greater reduction in heart rate variability following anterior infarction compared with inferior infarction, but the anterior infarctions tended to be more extensive, and this finding was not confirmed by Lombardi et al[236]. Perhaps surprisingly, there are no data available on the influence of myocardial ischaemia on heart rate variability, but it seems unlikely that transient episodes of ischaemia would have an important influence on 24 hour measurements.

SYMPATHO-VAGAL BALANCE

The spectral peaks in heart rate variability indicate the relative contributions of the sympathetic and parasympathetic nervous systems to the variation in R-R interval. As has been discussed, the low frequency band represents both of these systems, while the high frequency band is exclusively influenced by the parasympathetic nervous system. Investigators have used the ratio of low to high frequency peaks (LF/HF) as a marker of the balance between the two components of the autonomic nervous system; a measure of sympatho-vagal balance[253]. Pagani et al[253] showed that propranolol could abolish the increase in LF/HF ratio which was demonstrated during tilt, whereas controlled respiration caused a marked decrease in LF/HF ratio. Lombardi et al[236] have used the LF/HF ratio to show that the increase in sympathetic tone early following myocardial infarction returns towards normal after one year.