PLASMA CATECHOLAMINE CONCENTRATIONS IN RESPONSE TO EXERCISE IN PATIENTS WITH SYNDROME X.

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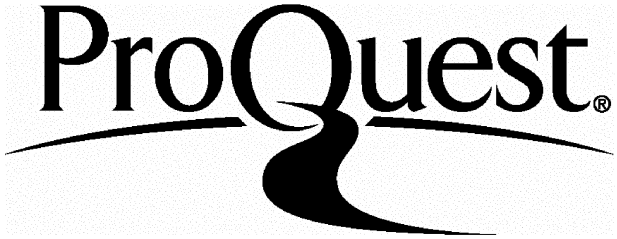

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ABSTRACT

Syndrome X is characterised by chest pain on exertion, indistinguishable from that due to myocardial ischaemia, a positive exercise test and unobstructed epicardial coronary arteries on angiography.
The underlying mechanism(s) remain unresolved.
A body of evidence favours the concept that in many patients myocardial ischaemia occurs due to impaired coronary artery dilator response, caused by prearteriolar vasoconstriction and sympathetic hyperactivity.
The main focus of the study was to examine the effect of exercise on the catecholamines, adrenaline and noradrenaline, in patients with syndrome X, compared to a normal control group.
In addition, measurements were included for blood lactate, plasma potassium, plasma bicarbonate and creatine kinase.

The study population consisted of two groups, thirty patients with chest pain, a positive ECG response to exercise, a normal coronary arteriogram and a normal ventricular angiogram (syndrome X group) and thirty apparently normal non-hospital staff subjects (control group).
All subjects underwent formal, symptom-limited treadmill exercise tests, according to the Bruce protocol. The study protocol involved two exercise tests in each group.
In syndrome X patients the first exercise test confirmed the presence of a positive test and the second was used in the study.
In the control subjects the first exercise test served as a familiarisation procedure and also to establish that the test was normal, and the second test was used for the purpose of the study.

Three venous blood samples were taken with the patient supine.
The first 20 minutes prior to exercising, the second immediately post-exercise and the third 20 minutes into the recovery period.
Samples were analysed for adrenaline and noradrenaline blind at another hospital and for the biochemical markers by the routine hospital laboratory.

Resting heart rates were similar in both the control and syndrome X groups. There was no statistical difference between them. (Two-sample t test, P=0.26).
Resting blood pressures were also similar in both groups and there was no significant statistical difference between them. (Two-sample t test, systolic P=0.99, diastolic P=0.77).

The duration of exercise tests was comparable in both control and syndrome X subjects and there was no significant statistical difference between them. (Two-sample t test, P=0.2).
The heart rate achieved immediately after exercise was also comparable in both groups and there was no significant statistical difference between them. (Two-sample t test, P=0.5).
The blood pressures achieved immediately post-exercise were again similar in both control and syndrome X groups. There was no significant statistical difference between them. (Two-sample T test, systolic P=0.56, diastolic P=0.84).

The main positive finding of this study was that the increase in plasma noradrenaline concentration from pre-exercise to immediately post-exercise was greater in the syndrome X group than the control group.
Thus, at the 95% significance level the data is compatible with there being a difference between control and syndrome X in immediately post-exercise plasma noradrenaline concentrations. (Mann-Whitney, P=0.04).
Furthermore, there was a statistical difference at the 99% level in delta plasma noradrenaline values (Mann-Whitney, P=0.005) and percentage noradrenaline increases from pre-exercise to immediately post-exercise (Mann-Whitney, P=0.002) between the two groups.

Resting, pre-exercise supine plasma catecholamine levels were similar in both control and syndrome X groups. (Mann-Whitney, adrenaline P=0.82, noradrenaline P=0.12).
Resting, pre-exercise supine other metabolic levels were also similar in both groups. (Lactate P=0.24, potassium P=0.16, bicarbonate P=0.56, creatine kinase P=0.96).
No significant differences were observed between the control and syndrome X groups in values from pre-exercise to immediately post-exercise (delta values) in respect of lactate (Mann-Whitney, P=0.61), potassium (Mann-Whitney, P=0.08), bicarbonate (Mann-Whitney, P=0.63) and creatine kinase (Mann-Whitney P= 0.58) concentrations.

There was no significant difference in plasma adrenaline increases from pre-exercise to immediately post-exercise (delta values) between the two groups. (Mann-Whitney, P= 0.87)

There was also no relation in the syndrome X patients between delta plasma catecholamine concentration changes from pre-exercise to immediately post-exercise (delta values) and immediately post-exercise ST segment depression. (Spearman Rank Correlation Coefficient, adrenaline P>0.2, noradrenaline, P>0.1).

These data show that the catecholamine response to exercise is different in syndrome X, in that patients with this condition increase plasma noradrenaline concentrations to a greater extent compared to apparently normal people without this condition.

The data are also consistent with the view that there may be an association between sympathetic overactivity and some patients with this condition and that catecholamines, and possibly other neurotransmitters, might be implicated in the pathogenesis.

A hypothesis is therefore advanced, that an enhanced catecholamine response over a period of time may have a deleterious effect on coronary artery endothelium, altering endothelial function and resulting in a susceptibility to true myocardial ischaemia during exercise.

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SECTION 1

Chapter 1.1. INTRODUCTION

A substantial percentage of patients referred for the investigation of chest pain are subsequently found to have normal epicardial coronary arteries (Kemp et al, 1986). This condition was first reported by Likoff and colleagues (Likoff et al, 1967) but it was Kemp in 1973 in his editorial who used the term "Syndrome X" (Kemp et al, 1973(a)). His comment was based on the article of Arbogast and Bourassa, in which a group of subjects with chest pain and angiographically normal coronary arteries was compared with a group of patients with chest pain and obstructed coronary arteries (Arbogast and Bourassa,1973).

Kemp suggested that the group of patients who had metabolic and electrocardiographic evidence of ischaemia but no evidence of coronary artery narrowing and left ventricular dysfunction should be labeled 'group X'.

The term denoted the uncertainty of the pathogenesis of the condition which still remains obscure 28 years later, although other terms have also been proposed to label these patients, including 'variant angina with normal coronary ateriograms' (Selzer et al, 1976) and 'microvascular angina' (Cannon and Epstein, 1988).

Maseri suggests that syndrome X continues to deserve its name because of the puzzling observations made even in homogeneous groups of patients (Maseri et al, 1991(a)).

Part of the difficulties may relate to the different criteria used in defining the condition and there is no consensus on the definition in the literature. It is therefore important to define for the purpose of this study precisely what one means by syndrome X.

The common denominator in the various definitions is the presence of chest pain, the nature of which is such that it cannot readily be distinguished from myocardial ischaemia. In general, under such circumstances the next step is therefore to proceed with coronary arteriography.

In a broader definition, patients with various cardiac and non-cardiac causes of chest pain, probably due to different pathologies, might be included. Hence some patients will have non-cardiac chest pain that is probably musculoskeletal or oesophageal in origin (Cannon et al, 1990(a)).

Others have cardiac pain which is not due to coronary arterial narrowing and this group includes patients with left ventricular hypertrophy, hypertrophic cardiomyopathy, valvular heart disease, e.g. aortic stenosis, severe anaemia and hypergammaglobulinaemia.

In an attempt to include under the definition a more homogeneous group of patients many authors use stricter criteria and a positive electrocardiographic response to exercise is required, i.e. the characteristic ST segment depression which in patients with documented coronary artery disease (CAD) is regarded as evidence of typical myocardial ischaemia. This has been recognised by Poole-Wilson and Crake who postulated that this syndrome does not define a homogeneous patient population and that an absolute requirement is the presence of a positive exercise test (Poole-Wilson and Crake, 1989). In their article they concluded that syndrome X describes an inhomogeneous group of patients with symptoms due to different pathologies. Recently this view has been supported by Kaski and colleagues who required the presence of a positive exercise test in the definition in order to reduce clinical heterogeneity and identify patients whose chest pain is more likely to be cardiac in origin (Kaski et al, 1995). However, in the absence of documented CAD such a response should be interpreted with caution and does not necessarily indicate myocardial ischaemia and the issue of the so called 'false positive' exercise test adds further confusion. Indeed, there are several common conditions causing 'false positive' ECG changes on exercise, among which hypertension, hypertrophic cardiomyopathy, mitral valve prolapse and the administration of digoxin are included.

The term syndrome X has been recently used for another syndrome (Reaven, 1988). This syndrome consists of a combination of insulin resistance, hyperinsulinaemia, high plasma triglyceride concentration, low high density lipoprotein (HDL), cholesterol concentration, raised blood pressure and obesity. Since insulin resistance seems to underlie these related disturbances in the pathogenesis of CAD the term 'insulin resistance syndrome' may be more appropriate for this metabolic syndrome X.

For the purpose of this study it was decided to adopt strict criteria for defining syndrome X in order to be able to investigate a group of patients being as homogeneous as possible. According to the definition adopted, syndrome X is the condition of patients fulfilling the following three criteria: firstly, chest pain indistinguishable clinically from that due to myocardial ischaemia; secondly, the demonstration of normal epicardial arteries and normal left ventricular angiograms; thirdly, an ischaemic ECG response to exercise together with a positive symptomatic response i.e. patients experiencing chest pain during exercise.

Whether patients experience pain or not on the exercise test is not often reported in the literature and some authors merely refer vaguely to a positive exercise test without specifying whether they mean just the positive ECG response to exercise or whether, additionally, patients experience their usual chest pain during the test.
It was also considered necessary that patients should not be receiving any medications during exercise testing as these may affect the occurrence of pain or the ECG configuration (Marcomichelakis et al, 1980).
Patients with chest pain and normal coronary arteries but also with evidence of hypertension, cardiac muscle hypertrophy, mitral valve prolapse or any important systemic diseases were not included in the present studies.

A body of opinion favours the concept that syndrome X encompasses an inhomogeneous group of patients with symptoms due to several different pathophysiological entities (Poole Wilson and Crake, 1989; Maseri, et al 1991(a); Cannon et al, 1992; Kaski et al, 1995).
However, several possibilities have been put forward to explain the pathogenesis of this intriguing condition, including dilated cardiomyopathy, coronary arterial spasm, small vessel disease, oestrogen deficiency, abnormal intracardiac noniception and others.
One theory which has gained considerable support is that there is probably a reduced vasodilatory response of coronary arteriolar vessels (Maseri et al,1991(b); Cannon et al,1992). According to this theory, the problem probably lies not at the level of the arteriolar vessels but before them, at the prearteriolar level, the vessels interposed between conductive coronary arteries and arteriolar vessels and the abnormality appears to be functional rather than organic (Maseri et al,1991(b)).

It is now becoming clear that potent vasoactive substances are involved in the regulation of the small coronary vessels. Furthermore, the interaction of these substances appears to be impaired in this condition. It has been suggested also that an inappropriate prearteriolar vasoconstriction might be, at least in part, an adrenergically mediated phenomenon (Cannon et al,1983; Bortone et al,1989).
This study was designed to test this hypothesis. The catecholamine, adrenaline and noradrenaline, response to treadmill exercise testing of a group of patients fulfilling our criteria for syndrome X was compared with a control group of apparently normal people.

Chapter 1.2. MYOCARDIAL ISCHAEMIA

1.2.1. Definition of myocardial ischaemia

Myocardial ischaemia means 'lack of sufficient blood for the cardiac muscle' as the word 'ischaemia' is derived from the ancient Greek word, ischaemia = lack of blood.
Myocardial ischaemia is frequently conceptualised as the result of an imbalance between myocardial oxygen supply and demand, occurring when the supply of oxygen, substrates and energy fails to meet the metabolic demands of the myocardium (Hearse, 1980).
In the normal heart this does not occur because changes in myocardial metabolic needs are promptly met by changes in blood flow and the balance between oxygen supply and demand is well preserved.
It is also noteworthy that an increase in oxygen supply to the heart is achieved by an increase of blood flow and not by an increase in O_2 extraction.
An alternative definition is that myocardial ischaemia occurs when there is an imbalance between the rate of consumption of adenosine triphosphate (ATP) and blood flow (Poole-Wilson, 1983). This results in lactate production by the heart (an indication of anaerobic metabolism), a fall in coronary sinus oxygen saturation and pH and an increase in coronary sinus potassium concentration (Crake et al, 1988).
Such a metabolic definition of myocardial ischaemia, however, is controversial.
Some authorities, for example, suggest that an increase of the lactate concentration in coronary sinus blood lactate is not always indicative of myocardial ischaemia unless coronary sinus blood lactate concentration is greater than that in the arterial blood, i.e. when there is evidence of net myocardial lactate production.

1.2.2. Supporting evidence for the detection of myocardial ischaemia

Myocardial ischaemia is usually manifested clinically as angina pectoris. However, angina pectoris does not equal myocardial ischaemia in every instance; asymptomatic myocardial ischaemia is not infrequent and there are other causes of chest pain.
Confirmatory evidence is usually required to support the clinical suspicion that this sensation in the chest is originating from the heart itself.
Physical examination is sometimes helpful. The presence of a fourth heart sound and/or a systolic murmur of functional papillary muscle dysfunction makes the diagnosis more likely.

Breathlessness during an attack due to a rise in left atrial pressure following a rise in left ventricular end diastolic pressure (LVEDP) may further suggest the presence of myocardial ischaemia.
Electrocardiographic changes at rest or during exercise involving the ST segment configuration are generally considered to be supportive evidence, especially when these changes are associated with chest discomfort, whereas transient T wave changes are usually difficult to interpret (Surawicz et al, 1983).
However, even in the absence of symptoms the possibility of 'silent ischaemia' should be entertained and the diagnosis of myocardial ischaemia should not be easily dismissed.

Myocardial perfusion scintigraphy and positron emission tomography have also been used successfully to identify regions of myocardial ischaemia at rest and during exercise, after dipyridamole and adenosine infusion.
Finally, regional left ventricular wall motion abnormalities using two-dimensional stress echocardiography or radionuclide scintigraphy and blood pool imaging during exercise have been employed to support the diagnosis of ischaemia.

1.2.3. Control of coronary circulation

In order to understand the mechanisms involved in the development of myocardial ischaemia and, in particular, its contribution in the manifestations of syndrome X, some description of the coronary circulation is necessary.
The coronary circulation may be regarded as an array of conductance and resistance vessels of which the latter are under metabolic control.
In the normal heart, the large epicardial coronary arteries constitute a small fraction of the total coronary artery resistance, estimated at less than 5%. However, during exercise this percentage increases.

Under normal circumstances, coronary artery resistance resides predominantly in arterioles >100 microns in diameter (Chilian et al, 1989). Approximately 25% of total coronary artery resistance resides in vessels >170 microns in diameter, whereas metabolic vasodilatation occurs predominantly in vessels <100 microns in diameter (Chilian et al,1989). Vasoconstriction of the larger coronary arteries may also be compensated for by vasodilatation of vessels <100 microns in diameter (Kanatsuka et al, 1990).

If, however, hypoperfusion has already caused metabolic coronary artery dilatation of the vessels <100 microns in diameter constriction of the prearteriolar vessels can no longer be compensated for by further dilatation of these arterioles. Therefore, if prearteriolar constriction occurs, hypoperfusion will be exaggerated. Furthermore, inappropriate constriction of the small diameter distal coronary artery vessels, rather than proximal, can cause myocardial ischaemia (Pupita et al,1990).
It is also noteworthy that alpha$_1$ and alpha$_2$-adrenergic receptors may have no effect on coronary arteries <100 microns in diameter during normal arterial flow, but that myocardial hypoperfusion results in unmasking alpha$_1$ and alpha$_2$-adrenergic receptor mediated coronary artery constriction of vessels of this size (Chilian,1991(a)).

The role of intramural penetrating arteries is also important. These vessels arise almost at right angles from the large extramural vessels and pass through the myocardium where they branch dichotomously, giving rise to progressively smaller branches to finally form a subendocardial plexus in the trabeculae (Marcus,1983).
In the normal heart intravascular pressure in coronary arteries of 100 microns in diameter is considerably lower in the subendocardium than in the subepicardium (Chilian,1991(b)). Thus, a significant pressure drop occurs across the penetrating arteries that traverse the left ventricular wall to deliver blood to the subendocardium. These penetrating arteries range from 50 to 500 microns in diameter with most around 200 microns in diameter (Estes et al,1966).

In normal circumstances, dilatation of the arteriolar bed would outweigh the effect of possible constriction of the penetrating coronary arteries. However, if they have already undergone maximal dilatation any significant constriction of the penetrating coronary arteries would outweigh any arteriolar dilatation causing a decrease in subendocardial flow and manifestations of ischaemia.
There is a greater susceptibility of the subendocardium to ischaemia, possibly because the subendocardium is subject to greater wall stress and higher oxygen consumption.
Additionally, because collateral flow increases from subendocardial layers to the subepicardium, the ischaemic damage of the jeopardised myocardium begins in the subendocardium and progresses as a 'wave front' as was shown by Reimer and colleagues in dogs (Reimer et al, 1977).

Forman and colleagues have carried out similar studies in humans and showed a similar sequence of events (Forman et al, 1983). Consequently, the coronary artery vasodilatory reserve is limited in the endocardial layers and therefore they may show signs of myocardial ischaemia before the more superficial layers (Griggs et al, 1973).

1.2.4. Metabolic consequences of myocardial ischaemia

Within seconds of coronary artery occlusion, there is impaired myocardial blood flow to the myocardial cell resulting in a disturbance of the transmembrane ionic balance (Hillis and Braunwald, 1977). The ionic changes are followed immediately by a reduction of mitochondrial activity and oxidative metabolism and a concordant fall in ATP production with a precipitous decline in contractile activity. In an effort to maintain ATP levels there is a rapid depletion of creatine phosphate stores with transfer of high energy phosphate to adenosine diphosphate (ADP).

The function of the coronary circulation is not only to provide oxygen to the heart but also to remove heat, acid, lactate and protons and prevent the development of acidosis. In humans acidosis can be manifested within seconds of occlusion of a coronary artery (Crake et al, 1987(a)). In order to avoid the occurrence of acidosis the coronary circulation removes the acid in the form of carbon dioxide. The production of lactate by the heart is generally considered as evidence of myocardial ischaemia.

However, it is difficult to interpret lactate measurements because an increase of the lactate concentration in coronary sinus could be due to increased lactate production, an increase in the arterial concentration, an increase of coronary blood flow, or a fall of consumption.

If the oxygen supply to the myocardium is insufficient to meet the requirements of the heart at a certain moment, then creatine phosphate is broken down and glycogenolysis is stimulated (Poole-Wilson, 1983). It is generally difficult to predict the critical levels of coronary flow and metabolic myocardial requirements which are able to produce myocardial ischaemia. In the normal human heart, a coronary blood flow of 60 to 90 ml/min per 100 gm of myocardial tissue is required for adequate myocardial function under basal physiological conditions (Braunwald and Sobel, 1992).

Myocardial ischaemia causes potassium loss from the myocardium (Wiegand et al, 1979). Extracellular potassium accumulates and intracellular sodium and chloride concentrations rise. These changes can also be detected within seconds following occlusion of a coronary artery (Webb et al, 1987).

Furthermore, the accumulation of potassium in the extracellular space and the devlopment of acidosis causes the changes of the action potential of the myocardium which are observed during ischaemia (Weiss and Shine, 1981).

Additionally, there is local release of catecholamines and lysophosphoglycerides, there is hypoxia, elevation of pCO_2 and low pH and stimulation of glycogenolysis follows (Janse and Wit, 1989).

Within minutes of ischaemia, there is increased leakage of adenosine, inosine and other metabolites into the extracellular space. There is increasing cellular acidosis and marked alteration of ionic balances.

Local coronary dilatation occurs and collateral blood flow is augmented. If ischaemia persists then structural changes of the myocytes occur and irreversible changes will follow.

1.2.5. Chest pain - Angina pectoris

One of the main criteria for the diagnosis of syndrome X is angina.
However, inconsistencies may arise in view of the incomplete agreement regarding the definition of angina pectoris and the classification of chest pains.
Literally, angina pectoris means pain in the chest (Greek, angina = pain, Latin, pectus = chest). It does not mean pain in the heart.
However, most physicians use this definition indicating the characteristic short-lived pain or discomfort in the chest arising only from conditions of the heart and most frequently caused by transient regional myocardial ischaemia due to coronary artery atheromatous narrowing.

Angina is characteristically a substernal 'pressure' produced or aggravated by exertion, emotion, heavy meals, or exposure to low atmospheric temperature.
Exertional angina most commonly occurs in patients with fixed coronary artery stenoses and is often associated with transient ST segment depression which is assumed to reflect subendocardial ischaemia. However, "such a definition assumes the cause of the symptom before it has been established" as was pointed out by Poole-Wilson and Crake (Poole-Wilson and Crake, 1989).
A broader definition of 'angina' is pain in the chest, originating from within the cardiac muscle, often due to functional ischaemia and not necessarily due to coronary artery narrowing. It can be caused by myocardial hypertrophy of whatever cause (hypertension, hypertrophic cardiomyopathy, aortic stenosis) rheological abnormalities of the blood (hypergammaglobulinaemia) and severe anaemia.

Non-invasive diagnostic techniques, like exercise testing and thallium scintigraphy, are used as an aid in diagnosis but even with the employment of these techniques the diagnosis is not always clear-cut.
The magnitude of the problem is shown by the fact that in some studies as many as 20% of patients undergoing coronary arteriography for the assessment of anginal-like pain, the epicardial coronary arteries have been found to be normal (Proudfit et al, 1966; Kemp et al,1986).

Furthermore, approximately 10% of patients referred for investigation of unstable angina have been shown to have normal coronary arteriograms (Alison et al, 1978) and such patients are investigated by many under the umbrella of syndrome X.

1.2.6. Non-cardiac causes of chest pain

Chest pain assumed to have originated from the heart can be shown to be due to various cardiac and non-cardiac causes. Patients with chest pain who are subsequently shown to have a normal coronary arteriogram present a common diagnostic problem, but in most cases the pain is not cardiac (Master, 1964).
It is known that pain of oesophageal origin may be indistinguishable from cardiac pain (Cannon et al,1990(a)). Oesophageal manometry studies show dysfunction in approximately 30% of syndrome X patients (Cannon et al, 1990(a); Chauhan et al, 1993(a)). However, even in the presence of such abnormalities it may be difficult to say with certainty in a particular case, whether the pain originates from the heart, the oesophagus or both.
Musculoskeletal pain originating from the chest wall is sometimes difficult to distinguish from that of cardiac origin (Epstein et al,1979).
Psychological factors may stimulate heart diseases, cause chest pains and even precipitate myocardial infarction in the absence of CAD (Bass et al, 1988; Lantinga et al,1988).

Anxiety neurosis, neurocirculatory asthenia and vasocirculatory asthenia are other well known causes of chest discomfort (Friesinger et al, 1972).
In the American civil war 'the soldier's irritable heart', in the first world war the 'disorderly action of the heart' and in the second world war the 'effort syndrome' were described (Wood,1941; White, 1942).
These syndromes are characterised by dyspnoea, palpitations, fatigue and usually left-sided chest pain.
Finally, hyperventilation is potentially associated with chest discomfort (Bass et al, 1983).

1.2.7. Cardiac causes of chest pain, not due to atheromatous coronary artery narrowing

Chest pain is not an infrequent symptom in many cardiac conditions which are not due to coronary arterial narrowing caused by atheroma. In these cases reduction of coronary blood flow is not the cause of myocardial ischaemia but other mechanisms are involved.

In situations where there is increased work of the heart and left ventricular hypertrophy develops with time, as in hypertension and aortic stenosis, chest pain may occur and is probably due to functional myocardial ischaemia.

Mitral valve prolapse is associated with chest pain. In fact, chest discomfort is the most common non-specific symptom in this condition, occurring in 60% of cases. It is usually precordial, left sided and characterised as sharp, stabbing or lancinating. Occasionally, however, it has an angina-like quality (Alpert et al,1991).

It is difficult to understand why patients with mitral valve prolapse experience chest pain. It is generally thought to be due to myocardial ischaemia although attempts to prove it have been, so far, unrewarding (Alpert et al,1991). It is also noteworthy that in the same article it was reported that mitral valve prolapse occurs more frequently in subjects with various causes of chest pain including coronary artery spasm, oesophageal spasm, panic disorders and chest wall pain than in normals. Thus, it is very difficult to say with certainty whether the pain that these patients experience is caused by the other conditions that co-exist or the prolapse itself or both. Epicardial coronary arterial spasm is often associated with chest pain and is due to functional myocardial ischaemia (Maseri et al,1978).

Multiple coronary arterial loops have been suspected of causing anginal pain as well as a positive ECG response to exercise as a result of myocardial ischaemia (Barilla et al, 1991).

A number of other causes of chest pains also require mentioning.

Dilated cardiomyopathy may cause cardiac pain. Connective tissue disorders with involvement of small intramyocardial coronary vessels is a known cause of cardiac pain.

Anginal pain originating from the cardiac muscle can be caused by systemic disorders which probably induce functional myocardial ischaemia. The cardiac muscle itself is not thickened and is normal in every respect; the coronary arteries are also normal and not obstructed. A good example is severe anaemia, where there is a reduced oxygen carrying capacity in the blood.

Rheological abnormalities of the heart such as hypergammaglobulinaemia is also another condition where chest pain is experienced and is caused by functional myocardial ischaemia due to insufficient delivery of oxygen to the myocardium.

If all the above cardiac and non cardiac conditions associated with chest pain and normal epicardial arteries are ruled out, a substantial number of patients remain in whom no obvious cause can be detected .
This study deals with this group of patients who were carefully characterised as syndrome X cases and fulfilled our pre-determined strict inclusion and exclusion criteria.

Chapter 1.3. TECHNIQUES FOR THE DETECTION OF MYOCARDIAL ISCHAEMIA IN SYNDROME X.

1.3.1. Resting electrocardiogram

The resting electrocardiogram has been the mainstay for the diagnosis of myocardial ischaemia since Einthoven discovered it almost 100 years ago.
However, the limitations of the resting electrocardiogram as an index of myocardial ischaemia are well recognised. It has been shown that ST segment shifts are both imprecise and non-specific (Fozzard and Das Gupta, 1976). Such electrocardiographic changes measure electrical gradients between ischaemic and normal myocardium and not the local electrophysiological changes in the ischaemic myocardium per se.
Therefore, any factor influencing membrane properties may affect the configuration of the ST segment irrespective of the presence or absence of ischaemia.
The insensitivity of the surface electrocardiogram has also been shown in human studies by many authors and different methodologies (Hauser et al, 1985; Taggart et al, 1989).
Displacement of the ST segment does not directly reflect local electrophysiological changes of the ischaemic myocardium but the electrical gradient between ischaemic and non-ischaemic myocardium attributed partly to a reduction in the amplitude of the plateau period of the action potential and partly to currents during diastole. Factors other than ischaemia such as electrolyte changes, antiarrhythmic drugs and heart rate variation can influence these ECG changes (Franz et al, 1984).

1.3.2. Exercise electrocardiogram

A greater than 1 mm ST segment depression, horizontal or downsloping in configuration, measured 80 ms after the junction of the QRS complex and the onset of the ST segment (the J point) is conventionally considered as evidence of a positive electrocardiographic response to exercise i.e. indicative of myocardial ischaemia (Bruce et al, 1963).
There are several problems regarding the interpretation of the ischaemic electrocardiographic response to exercise.
Myocardial ischaemia may occur in the absence of typical ischaemic ECG changes and, conversely, effort related ECG changes may occur in the absence of myocardial ischaemia.

The effectiveness of an exercise test is determined by three factors, namely sensitivity, specificity and prevalence of the disease (Diamond and Forrester, 1979).
The sensitivity of a test is defined as the ratio of the (true positives minus the false negatives) divided by the true positives, i.e. the ability of a test to avoid missing the diagnosis. The specificity of a test is defined as the ratio of (true negatives minus false positives) divided by true negatives, i.e. the ability of the test to avoid false positives.
Thus, sensitivity is the proportion of a positive test result in those patients with documented CAD, and specificity is the proportion of a negative response in those patients without evidence of CAD, on coronary arteriography. According to Bayes' theorem both sensitivity and specificity depend on the prevalence of the disease within the population being evaluated. If the prevalence of CAD is high, then these are also high. If the prevalence of the disease is low, as it is the case when studying asymptomatic people (with no chest pain), then these are also low.
For the exercise test figures in the region of 70% to 80% for specificity and 60% to 70% for sensitivity are quoted in the literature when referenced to coronary anatomy as determined by coronary arteriography (Melin et al, 1981; Gianrossi et al, 1989).

False negative ECG responses:
There are several possible explanations for the absence of ischaemic ECG changes on effort in the setting of myocardial ischaemia.
(a) The magnitude of the ischaemic zone may be such that the solid angle created across the ischaemic margins from the body surface leads is inadequate to generate ST segment changes on the body surface (Holland and Brooks, 1977).
(b) The location of the ischaemia may be electrically silent relative to the body surface ECG (Huey et al, 1988).
(c) The area of ischaemia may be so diffuse that the electrical gradients oriented in one direction will be cancelled by electrical gradients oriented in the opposite direction (Autenrieth et al, 1975).

False positive ECG responses:
Technical conditions which may interfere with the interpretation of the electrocardiogram should always be ruled out, as they may create the impression of a false positive result. These include:
(a) Signal-averaging of the electrocardiogram and inadequate skin preparation that results in noise, or a wandering baseline.

(b) Left ventricular hypertrophy of whatever cause, primary or secondary, including hypertension, may cause a false positive response, although the underlying basis is probably functional ischaemia (Detrano and Froelicher, 1988).
(c) Electrolyte abnormalities, especially hypokalaemia has long been known to induce ST segment depression (Detrano and Froelicher, 1988).
(d) Mitral valve prolapse is a condition associated with a false positive exercise test although the underlying basis is probably due to myocardial ischaemia.
(e) Pericarditis is also sometimes associated with a false positive ECG response.
(f) Several cardioactive drugs which may interfere with the electrocardiographic interpretation of an exercise test are also associated with this condition. Amongst them, digitalis is well documented, but probably antiarrhythmic drugs like flecainide and amiodarone may also cause repolarisation changes (Holland and Brooks, 1977; Detrano and Froelicher, 1988).
There is also an association with hyperventilation, neuroregulatory asthenia, intraventricular conduction defects and Wolff-Parkinson-White syndrome.
A false positive exercise test can also be recorded under psychological stress.
Another factor leading to 'false positivity' is the effect of the atrial repolarisation wave (Ta wave) on the ST segment (Ellestad,1991).
In leads with a positive P wave, the downsloping configuration of the PQ segment (atrial ST segment) and the inverted atrial T wave may cause ST segment depression which is indistinguishable from that caused by myocardial ischaemia (Gettes and Sapin, 1993).

The specificity of exercise testing has been reported to be lower in women than in men (Fletcher et al, 1990).
To explain this several authors have speculated on a possible role of oestrogens in contributing to the greater number of false positive results (Fletcher et al, 1990).
In a recent article Sullivan and co-workers reported that approximately 40% of women referred for the evaluation of chest pain were found on coronary angiography to have normal coronary arteries, compared with only 8% of men, confirming the lower specificity of exercise testing in women with chest pain and that chest pain in women is common and may not have a cardiac origin (Sullivan et al,1994).

Ischaemic ECG changes or their absence associated with exercise should not in themselves be considered an absolute marker for the presence or absence of ischaemia.
It should also be remembered that a proportion of 'false positive' exercise tests may in fact represent 'true positive' results as the potential for unrecognised genuine ischaemia exists when the 'gold standard' of coronary arteriography is used for comparison.
A good example of such a condition is probably a patient with coronary artery spasm when true ischaemia might be present in the absence of atheromatous CAD.

1.3.3. Studies of coronary flow reserve

Coronary flow reserve is the difference between baseline levels of coronary flow when under autoregulation and the coronary flow achieved by maximal vasodilatation.
It is critically dependent on the actual perfusion pressure and positions of the line of autoregulation and the maximal vasodilatation (Hoffman, 1990). In practice it entails measuring myocardial blood flow at rest and during maximal vasodilatation to test its capacity to increase perfusion. It is the only way in which to assess the coronary artery microcirculation which is not visible on coronary arteriography or by any other current in vivo technique.

Nuclear studies:

The physiological basis for myocardial perfusion scintigraphy is the principle that myocardial uptake and distribution of the radiotracer is proportional to regional blood flow and depends on the viability of the myocardial tissue.
Several radioactive particles have been used to study the coronary artery circulation.
Thalium-201 scintigraphy has been used extensively to identify regions of myocardial ischaemia at rest and during exercise, after dipyridamole and adenosine infusion. During the last seven years several technetium compounds have also been developed which may have a better image resolution and are comparable in their diagnostic efficacy to thallium-201 (Maddahi et al, 1990).

Exercise myocardial perfusion scintigraphy is usually performed in conjunction with exercise electrocardiography. The presence of myocardial ischaemia can be suggested if there is a focal defect in tracer uptake on the post-exercise myocardial image and if the initial defect is no longer seen on re-imaging after several hours of rest.

The sensitivity and specificity of myocardial perfusion scintigraphy is probably greater than exercise testing (Ritchie et al, 1978). However, it should be interpreted with caution as there are several causes for a reduced specificity, including artefactual defects due to breast attenuation or relative apical thinning (Fintel et al, 1989).
If a positive thallium test is associated with exercise-induced ECG changes and if the patient experiences his or her usual chest pain, then the diagnosis of myocardial ischaemia is almost certain. If, however, there are no ischaemic ST segment changes, no chest discomfort and the only 'abnormality' is a thallium defect seen after intravenous dipyridamole or adenosine, then one should be less confident about the diagnosis.

Pharmacological studies:

These are employed if the patients are unable to perform an adequate dynamic exercise test.
The pharmacological agents being used include specific vasodilators such as dipyridamole and adenosine. The diagnostic ability of these agents is comparable to that of conventional dynamic exercise (Gould et al, 1978; Botnivik and Dae, 1991) and their efficacy as stressors in coronary artery CAD and reproducibility are well recognised. However, dipyridamole may not always induce maximal myocardial blood flow and some patients may be less responsive to it.
Inotropes such as dobutamine have also been used to provoke myocardial ischaemia (Pennell et al, 1991).

Atrial pacing:

This technique for provoking myocardial ischaemia has become less popular since the advent of the above pharmacological agents. However, it has been extensively used in the investigation of syndrome X.

Positron Emission Tomography:

Positron emission tomography is another method for identifying myocardial ischaemia. Several radioisotopes have been used such as nitrogen-13, oxygen-15, carbon-11 palmitate and rubidium or cyclotron generated fluodeoxyglucose and these are probably sensitive markers of myocardial perfusion.

It permits the characterisation of myocardial metabolism and the detection of altered metabolism associated with ischaemia. The advent of positive electron tomography has made it possible to measure myocardial blood flow non-invasively in humans.
However, it is very difficult to rule out the existence of small regions of myocardial ischaemia below the level of resolution of the scanning technique which is approximately 8.4 mm (Araujo et al, 1991).
The main limiting factors for the routine use of positive emission tomography are the high cost of setting up and operating the scanner and the requirement for cyclotron generated isotopes.

1.3.4. Left ventricular wall motion evaluation techniques

Regional left wall motion abnormalities during exercise are probably due to transient myocardial ischaemia.
Several cardiac imaging techniques have been employed to detect these abnormalities, including conventional computed tomography scanning with ECG gating (Lipton et al, 1983) and magnetic resonance imaging (Pennell et al, 1990).
However, stress two-dimensional echocardiography and radionuclide ventriculography have been widely found by many investigators to be very accurate in the detection of myocardial ischaemia and are of practical importance and reliable despite the inherent difficulties (Armstrong, 1988). In particular, stress echocardiography is sufficiently validated to be introduced into routine practice, although it requires expensive equipment and well trained personnel (Mazeika et al, 1993).

It has been documented that patients with atheromatous CAD do develop detectable wall motion abnormalities early during myocardial stress (Armstrong,1988; Sheikh et al, 1990).
To date it is generally agreed that clinically important myocardial ischaemia should be associated with a transient regional left ventricular wall motion abnormality.
It is, however, very difficult to understand the significance of the absence of such abnormalities in the presence of symptoms. It might be that there is a spectrum of myocardial ischaemic abnormalities at the lower end of which the left ventricular function is little if at all affected, or alternatively that the changes are so subtle that they are not detected with the techniques available at present.

Chapter 1.4. CORONARY ARTERY RECEPTORS

The effect of the neurotransmitters and vasoactive substances on coronary artery tone may be modified by alterations of receptor function.
Factors modulating coronary artery receptor function may therefore play a role in the pathogenesis of syndrome X. The following is an attempt to briefly review this subject.

1.4.1. Introduction

Human coronary arteries contain receptors mediating contractile responses by calcium influx mechanisms of two types, i.e. 'receptor operated' and 'voltage sensitive' (Bohr, 1973). The receptor operated channel connects the agonist-receptor mediated stimulus with an intracellular store which is at the sarcoplasmic reticulum and is not affected by calcium antagonists. The voltage sensitive channel mediates calcium influx from a pool that is in rapid equilibrium with the extracellular space and is blocked by calcium antagonists (Ginsburg et al, 1984(a)).

Two models have been suggested (Baxter and Funder, 1979).
The first suggests a one to one relationship between receptor occupancy and cellular response, the maximum response occurring when the receptors are fully occupied.
In the second model the maximal cellular response occurs when receptors are less than fully occupied, therefore there are spare receptors.
Regional differences in reception concentration and distribution exist at different levels of the coronary artery tree (Montorsi et al, 1991).

Noradrenaline, after activation of alpha-adrenergic receptors increases the activity of phospholipase C which is an essential step in increasing the cytosolic calcium leading to vascular contraction.
Relaxation of the coronary arteries on the other hand is coupled to many receptors. It is thought that cyclic adenosine-3,5-monophosphate (cAMP) and cyclic guanosine-3,5-monophosphate (cGMP) are involved in receptor mediated coronary smooth muscle relaxation probably through regulation of intracellular calcium uptake (Schultz et al, 1977).

1.4.2. Presynaptic receptors

At the presynaptic level, alpha-adrenergic receptors are widely distributed in the coronary artery microcirculation. Both alpha$_1$ and alpha$_2$-adrenergic subtypes have been shown to cause coronary artery constriction (Heush et al,1984). Subtypes of alpha-adrenergic receptors i.e. a_1a, a_1b, a_2a and a_2b, have differing molecular structure, agonist and antagonist binding characteristics and intracellular effector mechanisms (Minneman,1988). The precise nature and function of alpha-adrenergic receptor subtypes on the endothelium and smooth muscle of coronary microvessels remains, however, unknown.

Classically alpha$_1$-adrenergic receptors are considered to be postsynaptically located and alpha$_2$ presynaptically located (Langer, 1981). Recently this view has been challenged because presynaptic alpha$_1$-adrenergic receptors and postsynaptic alpha$_2$-adrenergic receptors have been identified (Guth et el,1990).
At present there is no consensus regarding the exact contribution of the different receptor subtypes modulating alpha-adrenergic responses of the coronary arteries to a variety of physiological and pharmacological interventions.
Presynaptic alpha$_2$-adrenergic receptor activation inhibits noradrenaline release, a mechanism which probably constitutes a feedback system that regulates sympathetic drive and modulates the neuronal release of noradrenaline (Langer, 1981). Alpha$_2$-adrenergic activation in animals predominantly constricts coronary arterioles as was suggested in a recent study in dogs by Jones and co-workers (Jones et al, 1993). In humans presynaptic alpha$_2$-adrenrgic stimulation of coronary arteries probably mediates vasoconstriction.

In the coronary circulation activation of alpha-adrenergic receptors with noradrenaline produces proportionately similar increases in prearteriolar and arteriolar resistances (Kelley and Feigl, 1978). Chilian has shown that alpha$_1$ and alpha$_2$-adrenergic receptors in the coronary circulation are disributed differently, namely that alpha$_2$-adrenergic receptors are located primarily in coronary arterioles, whereas alpha$_1$-adrenergic receptors are located throughout the coronary tree (Chilian, 1991(a)). The authors suggested that with intact coronary vasomotor tone arterioles escape from the constrictor effects of alpha$_1$ and alpha$_2$-adrenergic agonists, whereas under hypoperfusion coronary arteries do not show such escape mechanisms but they show sustained constriction.

Subtypes of alpha-adrenergic receptors i.e., a_1a, a_1b, a_2a and a_2b have differing mechanisms mediating vasodilatation in the resistance prearteriolar coronary arteries (Vigorito et al, 1986).

A number of other pre-synaptic receptors require mentioning.

Presynaptic $beta_2$-adrenergic receptors, when stimulated mainly by adrenaline, probably facilitate noradrenaline release (Adler-Graschinsky and Langer, 1975).

Presynaptic dopamine receptors exist and when activated they inhibit noradrenaline release from postganglionic sympathetic nerves (Goldberg and Kohli, 1983).

Presynaptic Angiotensin II receptors also exist, and when activated they facilitate the release of noradrenaline (Hughes and Roth, 1971).

Presynaptic muscarinic receptors exist. Stimulation of these receptors in the human epicardial coronary arteries produces vasoconstriction that is probably endothelium-independent (Ginsburg et al, 1984(b)). However, the effect of muscarinic stimulation on the resistance coronary arterioles is not known.

There are also specific prostaglandin presynaptic receptors of the E type which inhibit the release of noradrenaline.

Histamine receptors are of two main classes, $histamine_1$ and $histamine_2$, as was first shown by Ash and Schild (Ash and Schild, 1966). $Histamine_1$ receptors in the human epicardial coronary arteries mediate vasoconstriction (Ginsburg et al, 1984(a)). $Histamine_1$ receptors appear also to mediate occasionally a vasodilatory effect that might involve stimulation of endothelium-dependent relaxing factor release (Godfraind and Miller,1983). [Endothelium-dependent relaxing factor has been shown to be nitric oxide or a nitric oxide containing compound, derived from the endogenous substrate L-arginine (Myers et al, 1990) and it is therefore now always referred to as nitric oxide]. $Histamine_2$ receptors in the human epicardial coronary arteries mediate vasodilatation (Ginsburg et al, 1980).

1.4.3. Postsynaptic receptors

At the postsynaptic level stimulation of $alpha_1$-adrenergic receptors results in vasoconstriction in both arteries and veins, probably by opening receptor operated calcium channels, and coronary artery resistance is increased (Kern et al, 1985). $Alpha_1$-adrenergic constriction occurs throughout the coronary microcirculation, whereas $alpha_2$-adrenergic constriction occurs mainly in arterioles <100 mm in diameter (Chilian, 1991(a)).

Stimulation of $alpha_2$-adrenergic receptors, which are present in both arteries and veins, causes vasoconstriction (Langer and Shepperson, 1982). These receptors respond to noradrenaline in the synaptic cleft by inhibiting further noradrenalin formation in the neuron and acting as a negative feedback.

A number of other post-synaptic receptors also exist and require mentioning.
Coronary artery beta-adrenergic receptors when activated mediate vasodilatation. It was assumed that the subtype involved was $beta_2$. However, a study in the porcine coronary arteries indicates that the majority of beta-adrenergic receptors are of the $beta_1$-adrenergic subtype (Schwartz and Velly,1983). It is, therefore, possible that a mixed population of beta-adrenergic receptors probably exists in the human coronary arteries. Beta-adrenergic receptors are present in arteries but probably not in veins (Francis, 1985).
Postsynaptic $dopamine_1$ receptors exist in arteries including coronary arteries and they modulate vasodilatation (Goldberg et al, 1978).
Postsynaptic Angiotensin II receptors are probably contained in smooth muscle arteriolar vasculature. Activation of such receptors probably causes vasoconstriction (Zimmerman,1978).
Angiotensin II enhances noradrenaline synthesis in the noradrenergic nerve terminal (Boadle et al, 1969) and releases adrenaline from the adrenal medulla (Feldberg and Lewis,1964). It also acts on the adrenal cortex to release aldosterone and stimulates central noradrenaline activity.

Acetylcholine receptors, which are normally activated by vagal stimulation, result in decreased coronary artery resistance and increased coronary artery flow (Feigl, 1969).

$Serotonin_1$ receptors exist and mediate vascular relaxation (Houston et al,1985). In animals serotonin (5-hydroxytryptamine) is a coronary vasoconstrictor (Porquet et al, 1982). Serotonin induced vasodilatation of the resistance coronary arteries is mediated by endothelial $serotonin_1$ like receptors, whereas large epicardial artery constriction involves either $serotonin_1$ like receptors (Ichikawa et al, 1989) or $serotonin_2$ receptors located on vascular smooth muscle cells (Brazenor and Angus, 1982).
$Serotonin_2$ receptors mediate vascular contraction.

Chapter 1.5. ROLE OF ENDOTHELIUM AS A SOURCE OF VASOACTIVE SUBSTANCES

The role of endothelium in the pathogenesis of syndrome X has been extensively investigated. In order to understand the possible mechanisms involved some description of endothelial function and, in particular, of the various endothelium-dependent and endothelium-independent agents is necessary.

1.5.1. Introduction

Coronary artery endothelium plays an active role in regulating vessel structure and function and its importance in controlling coronary flow has been recognised (Furchgott and Zawadzki, 1980). It has been established that normal endothelium behaves like a 'mini gland' and plays an important role in maintaining vessel wall homeostasis, synthesising and secreting a variety of biologically active substances that modulate vascular tone and hence regulating local coronary artery flow (Vane et al, 1990).

Endothelium exerts a regulating action on constriction caused by different stimuli.
There is experimental evidence that intact endothelium limits the constrictor effects of catecholamines, takes up and metabolises noradrenaline, provides a barrier to diffusion into the vessel lumen and inhibits the release of noradrenaline from sympathetic nerves (Cohen and Weisbrod, 1988). It has been reported that when the endothelium is removed from isolated arterial rings the sensitivity to constriction by adrenaline and noradrenaline is increased four to sixfold (Martin et al, 1986).
Endothelium-dependent relaxation probably modifies $alpha_1$-adrenergic constriction responding to shear stress during microvascular constriction by releasing nitric oxide. Endothelium-dependent vasodilatation is impaired in a number of conditions. In atherosclerosis abnormal epicardial coronary artery vasomotion has been demonstrated (Zeiher et al, 1991(a)). Furthermore, it has been shown that in patients with CAD there is endothelial dysfunction not only of the diseased segments but also in angiographically normal coronary arteries (Werns et al, 1989).

Hypercholesterolaemia has been shown to limit vasodilatation in both animal models and humans and there is impairment of the endothelium in modulating the tone of epicardial coronary arteries (Drexler et al,1991).

Furthermore, endothelial function in angiographically smooth coronary arteries in the presence of hypercholesterolaemia has been examined and found to be impaired (Zeiher et al, 1991(b)).

In patients with systemic hypertension and in animal models vasodilatation is attenuated (Panza et al, 1990).
Patients with normal epicardial coronary arteries but with risk factors for atherosclerosis like cigarette smoking and hyperlipidaemia show impaired endothelial-dependent responses (Vita et al, 1990(a)). Cigarette smoking is also associated with enhanced alpha-adrenergic constriction due to endothelial constriction in atherosclerotic patients (Winniford et al, 1986). In diabetes mellitus impaired endothelium response is present (Saenz de Tejada et al, 1989). Furthermore, hyperinsulinaemia has been demonstrated in syndrome X (Dean et al,1991).
In heart failure endothelium-dependent vasodilatation is impaired (Kubo et al,1991).
In dilated cardiomyopathy coronary artery dilatation is also impaired (Treasure et al,1990).
Finally, it has recently been suggested that endothelial dysfunction may be significantly implicated in the pathogenesis of syndrome X (Motz et al, 1991; Quyyumi et al, 1992).

1.5.2. Endothelium-dependent vasodilators

The endothelium releases vasodilators in response to alpha$_2$-adrenergic receptor agonists, increased blood flow and other factors (Furchgott, 1983; Cocks and Angus, 1983).
One of the major endothelium-dependent vasodilators, which was discovered in 1980 by Furchgott and Zawadzki, is nitric oxide and its existence in the human coronary arteries has been established (Furchogtt and Zawadzki, 1980).
Nitric oxide is secreted by the endothelium in response to muscarinic receptor stimulation by a large number of neurohumoral substances, hormones, and autacoids. These include adrenaline, noradrenaline (Cocks and Angus 1983), acetylcholine (Furchgott, 1983), histamine (Van de Voorde and Leusen, 1982), arginine vasopressine, bradykinin, and serotonin (Cohen et al, 1983).

Additionally, stimulation of muscarinic, alpha$_2$-adrenergic, histaminergic, purinergic, serotonin$_1$ and thrombin receptors which occur in endothelial cells, also enhances the secretion of nitric oxide (Vanhoutte, 1987). A variety of stimuli, including increased blood flow and shear stress can also trigger the same chain of events.

An absolute requirement for the endothelium to respond is to be intact anatomically and functionally; otherwise it loses its ability to respond to the above mentioned stimuli or to produce and secrete the appropriate, for the circumstances, amount of nitric oxide.

By direct action on coronary smooth muscle nitric oxide causes relaxation mainly by stimulating cGMP and subsequently vasodilatation when there is a local need for increased blood flow.

Nitric oxide has a short half life of about 4-6 seconds and is inactivated by haemoglobin (Griffith, 1985). It is thought to act locally by diffusion, rather than remotely by blood circulation. Nitric oxide release probably modulates resting coronary artery microvascular tone and opposes the constrictor action of catecholamines. It thus modulates alpha$_1$-adrenergic constriction mainly in arterioles and alpha$_2$-adrenergic constriction in small prearteriolar coronary arteries.

Nitric oxide inhibits noradrenaline release from adrenergic nerves in rabbit carotid arteries and dog mesenteric arteries (Cohen and Weisbrod, 1988). It is probable that alpha$_1$-adrenergic activation may mediate nitric oxide release (Jones et al, 1993). However, at present we cannot say with certainty how nitric oxide modulates, in human coronary arteries, alpha$_1$ and alpha$_2$-adrenergic constriction (Bertolet and Pepine, 1991; Vrints et al,1992).

Recently Quyyumi and colleagues investigated the contribution of nitric oxide to human coronary epicardial vessels and microvessels in a group of patients with chest pain and angiographically normal or near normal epicardial coronary arteries during pacing (Quyyumi et al, 1995). They assessed endothelium-dependent vasodilatation with intracoronary acetylcholine and endothelium-independent dilation with intracoronary sodium nitroprusside and adenosine. Measurements were repeated after the administration of the nitric oxide inhibitor N^G-monomethyl-L-arginine (L-NMMA). Their findings demonstrated that during metabolic stimulation of the human heart nitric oxide release contributes significantly to microvascular dilatation and is almost entirely responsible for the epicardial vasodilation.

Another similar vasodilator, an endothelium-derived hyperpolarization factor (EDHF) has been described (Taylor and Weston,1988). EDHF probably causes an increase in the rate of efflux of intracellular K^+, producing cellular hyperpolarization and vascular relaxation.

Acetycholine is the principal neurotransmitter released at the synapse between the pre- and the postganglionic neurons where its synthesis also takes place (Shepherd and Vanhoutte, 1979). It is stored in vesicles in the nerve terminals.
Acetylcholine is a potent coronary dilator in anatomically normal coronary arteries in vivo due to nitric oxide release (Ludmer et al, 1986). In contrast, however, in atherosclerotic coronary arteries it causes vasoconstriction.
Acetycholine causes dilatation by a combination of two completely different mechanisms. Firstly, it causes vascular relaxation by nitric oxide via the accumulation of cGMP. Secondly, it causes vascular relaxation produced by nitric oxide, via cellular hyperpolarisation (Ginsburg and Zera,1984).
Acetylcholine also causes vasoconstriction by direct action on the arteriolar smooth muscle. Consequently, the balance of its effects on the smooth muscle and the endothelium decides whether vasodilatation or vasoconstriction is the net result.

A number of prostaglandins are powerful vasoactive agents and cause coronary artery dilatation. These substances are locally produced, short-lived and are therefore suitable for regulating blood flow. In the normal heart they act to minimise the effects of systemic vasoconstrictor activity but this mechanism is not powerful enough to lessen the degree of vasoconstriction. They modulate the effects of vasoactive agents such as vasopressin, Angiotensin II and noradrenaline which in turn may modulate the effects of bradykinin and the arachidonic acid metabolites.
Prostaglandin PGI_2, i.e. prostacycline, is a coronary dilator and an inhibitor of platelet aggregation. It is synthesised in the vascular wall, mostly in the endothelial layer, from cyclic endopoxides which are formed from arachidonic acid (Needleman and Kaley, 1978). Prostaglandin PGE_2 is also a coronary vasodilator (Needleman and Kaley, 1978). They both have a prejunctional inhibitory effect on the release of noradrenaline and this is probably the mode of their vasodilatory function (Needleman and Kaley, 1978).

A number of other endothelium-dependent agents require mentioning.

The kallikrein-kinin system is an enzyme system that is capable of generating the vasodilator peptide bradykinin from naturally occurring substrates.

Bradykinin is a powerful coronary vasodilator (Cocks and Angus, 1983). The vasodilatory effect appears to be related to the production of prostaglandin PGE_2 and prostacyclin. The substance is rapidly destroyed by a myocardial bradykinase (Needleman and Kaley,1978).

Substance P, which is obtained in sympathetic C fibre afferents, is a vasodilator (Franco-Cereceda, 1988). Cocks and Angus, in isolated coronary arteries of pigs, demonstrated that in all endothelium-intact rings of artery substance P inhibited the contraction induced by serotonin and noradrenaline. However in rings where endothelium was removed, substance P had no effect (Cocks and Angus,1983).

1.5.3. Endothelium-dependent vasoconstrictors

Endothelium produces and releases endothelin which is an endothelium-derived constricting factor (EDCF) (Rubanyi and Vanhoutte, 1985).

It is a 21-aminoacid peptide which has been isolated, sequenced and shown to be a potent vasoconstrictor, approximately 450 times more potent than noradrenaline (Yanagisawa et al, 1988).

The substance is also synthesized by neurons in the paraventricular nucleus of the hypothalamus and stored in the posterior pituitary (Yoshizawa et al, 1989). Production and release is stimulated with thrombin and catecholamines (Yang et al, 1990). Emori and colleagues have also found that Angiotensin II, vasopressin and protein kinase C activation increased the amount released (Emori et al, 1989).

Endothelin release from endothelial cells is triggered by local haemodynamic factors such as changes in shear stress and/or pressure. The vasoconstrictor effect lasts longer compared to the other vasoconstrictor peptides.

1.5.4. Endothelium-independent vasoactive substances

Superimposed on the above endothelium-dependent substances are the effects of a number of circulating hormones and agents, which are not dependent on endothelium and are produced locally from cell membranes and platelets. The storage granules in the nerve endings contain and release not only noradrenaline but also dopamine, vasoactive intestinal polypeptide, substance P, and neuropeptide Y. The physiological role of many of these agents in coronary flow regulation is not quite clear, although their presence has been identified in the myocardium (Marcus, 1983).
Furthermore, the interaction of these substances and the possible potentiation or otherwise of other vasoactive substances is a matter of speculation. In any case these agents may be active even in low concentrations and most probably affect the coronary artery tone.

1.5.5. Endothelium-independent vasodilators

In the human coronary arteries, atrial natriuretic peptide mediates coronary artery dilatation by activating particulate granulate cyclase to form cGMP (Ljung and Kjellstedt, 1987). This 28-amino peptide is released from granules from the cardiac atria, especially the right, and binds to receptors in various tissues including the vascular endothelium (Napier et al, 1984). The sympathetic nervous system probably potentiates its release from the heart. Once released, atrial natriuretic peptide not only exerts direct vasodilatation but also antagonises the action of most endogenous vasoconstrictor substances. There is experimental evidence that atrial natriuretic peptide inhibits the release of noradrenaline from nerve endings as well as the vasoconstrictor effect of noradrenaline on systemic vessels.
Additionally, it inhibits the activation of the renin-angiotensin system. The vasodilatory effect of atrial natriuretic peptide is considered to be generally mild and it probably modulates the effects of endogenous vasoactive substances to achieve homeostatic balance.
Atrial natriuretic peptide antagonises the vasoconstrictor effect of noradrenaline and Angiotensin II.

Serotonin can act as either a vasodilator or a vasoconstrictor. It may dilate coronary artery resistance vessels, especially with diameter <100mm, but may cause constriction of the larger conductance coronary arteries (Lamping et al, 1989). Serotonin induced vasodilatation is mediated by endothelial serotonin$_1$-like receptors (Ichikawa et al, 1989)

Adenosine is generally considered to be important in regulating the coronary circulation, although its exact role is not absolutely clear (Berne, 1980). It is a potent vasodilator in the human epicardial coronary arteries through action on the alpha$_2$-adrenergic receptors (Wilson et al, 1990).
However, the effect on the prearteriolar coronary resistance vessels is not known, although it has been reported that it dilates arterioles with diameters <100 microns (Chilian, 1991(b)).
It is assumed that the formation and release of adenosine is increased under conditions of increased myocardial oxygen demand or decreased oxygen supply or increased myocardial performance (Nees,1989). Local increase in interstitial adenosine then causes stimulation of adenosine receptors of the coronary arteries and dilatation of the adjacent blood vessels (Clarke and Coupe, 1989). The adenosine is then rapidly removed, partly by uptake by endothelial cells, muscle cells and red blood cells and partly by degradation to inosine and hypoxanthine.
Emdin and colleagues investigated the effect of aminophylline in a group of patients with syndrome X, with a dose sufficient to inhibit adenosine receptors, exercise-induced symptoms and ischaemic ECG changes. They hypothesised that there was probably inappropriate adenosine release on exercise in the presence of increased coronary resistance at the level of small intramural coronary arteries which was prevented by aminophylline (Emdin et al, 1989).
Adenosine possesses marked cardioprotective properties. The mechanisms for its beneficial effects, however, are not clear. These not only include the above mentioned coronary arteriolar dilatation but also modulation of catecholamine activity.
There is probably an alteration in the cellular response to catecholamine stimulation but this does not adequately explain its properties (Murry et al, 1991).

A number of other endothelium-independent vasodilators also require mentioning.
Calcitonin gene-related product can produce powerful vasodilatation. It is a neuropeptide derived from alternative processing of the primary transcript of the calcitonin gene. It is contained in sympathetic C fibre afferents (Franco-Cereceda, 1988).

Vasoactive intestinal polypeptide is contained in postganglionic parasympathetic fibres. Vasoactive intestinal polypeptide probably mediates vasodilation in the coronary arteries of animals (Anderson et al, 1988). Its effect on the human coronary artery circulation is unknown. However, it is believed that it facilitates the production of nitric oxide.

Sodium nitroprusside is an endothelium-independent nitrovasodilator and smooth muscle relaxant (Quyyumi et al, 1992).

Papaverine is an endothelium-independent dilator (Franco-Cereceda, 1988).

Neurokinin A is also a vasodilator (Franco-Cereceda, 1988).

Parathyroid hormone has an arterial vasodilatory effect, but its effect on the coronary arteries is not well known.

Progesterone causes direct vasodilatation (Kumar, 1962). However, its effect on the coronary circulation is not known.

Potassium has a direct vasodilatory effect on arterioles. It also alters the central nervous function resulting in decreased plasma noradrenaline levels.

1.5.6. Endothelium-independent vasoconstrictors

A considerable number of prostaglandins cause vasoconstriction.

Thromboxane A_2, which is produced by conversion of endopoxides by platelets, is a potent vasoconstrictor and causes platelet aggregation (Needleman and Kaley, 1978). Platelets also release another powerful vasoconstrictor, serotonin, and the two substances are probably acting in a synergistic fashion to stimulate platelet activity and smooth muscle vasoconstriction. Such an action has been demonstrated in dog coronary arteries in vivo (Ashton et al,1987).

Another prostaglandin, namely PGF_{2a}, also causes vasoconstriction and platelet aggregation. Prostaglandin PGD_2 and Leucotriene D_4 are also powerful vasoconstrictor agents.

There is evidence that the renin-angiotensin system plays an important role in controlling the vascular tone (Magrini et al, 1988).

Angiotensin II is an arteriolar constrictor peptide (Bevan and Brayden, 1987). It can activate the sympathetic nervous system by increasing the biosynthesis of catecholamines, facilitating neurotransmitter release, inhibiting the re-uptake of noradrenaline and potentiating the vascular responses to neurotransmitters (Ramsay, 1982).

Arginine vasopressin is an octapeptide hormone produced by the supraoptic, paraventricular and filiform nuclei of the anterior hypothalamus. Arginine vasopressin has a direct potent vasoconstrictor action (Goldsmith, 1987). It is probably capable of influencing local tissue perfusion. However, regional vascular beds pose different sensitivities to arginine vasopressin. It is also thought to function as a neurotransmitter and/or a neuromodulator. The effect of arginine vasopressin on coronary arteries is not well known.

Neuropeptide Y is a 36-amino acid peptide which is widely distributed in the brain and spinal cord, adrenal medulla and peripheral sympathetic nerves (Waeber et al, 1988). It is contained in the postganglionic nerve terminals and in perivascular nerve terminals together with noradrenaline (Varndell et al, 1984). This striking association between the distribution of neuropeptide Y and noradrenaline provides evidence that neuropeptide Y may play a role in the modulation of noradrenaline release.
The release of neuropeptide Y is augmented by the $alpha_2$-adrenergic receptor antagonists and attenuated by $alpha_2$-adrenergic receptor agonists (Pernow et al, 1987).
The action of neuropeptide Y on the coronary arteries is important. Tseng has has observed strong coronary artery constriction in the presence of neuropeptide Y and suggested that the effect of neuropeptide Y on coronary arteries is not dependent on $alpha_1$-adrenergic receptor stimulation, beta-adrenergic receptor stimulation or on the release of cyclooxygenase products (Tseng et al, 1988). Its action predominantly is to potentiate the vasoconstrictor effects of a variety of substances including noradrenaline. Neuropeptide Y probably regulates the release of noradrenaline from central adrenergic neurons and its action with noradrenaline is synergistic.
Additionally, it has direct vasoconstrictor properties independent of simultaneous adrenergic stimulation. It also plays a part in regulating the release of other vasoactive hormones like atrial natriuretic peptide and Angiotensin II. It has not been determined whether the neuropeptide Y response is endothelium-dependent or not, but it has been suggested that neuropeptide Y may also modulate adrenergic neurotransmission by an endothelium-dependent mechanism (McDermott et al,1993).
Clarke and colleagues showed in a group of patients with angina pectoris that the intracoronary administration of neuropeptide Y caused reduction in the diameter of epicardial coronary arteries and a significant increase in coronary artery resistance (Clarke et al, 1987). This observation indicates that the primary vasoconstrictive effect in the coronary artery tree is probably localised in small coronary arteries.

Serotonin is liberated from platelets and is also found in the gut and in the central nervous system. Serotonin intensifies vasoconstriction of the epicardial coronary arteries, involving either serotonin$_1$ like receptors or serotonin$_2$ receptors (Ginsburg et al, 1984(b)). It causes, when liberated during platelet aggregation, vasoconstriction of the large epicardial coronary arteries, especially when the endothelium is damaged (Lamping et al, 1989).

Serotonin potentiates collagen and adrenaline induced platelet aggregation in a synergistic manner and also amplifies contractions induced by thromboxane A_2 in canine coronary arteries (Ashton et al, 1986; Ashton et al, 1987). The synergistic effect with thromboxane A_2 has already been mentioned (Chester et al, 1993). It is also reported to be involved in coronary spasm in animal models (Ashton et al, 1986).

SECTION 2

Chapter 2.1. PROPOSED PATHOPHYSIOLOGIC MECHANISMS FOR SYNDROME X

Several mechanisms have been proposed in an attempt to explain the pathogenesis of syndrome X. However, despite the extensive investigative effort, the underlying pathophysiology remains incompletely understood (Maseri et al,1991(b); Cannon et al, 1992; Kaski et al,1995).
The following is an attempt to review the vast literature on this subject.

2.1.1. Hyperventilation - Mental stress

Forced hyperventilation produces hypocapnia, i.e. reduction in arterial pCO_2 and respiratory alkalosis. Furthermore, hyperventilation per se has been shown to induce ST segment depression (Lary and Goldschlanger, 1974).
Alkalosis, which is associated with hyperventilation, can also induce coronary vasoconstriction (Takaoka et al, 1988).

It has been suggested that hyperventilation might be a possible cause of symptoms in syndrome X patients (Chambers et al, 1988). In the latter study, hyperventilation reproduced pain in about 50% of patients with chest pain and normal coronary arteries (Chambers et al, 1988).
Similarly, Bass and colleagues showed that not only hyperventilation, but also anxiety and stress can produce chest pain and ischaemic ECG changes in syndrome X patients (Bass et al, 1988). To explain this phenomenon a diffuse abnormal epicardial coronary artery constrictor response has been suggested (Bugiardini et al, 1987).
In a recent study Chauhan and co-workers have also shown that both hyperventilation and mental stress can produce chest pain in patients with syndrome X which is associated with a reduction in coronary blood flow (Chauhan et al,1993(a)). In the same study the authors found increased plasma levels of catecholamines in the patients that experienced chest pain on hyperventilation and suggested that this may cause an increase in microvascular resistance leading to a reduction in coronary blood flow.
However, these observations have not been confirmed by others (Lewis et al, 1991). The authors found that forced hyperventilation did not induce chest pain or ischaemic electrocardiographic changes, but only hypocapnia and respiratory alkalosis. They also reported that there was no evidence of inappropriate hyperventilation, either at rest or on exercise, but of appropriate hyperventilation as a result of an increased physiological dead space.

The authors concluded that inappropriate hyperventilation is not the cause of symptoms in this condition. Moreover, the syndrome X patients showed reduced maximum oxygen consumption and metabolic acidosis at peak exercise supporting the existing evidence of cardiac dysfunction in syndrome X.
To date there is no evidence to support the view that hyperventilation is implicated in the pathogenesis of the syndrome.

2.1.2. Psychiatric disorders

It has been suggested that in some cases of syndrome X the manifestations can be attributed to psychiatric disorders (Bass et al, 1983; Lantinga et al,1988). However, to date there is only very limited evidence to support this view.

2.1.3. Abnormal affinity of the red blood cells to haemoglobin

Eliot and Bratt suggested that an abnormal affinity of the red blood cells of haemoglobin for oxygen might be responsible for the ischaemic manifestations of syndrome X (Eliot and Bratt, 1969). They studied 15 patients with angina, normal coronary arteriograms and electrocardiographic evidence of ischaemia, and 14 of them were reported to have abnormal haemoglobin-oxygen dissociation curves.
However, the existence of a defect of haemoglobin dissociation curve is disputed for several reasons (Vokonas et al, 1974). If such a defect exists, it would be expected to cause firstly, a high resting coronary blood flow, secondly, low oxygen extraction and thirdly, high coronary venous oxygen content, which was not the case in the syndrome X group of patients that Eliot and Bratt studied.

2.1.4. Difficulties and limitations of interpreting coronary arteriography

Misinterpretation of coronary arteriograms has been suggested as a possible explanation for the occurrence of syndrome X (James, 1970).
Alternatively, according to this theory, syndrome X may be due to myocardial ischaemia caused by occlusive disease of small coronary arteries not visualised by coronary arteriography (James, 1977).
It should be borne in mind that angiography cannot detect abnormalities of vessels less than 400 microns in diameter and that electromicroscopy and light histology of biopsies visualises vessels less than 150 microns in diameter and therefore it is not possible to detect abnormalities of intermediate size.

2.1.5. Hyperdynamic ventricular contraction

Hyperdynamic ventricular contraction, resulting in increased myocardial oxygen consumption, has been proposed as a possible mechanism for the manifestations of this entity (Pepine et al, 1974).
Recently, Tousoulis and colleagues examined the left ventricular function at rest in a group of patients with syndrome X and related it to exercise capacity and ECG changes on exercise testing and ambulatory ECG monitoring (Tousoulis et al, 1993).
Their results showed that approximately one third of these patients had hyperdynamic left ventricles at rest associated with the development of ischaemic ECG changes on exercise at a lower heart rate and work load. These observations favour the hypothesis that increased sympathetic activity may play a role in the pathogenesis of the syndrome.

Although hyperdynamic ventricular contraction may contribute to the manifestations of the syndrome in some cases, there is not enough evidence to suggest that it is causally associated with the pathogenesis. Furthermore, beta blockers have no beneficial effect in abolishing either the pain or ischaemic ECG changes.

2.1.6. Hypercholesterolaemia

There is accumulating evidence from the literature for the role of hypercholesterolaemia on the function of vessels. In humans, studies have shown that high plasma levels of cholesterol and also other risk factors are associated with abnormal vasodilator responses, not only in patients with angiographically proven atherosclerosis but also in persons with normal vessels (Vita et al, 1990(a); Zeiher et al, 1991(b)).

Casino and colleagues recently showed that patients with high cholesterol levels have impaired endothelium-dependent vasodilation probably due to a defective nitric oxide (Casino et al, 1993).
Animals fed with cholesterol also show attenuation of endothelium-dependent vasodilation before and after the development of atherosclerosis (McLenachan et al, 1991).
The hypothesis that cholesterol might influence the vasomotion of angiographically normal coronary arteries was proposed recently by Seiler and colleagues. They showed that in a group of patients with normal epicardial arteries, hypercholesterolaemia impaired exercise-induced coronary dilation (Seiler et al, 1993).

They speculated that although the precise mechanism by which the impaired vasomotion is mediated is unknown, a direct negative effect of hypercholesterolaemia on endothelial function of early atherosclerosis resulted in the attenuation in the release of endothelium-derived relaxing factors.
Tanner and colleagues have shown that oxidised LDL cholesterol inhibits endothelium-dependent relaxation of coronary arteries, and may activate scavenger receptors on endothelial cells and inhibits the receptor-operated formation of nitric oxide in epicardial coronary arteries (Tanner et al, 1991).

2.1.7. Left ventricular function abnormalities - Dilated cardiomyopathy

Most patients with syndrome X have normal left ventricular function and a good prognosis (Arbogast and Bourassa, 1973; Kemp et al, 1973(a)).
Picano and co-workers used dipyridamole infusion rather than exercise and performed two-dimensional echocardiography which revealed the absence of impaired left ventricular functional reserve (Picano et al, 1987).
Nadazdin and colleagues studied a group of patients with syndrome X using two-dimensional echocardiography and doppler during dipyridamole infusion (Nadazdin et al, 1991). None of their patients had any evidence of regional wall motion abnormalities, despite dipyridamole-induced ST segment depression. The authors thought that the absence of regional wall motion abnormalities indicated that the myocardial ischaemia present was diffuse, rather than regional.
Recently, Nihoyannopoulos and colleagues also carried out two-dimensional stress echocardiography and atrial pacing, at rest and immediately post-exercise, in a group of syndrome X patients and a normal control group (Nihoyannopoulos et al, 1991). They found that none of the patients exhibited regional wall motion abnormalities, despite the presence of ischaemic electrocardiographic abnormalities and the occurrence of concomitant angina. In their study, images were obtained within a minute after terminating the exercise test, while the ST segment was still depressed.

The above echocardiographic studies, showing that the left ventricular function is normal in syndrome X, are in disagreement with a number of studies suggesting that regional wall motion abnormalities occur (Legrand et al, 1985; Schofield et al, 1986). Such abnormalities are similar to those concomitant wall motion abnormalities exhibited in patients with CAD due to atherosclerosis, who develop chest pain and ischaemic changes on exercise (Sheikh et al, 1990).

A significant percentage of patients (20% to 50%) also have abnormalities of left ventricular function during exercise, when assessed by radionuclide angiography, even when electrocardiographic evidence of myocardial ischaemia is lacking (Schofield et al, 1986; Favaro et al, 1987). Some syndrome X patients also develop such abnormalities after intravenous infusion of dipyridamole (Korhola et al, 1977; Meller et al, 1979).
In a recent study of Yoshio and colleagues (Yoshio et al, 1993) left ventricular functional reserve was evaluated using the continuous radionuclide ventricular function monitor. The authors reported that patients with syndrome X have well preserved left ventricular function before ST segment depression occurs, whereas after ST segment depression appears, it becomes progressively impaired with an increasing degree of ST segment depression, and that the left ventricular dysfunction persisted well into the recovery period.

There are also some reports on findings of left and right ventricular biopsies in patients with syndrome X suggesting that there are no histological abnormalities.
Richardson and colleagues in 1974 reported seven syndrome X patients in whom endomyocardial biopsy specimens showed no vascular abnormalities of coronary vessels less than 150 microns in diameter (Richardson et al, 1974).
Opherk and co-workers took myocardial biopsies from the left ventricular wall and showed normal intramyocardial vessels, arterioles, metarterioles, capillaries and venules (Opherk et al, 1981). No structural myocardial cell abnormalities could be demonstrated with the only exception being mitochondrial swelling, combined with deposits of small myelin figures.
The absence of histologic coronary vessel abnormalities was also later confirmed by other studies (Kubler and Opherk, 1985).

However, there are some reports in a small number of syndrome X cases suggesting that there are some histological abnormalities. Pasternac and Bourassa reported that a myopathic process may play a part in the pathogenesis (Pasternac and Bourassa, 1983).
Similarly, Opherk and co-workers later reported that patients with syndrome X may develop dilated cardiomyopathy (Opherk et al, 1989). They followed up, over a period of four years, a group of 40 patients with typical effort-related anginal pain, normal coronary arteries and a reduced coronary artery dilatory capacity and assessed their left ventricular function during exercise by gated blood pool scintigraphy.

In this study all subjects had normal left ventricular function at rest, but a subset of patients with left bundle branch block demonstrated deterioration of left ventricular ejection fraction over this period (>5% change in left ventricular ejection fraction, exercise pulmonary pressure, progressive left ventricular dilation), suggesting a possible co-existent cardiomyopathic process. In contrast, the subgroup with apparently ischaemic ECG responses to exercise showed preserved left ventricular function.

Also, Romeo and colleagues reported a deterioration of left ventricular function at follow-up in eight patients with syndrome X and left bundle block branch presentation (Romeo et al, 1993).

The conflicting results of the above studies might be attributed to the fact that they might have included heterogeneous groups of patients.

A decline in left ventricular function with time in some patients with syndrome X was also demonstrated in another follow-up study (Cannon et al, 1991).

The left ventricular function deterioration over the 4 1/2 year period observed in a significant percentage of the patients studied (25%) was regardless of the presence or absence of evidence of myocardial ischaemia on exercise testing.

In contrast to Opherk's study the worsening in resting left ventricular function was not restricted to patients with left bundle block. Patients with conduction abnormalities were not included in this study.

Left ventricular endocardial biopsies were also carried out in a subset of patients and showed patchy fibrosis interspersed with myocellular hypertrophy, even in normotensive subjects, but in no case evidence of inflammation or amyloid deposition.

Slight endocardial biopsy abnormalities were also reported by Van Hoeven and Factor (Van Hoeven and Factor, 1990).

Mosseri and co-workers suggested that patients with syndrome X may have histologic abnormalities of the small coronary vessels but this conclusion is controversial as a significant number were hypertensive and had left ventricular hypertrophy (Mosseri et al, 1986).

2.1.8. Coronary arterial spasm of the large epicardial arteries

Boden and colleagues suggested that coronary artery spasm might be implicated in the pathogenesis of syndrome X (Boden et al, 1981).
Kemp and colleagues later reported that patients with syndrome X have exercise-induced vasoconstriction of the epicardial coronary arteries which would not be observed on coronary arteriography (Kemp et al, 1986).
Further evidence comes from the work of Bortone and colleagues, who also have reported an abnormal reaction of the epicardial coronary arteries to physical exercise in syndrome X patients (Bortone et al,1989).
In disagreement with the view that coronary artery spasm might be a contributory factor, Cannon and co-workers have not observed significant coronary narrowing of the epicardial coronary arteries after provocation with ergonovine (Cannon et al, 1987).
Nonetheless, the possibility that epicardial coronary artery spasm or diffuse vasoconstriction is implicated in the pathogenesis is unlikely because these phenomena are generally believed to cause the so called 'variant angina', which is not usually effort-induced and is not accompanied by reduced coronary dilator capacity during the angina-free periods (Feldman et al, 1980).
Furthermore, ST segment elevation which is typical in this condition is not a feature of syndrome X. Therefore, syndrome X patients should be regarded as a separate group from those referred to as having 'variant angina' who may have a different underlying pathogenic mechanism.

2.1.9. Small vessel disease

On theoretical grounds it is possible to suggest that the impaired coronary flow reserve and signs of ischaemia observed in syndrome X patients are likely to be caused by a disease of the small coronary arteries. Such a 'disease' might be organic or functional.
Richardson and colleagues excluded the presence of atheromatous changes and showed no structural abnormalities in the very small coronary arteries, i.e. in vessels less than 150 microns in diameter (Richardson et al, 1974).
Opherk and colleagues examined left ventricular catheter biopsy specimens in a group of patients with syndrome X and found no evidence of small coronary artery abnormalities; arterioles, metarterioles, capillaries and venules were all normal (Opherk et al,1981).

The only histologic abnormalities which were observed were alterations of mitochondria, varying from moderate separation of cristae to severe vacuation and swelling .
The same group noticed later in another study that there were no structural abnormalities of the small coronary vessels (Kubler and Opherk, 1985).

It was Selzer and colleagues, in 1977, who put forward the possibility that CAD of the small coronary vessels not visualised by coronary arteriography is possibly the cause of the syndrome (Selzer, 1977).
Small vessel histological abnormalities have only been reported in patients with additional abnormalities who probably have myocardial diseases of various aetiologies (Mosseri et al, 1986; Van Hoeven and Factor, 1990). This is probably because a significant number of the syndrome X patients that they studied had hypertension and evidence of left ventricular hypertrophy.

A body of opinion favours morphological abnormalities of the small coronary vessels as a secondary phenomenon, rather than the actual cause of the disease (Cannon et al, 1983; Cannon et al, 1987; Maseri et al, 1991(b)).
It should also be considered that neither angiography or electromicroscopy and light histology of biopsies can detect abnormalities of intermediate size coronary vessels. These arteries could conceivably be the site of abnormalities responsible for ischaemia in some patients with syndrome X.
At present the evidence that there is a flow-limiting structural abnormality of the small coronary arteries is slender and there is accumulating evidence that if such an abnormality exists, it is probably functional.

2.1.10. Abnormal cardiac metabolism

Metabolic abnormalities as an index of myocardial ischaemia have been reported in patients with syndrome X and it has been suggested that this may be causally associated with its pathogenesis (Kemp, 1973(a); Boudoulas et al, 1974).
However, recently the view has been supported that although metabolic abnormalities might be implicated in the mechanisms involved in the development of some cases with this condition, syndrome X probably encompasses several pathophysiological disease entities (Cannon et al, 1992).

Lactate production as an index of myocardial ischaemia has been demonstrated in 13% to 100% of patients with syndrome X (Cannon et al, 1992).
Such an abnormal handling probably favours the presence of myocardial ischaemia in some cases of syndrome X (Boudoulas et al, 1974; Opherk et al, 1981; Cannon et al, 1983; Opherk et al, 1989). However, a causal association has not been proved.

Arbogast and Bourassa showed lactate production during atrial pacing in five out of ten patients with syndrome X that they studied (Arbogast and Bourassa, 1973).
Cannon and colleagues made lactate measurements during atrial pacing (Cannon et al, 1983). The authors reported that lactate consumption (arterial lactate concentration minus great cardiac vein lactate concentration multiplied by flow) was significantly lower in those patients with a microvascular constrictor response to ergonovine than those without such response and that actual lactate production was demonstrated in only 10% of patients.
Evidence of abnormal lactate production was also obtained by Greenberg and colleagues during atrial pacing in a subset of patients with syndrome X (Greenberg et al, 1987). The subset with pacing-induced lactate production had significantly less increase in coronary sinus venous flow (thermodilution measurement) in response to pacing that the subset of patients without lactate production.

These studies contrast with the work of Camici and colleagues (Camici et al, 1991). In this study they investigated myocardial metabolism by using pacing-induced angina in a group of women with typical anginal pain, positive exercise tests and normal coronary arteries and a control group consisting of patients with chest pain but negative ECG responses to exercise. It was reported that in their syndrome X patients, there was no evidence of myocardial lactate production and that there was a positive rather than negative relation between cardiac work and lactate extraction. Lactate was also extracted to a similar extent in the control group.
However, the authors demonstrated that in syndrome X patients glycerol was extracted more efficiently, puryvate less efficiently, and that significant myocardial extraction of alanine and greater carbohydrate oxidation of lipids occurred.
Such a metabolic pattern is perhaps more compatible with increased lipid oxidation and may be due to enhanced sympathetic drive, rather than ischaemia per se.

Many patients with this condition also have abnormal lactate production during infusion of isoprotenerol (Cannon et al, 1985(a)).
It should be noted as well that some patients with chest pain and normal coronary arteries demonstrate decreased lactate production as a response to increased myocardial demand since lactate is used as a metabolic substrate.

However, it is not always easy to interpret lactate measurements. The timing of sampling is very important since after ischaemia there is a washout of lactate. Arteriovenous differences also may be misleading because lactate is consumed by the normal heart.
Lactate measurements may indicate myocardial ischaemia with some certainty only when coronary sinus blood concentration is greater than the concentration in the arterial blood.
Another reason for the difficult interpretation of lactate measurements in syndrome X is the association in some cases with hyperinsulinaemia (Dean et al, 1991).
This is because it is possible in these cases that myocardial handling of glucose and lactate is abnormal because of higher circulating levels of gluconeogenetic substrates, such as alanine and lactate, as has been shown in non-insulin dependent diabetes mellitus (Consoli et al, 1990).
Insulin resistance has also been reported in patients with chest pain and normal coronary arteries and will be dealt with in section 2.1.13.
A focus of interest has also been centered around potassium handling and will be dealt with in section 2.1.11.

2.1.11. Abnormal potassium handling - "Normal phenomenon"

It has been postulated that syndrome X might be attributable to either myocardial ischaemia or a normal phenomenon due to abnormal potassium handling.
Poole-Wilson and colleagues have suggested that the manifestations of the syndrome might represent a 'normal phenomenon' and could be explained in terms of an abnormality of potassium flux across the cardiomyocyte membrane resulting in accumulation of potassium into the extracellular space (Poole-Wilson and Crake, 1989; Holdright et al, 1992). Failure to correct the rise in extracellular potassium may bring about changes of the action potential and may register as ST segment shift in the ECG. Such a biochemical lesion could also account for the manifestation of chest pain (Poole-Wilson and Crake, 1989; Holdright et al, 1992).

2.1.12. Steal phenomenon

A steal phenomenon, which has been well described in CAD, (Klocke, 1983) has been put forward as a possibility to explain the pathogenesis of syndrome X.
It has been suggested that in sites of inappropriately high resistance at the prearteriolar level of the coronary artery tree, a 'steal' effect could occur between the endocardium and the epicardium, with increases in flow away from the subendocardium and preferentially to the subepicardium (Epstein and Cannon, 1986).
This phenomenon usually depends on a decrease in coronary perfusion pressure when flow is prevented from increasing, from whatever cause. Interaction between the decreased intravascular distending pressure and extravascular compressive forces which are highest at the subendocardium results in passive redistribution of flow away from the subendocardium (Epstein and Cannon, 1986). Transmural myocardial blood flow 'steal' effect can develop during metabolic and pharmacological arteriolar vasodilatation (Cannon et al, 1990(b)).

Maseri and colleagues agreed with this concept. According to their theoretical model transmural myocardial blood flow steal can occur during metabolic or pharmacological arteriolar dilatation through various different mechanisms. Firstly, if there is exaggerated prearteriolar constriction at a branch there is redirection of blood to another branch because the driving pressure becomes insufficient to profuse adequately the inappropriately constricted branch. Secondly, by another mechanism, if there is a marked pressure decrease proximal to the branching point of two branches with a different degree of constriction, a steal phenomenon may also occur (Maseri et al, 1991(b)).
Clarification of these issues probably awaits refinement of techniques to measure local blood flow in the myocardium (Poole Wilson and Crake, 1989).

2.1.13. Insulin effect in coronary microvasculature

Some patients with syndrome X exhibit an increased concentration of insulin in response to a glucose load. This may induce coronary microvascular dysfunction, either endothelial, vascular or both, and therefore hyperinsulinaemia has been implicated as a possible pathogenetic mechanism in syndrome X (Dean et al, 1991).

The authors proposed that the disorder may represent one part of a clinical spectrum of microvascular disease which also includes diabetes and hypertension, in which hyperinsulinaemia is commonly found (Modan et al,1985).
It is noteworthy that diabetes mellitus is an insulin resistant state and has been linked with impaired endothelium-dependent vasodilatation (Johnstone et al, 1993) and reduced activity of nitric oxide (Saenz de Tejada et al, 1989).
Insulin resistance, using the euglycaemic clamp method, has also been demonstrated in a syndrome X group of eleven patients which was compared with a control group consisting of nine subjects with presumably non-cardiac pain (Botker et al, 1993). The results showed that there was no significant difference between the groups in serum cholesterol, triglycerides, high densiy lipoprotein (HDL) cholesterol or blood pressure.
In contrast, recently Swan and colleagues found that all male non-obese patients with syndrome X that they studied were insulin resistant, hyperinsulinaemic and had higher concentrations of triglycerides and lower HDL cholesterol compared to a healthy control group (Swan et al, 1994). They postulated that men with 'cardiological' syndrome X have all the characteristics of the 'non-cardiological syndrome X', or otherwise 'insulin resistance syndrome', which is characterised predominantly by insulin resistance, but also by hyperinsulinaemia, high plasma triglyceride concentrations, low HDL cholesterol concentration, and raised blood pressure (Reaven, 1988).

In a recent study, Chauhan and colleagues compared the insulin responses to an oral glucose load in a group of patients with syndrome X, a group of patients with CAD and a normal control group and compared the insulin responses to an oral glucose load (Chauhan et al, 1994). They found that both syndrome X patients and patients with CAD exhibit stimulated hyperinsulinaemia which was not evident in the control group. The similarity of the insulin response of the syndrome X group to the CAD group, according to the authors, supports the view that insulin resistance may contribute to the coronary artery dysfunction reported in some patients with this condition.

Further support for the involvement of insulin resistance and hyperinsulinaemia in the development of syndrome X derives from the study of Ley and colleagues (Ley et al, 1994). The authors studied patients with angina and both abnormal and normal coronary arteriograms, and a normal control group. They showed significant metabolic abnormalities in both groups with angina (CAD and syndrome X group) including increased insulin resistance with increased second phase insulin secretion, increased triglycerides and decreased HDL cholesterol and HDL cholesterol subfraction 2.

The possibility, therefore, of a link between insulin resistance and hyperinsulinaemia and syndrome X may exist, as is the case in CAD (Saenz de Tejada et al,1989).
Godsland and colleagues recently studied 20 postmenopausal women with syndrome X and 20 controls who underwent measurements of insulin resistance and a range of other metabolic variables. They found that women with syndrome X tend to be insulin resistant, have high triglycerides and low HDL cholesterol but do not exhibit all the characteristics of insulin resistant syndrome. Blood pressure, glucose tolerance, uric acid concentration and body fat distribution did not differ from controls (Godsland et al, 1995).

2.1.14. Abnormal intracardiac noniception - Role of adenosine

Altered perception of painful stimuli may be a contributory factor. Several studies have suggested that some patients with syndrome X have a lowered pain threshold, or a heightened sensitivity to various possible triggering factors, including changes in heart rate, rhythm, loading conditions and plasma catecholamine levels.
Shapiro and colleagues showed that in most of the patients with syndrome X that they studied their typical anginal pain could be reproduced by manipulating the catheter against the high atrium and by injecting intra-atrial boluses of normal saline (Shapiro et al, 1988).
Cannon and co-workers suggested that such an increased sensitivity to pain may be of causal importance and may heighten the perception of chest pain (Cannon et al, 1990(c)). They also observed that the patients' typical pain could be provoked by manipulating the catheter in the right ventricular apex of the heart, by electrical pacing and by injection of contrast media into the left coronary artery.
It has also been shown that patients with syndrome X have an exaggerated sensitivity to pain compared with patients with CAD or valvular heart disease (Chauhan et al, 1993(b)).

Another possibility is that increased coronary artery resistance caused by prearteriolar constriction may lead to inappropriate release of adenosine at the arteriolar level and arteriolar vasodilatation.
Data from humans and animals support the view that adenosine is probably the mediator of stimulation of the pain fibres that are responsible for the sensation of angina (Thames et al, 1993).

Therefore adenosine itself, being a metabolic messenger, may stimulate pain receptors and this might explain at least in part the pain that occurs in this condition (Sylven et al, 1986).
Crea and colleagues also showed that intracoronary infusion of adenosine in syndrome X patients caused anginal pain similar to their usual chest pain (Crea et al, 1990).
The discomfort could be provoked by selective injection of adenosine into the non-diseased coronary arteries of patients with CAD.
Turiel and colleagues reported a lower threshold and tolerance to both pain and electrical skin stimulation on the forearm of women with syndrome X compared to a control group of women with CAD (Turiel et al, 1987).
Lagerqvist and co-workers also found a lower pain threshold and low tolerance to pain induced by intravenous adenosine compared to a normal control group (Lagerqvist et al, 1992).

The role of adenosine in producing pain in syndrome X has been supported by the work of Emdin and colleagues (Emdin et al, 1989).
They investigated the effect of aminophylline on the ischaemic ECG changes and exercise-induced chest pain. They reported that with a dosage that should inhibit adenosine receptors there was a beneficial effect on both of the above changes. They hypothesised that the effect on pain was through the prevention of inappropriate adenosine release during exercise in the presence of increased prearteriolar coronary artery resistance.
Maseri and co-workers have postulated that a focal compensatory production or release of adenosine as a result of the prearteriolar reduced vasodilator capacity may become sufficient to stimulate cardiac afferent nerves and explain the development of chest pain (Maseri et al, 1991(b)). This, they suggested, occurs in the presence of unevenly distributed prearteriolar coronary artery constriction and myocardial ischaemia, or even in the absence of ischaemia. They concluded that chest pain in syndrome X might occur in the absence of ischaemia if focal increase in adenosine concentration distal to the severely constricted arterioles takes place.

A further possibility is that there might be an abnormality of adenosine receptor density or function, in some patients with syndrome X (Rosano and Crea,1992). Adenosine receptors have been found in coronary artery walls and when stimulated induce smooth muscle relaxation and blood flow increase (Clarke and Coupe, 1989).

To date it is not clear whether the heightened pain sensitivity seen in some patients with syndrome X represents an extreme of normal visceral sensitivity or, otherwise, is evidence of abnormal visceral function.

2.1.15. Oestrogen deficiency

The importance of the ovarian hormones in women with this condition has been investigated and has been implicated as a possible cause.
Rosano and co-workers found a preponderance of women and a high incidence of hypo-oestrogenicity in a large unselected population of patients with syndrome X (Rosano et al, 1992). They postulated that women with syndrome X might have a generalised alteration of vasomotor control, including dysfunction of the coronary microcirculation secondary to ovarian hormonal deficiency, and hence oestrogen deficiency may play a pathogenetic role.
Sarrel and colleagues investigated a group of 30 women with syndrome X (Sarrel et al, 1992). They reported that oestrogen replacement alleviated their chest pain and therefore might play an important role in the pathogenesis in women with this syndrome.
Recently, also, Rosano and colleagues evaluated the hyperemic response to ischaemia in women with syndrome X and found that there was an improvement after eostrogen replacement therapy (Rosano et al, 1993).
However, although the importance of these observations cannot be disputed, it does not explain the occurrence of the syndrome in men.

2.1.16. Endothelial dysfunction

The role of nitric oxide, which is released in response to many pharmacological and chemical stimuli (acetylcholine, adenosine, histamine), may be important in the pathogenesis of the syndrome not only because it causes vascular smooth muscle relaxation, but also because it inhibits platelet adhesion and aggregation (Cocks and Angus, 1983; Furchott,1983; Ginsburg and Zera, 1984). Additionally, reduced levels of nitric oxide could enhance vascular injury and disease by facilitating platelet-vascular wall interaction, adhesion of circulating monocytes to the endothelial surface, and vascular smooth muscle proliferation (Garg and Hassid,1989; Radomski et al, 1990; Kubes et al, 1991)

Endothelial dysfunction may also lead to increased coronary artery constriction in response to catecholamines, in a similar manner to that already demonstrated in atherosclerosis (Vita et al, 1990(b)).

Many investigators have suggested that endothelial dysfunction may play a role in the pathogenesis of the syndrome (Kaski et al, 1991; Maseri et al, 1991(b)).
Motz and colleagues investigated the response of coronary blood flow to acetylcholine and dipyridamole in a large group of patients with syndrome X. They postulated that the presence of endothelial dysfunction affecting the coronary resistance vessels might be the cause of the impaired vasodilator response and could result in derangement in the control and release of vasoactive substances (Motz et al, 1991). However, many of their patients had arterial hypertension and diabetes mellitus which are known to be associated with impaired endothelial function (Furchgott, 1983; Bassenge and Busse; 1988). It is possible that due to a local deficit of nitric oxide prearterioles do not dilate when arterioles dilate, resulting in a large pressure decrease at the end of prearteriolar vessels (Bassenge and Busse, 1988).

Vrints and colleagues studied a group of patients with angina and normal coronary arteries with acetycholine infusion (Vrints et al, 1992). They showed that the release of nitric oxide is depressed in this condition, and suggested that the endothelium-dependent coronary artery dilatation of the large coronary arteries is impaired (Vrints et al, 1992).
Quyyumi and co-workers from Cannon's group further supported the view that endothelium might be significantly implicated in the pathogenesis of the condition (Quyyumi et al, 1992). They investigated a large group of patients with syndrome X with atrial pacing and reported that coronary microvascular endothelial dysfunction may contribute to the reduced vasodilator reserve. They reported that patients with a depressed dilator response to acetylcholine also had a depressed dilator response to atrial pacing.

Recently Egashira and colleagues assessed endothelial function in a small homogeneous group of patients with angina and normal coronary arteries with no arterial hypertension, diabetes mellitus or hypercholesterolaemia and a control group of subjects with atypical chest pain and normal coronary arteries, with intracoronary infusion of acetylcholine, papaverine and isosorbide dinitrate (Egashira et al, 1993(a)).

The authors showed that there was marked attenuation of the increase in coronary blood flow (measured by a doppler flow-velocity catheter) with intracoronary acetylcholine, whereas the increase in coronary blood flow in response to isosorbide dinitrate and papaverine was not affected. These findings suggested that at least in some patients with syndrome X, endothelium-dependent vasodilatation of resistance coronary vessels is impaired. More importantly, they demonstrated that the attenuated response of coronary blood flow to acetylcholine in the patients with syndrome X that they studied did not result from excessive vasoconstriction of the large epicardial coronary arteries.

2.1.17. Impaired coronary artery dilator response

Historical perspective

Evidence has accumulated over the years that a substantial number of patients with syndrome X have signs of myocardial ischaemia most likely due to an abnormal coronary flow reserve, the main consequence of which is a limitation in the ability of the coronary vasculature to meet the extra demand of stress or exercise.
This is characterised by an inadequate vasodilator response to metabolic and pharmacological stimuli and by a hypersensitivity to vasoconstrictor and neural or humoral stimuli. As a result myocardial oxygen supply might fail at some stage to meet demand and myocardial ischaemia might result.

The behaviour of the prearteriolar vessels is supposed to be impaired because they do not dilate when arterioles dilate responding to the local metabolic demand. This has been shown using different methods and by several investigators. In 1981 Opherk and co-workers reported an abnormally small increase in coronary blood flow after dipyridamole in a group of patients with syndrome X (Opherk et al, 1981) and suggested that myocardial ischaemia due to limited vasodilator response of the distal coronary arterioles may be the underlying pathophysiological mechanism responsible.
Cannon and colleagues in 1983 reported that syndrome X patients also have a limited increase in coronary flow in response to pacing (Cannon et al,1983).
Kaski and co-workers proposed that increased constriction of the coronary microvasculature causes a reduction in coronary blood flow in some cases of syndrome X (Kaski et al,1986).

From Cannon's group later it was confirmed that in the majority of syndrome X patients coronary vascular resistance is usually elevated (Cannon et al,1987).
In 1988 Cannon and Epstein suggested that increased coronary resistance at the level of coronary microcirculation, i.e. those coronary vessels in the region of 50 to 500 microns in diameter, might be implicated in the pathogenesis. They named this clinical syndrome and pattern of abnormal coronary flow and resistance response as 'microvascular angina' (Cannon and Epstein, 1988). According to the authors a distinct clinical syndrome was identified, resulting from a reduced dilator capacity of the distal arteriolar coronary arteries caused by an abnormality of the intramural coronary artery resistance vessels to respond to prearteriolar vasoconstrictor and vasodilator stimuli, potentially leading to effort related myocardial ischaemia.
Epstein and Cannon proposed that the impediment to flow may be located in the small prearteriolar vessels before they give off subepicardial branches. It was assumed that a 'steal phenomenon' is in operation and is the cause of myocardial ischaemia. They showed that the administration of dipyridamole precipitated chest pain in the large majority of patients with microvascular angina. They postulated that the site of microvascular abnormality lies proximal to the coronary arterioles and that dysfunction of the small intramural prearteriolar coronary arteries might be the cause of the 'microvascular angina' syndrome (Epstein and Cannon, 1986; Cannon and Epstein, 1988).

Pupita and colleagues showed that inappropriate constriction of small diameter distal vessels, rather than proximal, can cause myocardial ischaemia (Pupita et al,1990).
Maseri and co-workers suggested that the abnormality might reside in a well identified functional segment of resistive vessels (Maseri et al,1991(b)). They proposed the functional definition of arteriolar and prearteriolar vessels; arteriolar vessels defined as those vessels responsible for the continuous physiologic matching of coronary blood flow to myocardial oxygen consumption, and prearteriolar vessels defined as those vessels with significant resistance to flow interposed between conductive coronary arteries and arteriolar vessels.
They suggested that the vascular abnormality responsible is located in the prearteriolar vessels and that it might be unevenly distributed. This 'patchy' distribution of small vessel vasoconstrictor zones may explain the variety of vasomotor responses in patients with syndrome X.
The more extensive and severe the inappropriate prearteriolar response becomes, the more detectable the evidence of ischaemia would be.

Possible causes of abnormal vasodilator reserve in syndrome X

The cause(s) of abnormal vasodilator reserve in patients with this condition is unknown. Cannon and colleagues were the first to propose that a heightened sympathetic drive is a possible cause of coronary prearteriolar vasoconstriction (Cannon et al, 1983).
Since, this possibility has been suggested by several other groups of investigators (Bortone et al,1989; Montorsi et al,1989; Ishihara et al,1990; Galassi et al,1991).
Romeo and co-workers reported some syndrome X patients with increased sympathetic drive that caused a rapid increase in heart rate/blood pressure product during exercise (Romeo et al, 1988).
Bugiardini and colleagues suggested that transient myocardial ischaemia might be precipitated by an increase in oxygen consumption, presumably due to a heightened sympathetic activity (Bugiardini et al, 1989).
Increased sympathetic drive has also been proposed as a mechanism later in another paper by Bugiardini (Bugiardini, 1992).

However, against the hypothesis that increased sympathetic activity is causally implicated in the abnormal vasodilator response is the work of Galassi and co-workers (Galassi et al, 1989). The authors failed to confirm that a receptor mediated mechanism may provoke transient myocardial ischaemia in syndrome X and did not find selective alpha-adrenergic blockade to be of any symptomatic benefit to these patients. This discrepancy might be explained because $alpha_1$ and $alpha_2$-adrenergic receptors have different effects on different parts of the coronary tree. Furthermore, they have no effect on coronary arteries <100 microns in diameter during normal arterial flow, but probably myocardial hypoperfusion results in unmasking $alpha_1$ and $alpha_2$ receptor mediated coronary artery constriction of vessels of this size (Chilian, 1991(a)).

Cannon and colleagues have suggested that the myogenic prearteriolar coronary tone may be abnormal due to intracellularly deranged calcium levels (Cannon and Epstein,1988). Montorsi and colleagues reported a group of patients who presented with effort-related chest pain and normal coronary arteriograms and suggested that the limit to prearteriolar vasodilatation is probably not fixed (Montorsi et al, 1990).
These authors showed that abnormalities in coronary microvascular function can be reversed in part by drugs capable of inhibiting the entry of calcium into cells.

The administration of nifedipine increased coronary artery diameter, coronary blood flow and noradrenaline plasma levels, and decreased ST segment depression in most patients. In those patients who showed chronic symptomatic improvement plasma noradrenaline levels were decreased.

It has been postulated that the impairment of dilator reserve is limited to the arteries of the heart and that there is no evidence of a generalised disorder of vascular reactivity (Sutsch et al, 1992). These findings were based on the fact that successful vasodilatation of coronary arteries by dipyridamole in control subjects and reduced response in syndrome X patients were not accompanied by changes in skin perfusion during reactive hyperaemia at the microvascular level.

However, Sax and co-workers have suggested that the impaired arterial response affects not only the coronary circulation but also the peripheral arterial bed and that it may be part of a more generalised disorder of regulation of the microvasculature with impaired vascular tone of both systemic and coronary smooth muscle (Sax et al,1987). Their suggestions were based on the observation of an abnormal vasomotor response in the forearm in a syndrome X group of patients most of whom had no ischaemic ECG changes during exercise.

Several authors have focused attention on the involvement of large epicardial coronary arteries in the pathogenesis of the syndrome, and reported increased sympathetic drive of both epicardial and small coronary arteries (Montorsi et al,1989; Bugiardini et al, 1992).

Recently, Bugiardini and colleagues again showed that vasoconstrictor stimuli may trigger a diffuse abnormal response of both epicardial and resistance vessels in some patients with syndrome X (Bugiardini et al,1993). They demonstrated that both ergonovine and hyperventilation induced diffuse epicardial coronary artery diameter reduction, which was severe in patients with syndrome X, but marginal in the control subjects that were also studied.

These observations, however, are in conflict with data from other studies which suggest that epicardial coronary vessels are not involved in the process (Feldman et al,1980; Cannon et al, 1987). Kaski and colleagues reported the angiographic responses of the coronary arteries to nitroglycerine and ergonovine malate in a group of syndrome X patients and two control groups, one comprising patients with stable chronic angina with angiographically confirmed CAD and a second group of subjects with atypical chest pain (Kaski et al, 1991).

The authors found that constriction in response to ergonovine and dilatation in response to nitrates was not different in proximal and distal segments of the coronary arteries of the three different groups. They concluded that the reactivity of the large epicardial vessels to nitrates and ergonovine appears to be within the physiological range, supporting the view that the prearteriolar rather than conduit coronary artery level of the coronary artery tree is the focus responsible for the impaired coronary artery reserve. Such a view is probably correct on theoretical grounds because, as stated earlier, the contribution of the epicardial coronary arteries to resistance is negligible compared with that of the microvascular component.

Further supporting evidence that epicardial vessels are not involved comes from the work of Chauhan and co-workers who found changes in coronary blood flow velocity in the absence of any changes in the diameter of the epicardial coronary arteries in a group of syndrome X patients that they studied (Chauhan et al, 1993(a)). Different selection criteria may explain the different results in the above studies.

Nonetheless, the evidence is growing that indeed an abnormal tone of the prearteriolar coronary vessels may be responsible for the impaired coronary flow reserve found in many patients with syndrome X (Cannon and Epstein,1988; Maseri et al, 1991(b)).

Such impaired neurohumoral regulation may be effective through stimulation of $alpha_1$ and $alpha_2$-adrenergic receptors.Enhanced $alpha_1$ and $alpha_2$-adrenergic activity of the small resistance vessels might compromise the ability of the distal arterioles to dilate especially on exercise when the dilatation is needed to meet the metabolic demand of the myocardium. It is noteworthy that there is a different distribution of the two subtypes of alpha-adrenergic receptors, i.e. $alpha_1$ and $alpha_2$ in the coronary vessel segments. It appears that $alpha_2$-adrenergic receptors regulate mainly vasoconstriction of resistance vessels rather than that of the large superficial coronary arteries.

During exercise focal myocardial ischaemia can result from the reduction in coronary flow reserve because some flow reserve has already been utilised at rest to compensate for the prearteriolar constriction.

There is also evidence from the literature that sympathetic overactivity or exogenous norepinephrine administration may result in an increase in coronary resistance and a decrease in myocardial blood flow (Vatner et al, 1974; Mudge et al, 1979).

It is worth adding that the presence of endothelial dysfunction affecting the coronary resistance vessels might indirectly play a role in enhancing sympathetic activity. Such a dysfunction may lead to increased coronary constriction in response to catecholamines as has been shown in atherosclerosis (Vita et al,1990(b)).

Chapter 2.2. CATECHOLAMINES

2.2.1. Introduction

These compounds are amine derivatives of the catechol (dihydrobenzene) nucleus. Sympathetic neurons synthesize and release catecholamines and such neurons are found throughout the body, especially in the central nervous system and in ganglia outside the spinal cord. In the periphery they are found in the heart, blood vessels, smooth muscle of the gastrointestinal tract, salivary glands, adipose tissue and adrenal medulla.
Since the introduction of sensitive biochemical methods for measuring plasma concentrations of catecholamines it has been possible to elucidate the function of the autonomic nervous system and to study the effect of various stimuli on plasma catecholamines.

Catecholamine resting values probably do not represent true baseline measurements but may reflect the anticipation of the task to be performed. Basal adrenergic tone can probably be attributed to a background release of noradrenaline from sympathetic neurons. Because of this it is generally believed that changes in plasma noradrenaline concentrations reflect the activity of the sympathetic nervous system (Vecht et al, 1978). However, there is also evidence that noradrenaline concentrations may be relatively insensitive measures of sympathetic tone and do not consistently reflect variations in sympathetic neuronal activity (Floras et al, 1986).

Plasma concentrations of catecholamines increase during a variety of cardiovascular stresses and conditions (Dimsdale and Zeigler, 1991). Physical exercise is associated with increased plasma concentrations of both catecholamines but predominantly of noradrenaline (Robertson et al, 1979; Sheehan et al, 1983).
Emotional stresses raise, to a different degree, both adrenaline and noradrenaline as has been demonstrated mainly by the work of Taggart and colleagues (Taggart et al, 1969; Taggart et al,1972; Taggart et al, 1976).
Other investigators have come to similar conclusions (Goldstein et al, 1982). In particular both catecholamines have been reported to be raised in anxiety neurosis and panic disorders (Charney et al, 1990).
Upright posture is associated with elevated plasma catecholamines (Osikowska and Sever,1976; Robertson et al,1979).

Standing up abruptly decreases venous return to the heart. Baroceptors are then activated and the standing blood pressure is maintained by increasing peripheral vascular resistance. This results in dramatic increase in plasma noradrenaline and a smaller increase in adrenaline, probably because the adrenal medulla is not stimulated by posture as it is stimulated by physical exercise (Cryer et al,1974).

There are also other conditions in which plasma catecholamines are found to be elevated. In syncope primary adrenomedullary discharge occurs (Chien, 1967).
Smoking causes elevation of plasma catecholamines (Cryer et al, 1976).
Caffeine causes primary adrenomedullary stimulation (Robertson et al, 1978).
Plasma catecholamines are also raised in patients who have suffered an acute myocardial infarction (Karlsberg et al, 1981). In patients with diabetic ketoacidosis plasma catecholamines are markedly elevated and furthermore the catecholamine response to exercise is exaggerated in patients with poorly controlled diabetes mellitus (Christensen, 1974) .
Mitral valve prolapse is associated with elevated plasma catecholamines (Puddu et al, 1983). In essential hypertension plasma catecholamines are elevated (Osikowska and Sever, 1976). Furthermore, it is believed that an inappropriate exaggerated sympathetic activity might play a role in the pathogenesis of essential hypertension.
In coronary artery spasm plasma catecholamine levels have been reported to be elevated (Robertson et al, 1983). Patients with congestive cardiac failure have also raised resting catecholamine levels (Francis et al, 1982).
Hasking and colleagues have reported that such patients have elevated plasma catecholamine concentrations due to both reduced plasma clearance and increased spillover to plasma (Hasking et al, 1986). They found that there was evidence of intense cardiorenin sympathetic nervous stimulation at rest in patients with cardiac failure, indicating increased maximal cardiac sympathetic stimulation.
Conversely, catecholamines may be reduced in conditions in which the autonomic nervous function is impaired (Bannister et al, 1977). These include diabetic peripheral autonomic neuropathy, amyloid peripheral autonomic neuropathy and the Shy-Drager syndrome (idiopathic autonomic insufficiency). Catecholamines are also lowered by drugs that interfere with the action of the sympathetic nervous system (Louis et al, 1973).

2.2.2. Adrenaline

Adrenaline is a true circulating hormone and it is predominantly synthesised by chromaffin cells and released mainly by the adrenal medulla. It is also synthesised and released by parts of the brain and probably in small amounts by the peripheral nerves. Adrenaline has proportionately greater beta-adrenergic potency than noradrenaline (Landsberg, 1977; Engelman, 1979). Adrenaline is a potent direct vasoconstrictor in the skin. However, systemic administration produces generalised vasodilatation, decreased peripheral resistance and increased cardiac output and heart rate. Following adrenaline administration the systolic pressure is increased but the diastolic pressure remains unchanged or falls slightly and there is little change in mean arterial pressure.
The plasma concentration of adrenaline at any moment represents a balance between release by the adrenal medulla, excretion and metabolism. Adrenaline is usually present in the circulation at a concentration of approximately 0.03ng/ml and may increase to 0.5-1ng/ml with sympathetic stimulation (Lubbecke et al,1991).

The proaggregatory effect of catecholamines is well known (Ardlie et al,1985). Furthermore, it has been suggested that an increase in adrenaline is thrombogenic (Ardlie et al,1966). In this study, the authors found that adrenaline not only caused platelet aggregation but also enhanced the aggregation induced by other agonists such as ADP. In another experimental study with canine coronary arteries it was found that with an increase in the plasma concentration of adrenaline to 1-10ng/ml, thrombus was formed mainly composed of platelets (Folts et al, 1982).
Adrenaline is about 10 times more potent than noradrenaline in producing metabolic effects. There has been much discussion whether different emotions, e.g. fear as against anger are associated with different relative concentrations of adrenaline and noradrenaline in plasma and urine. This question remains largely unresolved (Levine et al,1982; Robertson et al,1979).

Dimsdale and Moss have also investigated the effect of public speaking on plasma catecholamines and found that both catecholamines show a significant increase following the speech (Dimsdale and Moss,1980). However, Taggart and colleagues demonstrated, in a similar study, a significant elevation of noradrenaline immediately after speeches, but not of adrenaline, the concentration of which remained unchanged (Taggart et al,1973).

These differences are probably not only due to differences in the timing of sampling and to different measuring techniques, but also, as was pointed out by Taggart, that according to the rapport that an individual speaker establishes with the audience, his or her mood changes to various levels of anxiety and emotional feelings (Taggart et al,1973).
Therefore, it is conceivable that such a varying mixure of feelings may be reflected in the plasma with varying unpredictable degrees of adrenaline and noradrenaline concentrations. It has also been shown that when awaiting dental extraction an exaggerated adrenaline response is clearly observed (Goldstein et al,1982). Venepuncture, being a mildly uncomfortable procedure, has been associated with increased plasma concentrations of adrenaline, but not noradrenaline (Carruthers et al, 1970). However, Robertson and colleagues demonstrated that there were no significant differences in catecholamine measurements obtained from an indwelling catheter or straightforward venepuncture (Robertson et al, 1979).

2.2.3. Noradrenaline

Noradrenaline is not a circulating hormone but is primarily a neurotransmitter. It is mainly synthesised and released from sympathetic postganglionic neurons during excitation of sympathetic nerves. The adrenal medulla also releases some noradrenaline and occasionally can become a major source especially under certain conditions such as hypoglycaemia. If plasma concentrations rise to levels that produce biologic effects i.e., approximately 1500 to 2000 pg/ml, noradrenaline may also act as a hormone (Silverberg et al, 1978). However, high concentrations are unusual under most physiological conditions and the biological actions are due to its function as a neurotransmitter. This substance in the heart interacts mainly with $beta_1$-adrenergic receptors, whereas in the vascular smooth muscle with alpha-adrenergic receptors.

Noradrenaline is responsible for greater tonic activation of alpha-adrenergic receptors compared to adrenaline.
Noradrenaline causes increases in both systolic and diastolic pressure, due to generalised vasoconstriction. The increased blood pressure causes reflex bradycardia resulting in little change or a decrease in cardiac output. Circulating noradrenaline is considered to be an index of average sympathetic nervous system activity; it generally reflects the amount of sympathetic activity at a certain moment (Goldstein, 1981).

At any moment the circulating concentration of noradrenaline represents a balance between the amount of noradrenaline which is released, a small amount that escapes re-uptake into the nerve terminals and the amount of noradrenaline which is being eliminated by excretion and metabolism. The plasma concentration of noradrenaline is only a small fraction of the amount released into the synaptic cleft (Francis,1985).
In physiological conditions, L-tyrosine is transported from the blood across the membrane of the sympathetic nerves by a special concentrating mechanism.
The enzyme tyrosine hydroxylase then acts upon L-tyrosine and converts it to L-dihydroxyphenylanine (DOPA). The activity of the enzyme tyrosine hydroxylase is inhibited by noradrenaline (Nagatsu et al, 1964). DOPA is then decarboxylated to dopamine by the action of the enzyme decarboxylase. Subsequently, it enters the small granulated vesicles and the enzyme dopamine-beta-hydroxylase (DBH) catalyses the conversion of dopamine to noradrenaline in the postganglionic sympathetic neuron. DBH is released together with noradrenaline with adrenergic stimulation (Weinshilboum et al,1971).
More than 80% of released noradrenaline is dissipated by mechanisms other than escape into the plasma (Silverberg et al,1978). A significant quantity of the noradrenaline released by the nerve ending is taken back up into postganglionic synaptic nerve terminals by active transport mechanisms and this process is known as uptake 1. Re-uptake of released noradrenaline is the major determinant of synaptic cleft concentrations and is a major contribution to neuronal stores. Uptake 1 is a relatively high-affinity, low-capacity system and has a higher affinity for noradrenaline. Additionally a small quantity diffuses into the blood stream, binds to postsynaptic receptors or is actively taken up by extraneuronal cells such as muscle tissue. This process is known as uptake 2. Subsequently, it is metabolised by catechol-o-methyl transferase and monoame oxidase (Iversen, 1975). Uptake 2 is a low-affinity, high-capacity system with a higher affinity for adrenaline.
The rate-limiting step involved in regulating noradrenaline is the conversion of tyrosine to DOPA.

The noradrenaline is stored in storage granules until excitation of the sympathetic ending occurs when the phenomenon of exocytosis takes place, i.e. the process whereby storage granules move to the surface of the nerve membrane and expel their contents into the synaptic cleft.

It is generally thought that elevated baseline plasma levels of noradrenaline might be due to either reduced clearance or increased spillover to plasma, or both.
Hasking and co-workers have shown that the major sites of clearance of noradrenaline from plasma are the lungs and the liver and less so the skeletal muscles (Hasking et al,1986).

Plasma noradrenaline concentrations increase with age by approximately 13% per decade in normal subjects (Sever et al, 1977; Esler et al, 1981). As far as the underlying mechanism for this increase is concerned, it is not clear whether this reflects reduced clearance with increasing age or increased total noradrenaline release occurring in the elderly (Esler et al,1981).

Dynamic exercise is par excellence the most physiologic and powerful stimulus for catecholamine discharge and is mainly associated with increased plasma concentrations of noradrenaline, although adrenaline is raised as well (Chilian et al,1986). At low work levels this is probably due to a progressive withdrawal of vagal tone whereas at higher levels of exercise is elicited through increased sympathetic activity (Robertson et al, 1979). Plasma catecholamine concentrations are reported to increase curvelinearly at work levels that are less than 50% of maximum (Davies et al, 1974).
Noise, also, is known to stimulate the release of mainly noradrenaline from sympathetic postganglionic nerve terminals (Aronow et al, 1973).
With low sodium diet noradrenaline but not adrenaline is usually increased as well (Robertson et al, 1977).

2.2.4. Cardiotoxicity of catecholamines and other vasoactive substances

The endogenous release of neurotransmitters usually plays a beneficial role in supporting cardiac function and has a major role in the short term cardiovascular response to physiological stress. However when excessive, long term, or inappropriate it has the potential to exert damaging effects on the circulation. It has been suggested that prolonged and/or intense activation of the sympathetic system exerts a direct harmful effect on myocardial cells and accelerates myocardial degeneration (Tan et al, 1991; Mann et al,1992).

Possible mechanisms for catecholamine-induced myocardial toxicity

Catecholamine mediated myocardial toxicity was first reported in 1907 by Josue (Josue, 1907). Since this time several experimental studies have sought to determine the mechanisms responsible for catecholamine induced toxicity.

In 1959 Rona and co-workers injected isoprotenerol into rats and produced myocardial necrosis in the absence of significant atherosclerotic lesions, giving rise to the relative hypoxia theory of myocardial necrosis (Rona et al,1959).

Waldestrom and colleagues have also reported that elevation of sympathetic activity causes an increase in myocardial energy demand, local release of noradrenaline and development of ischaemia (Waldenstrom et al,1978). Furthermore, they suggested that short periods of ischaemia caused by a release of myocardial noradrenaline could lead to an aggravation of the primary ischaemia.

The importance of the microcirculatory effects of catecholamines in producing cardiotoxicity was later demonstrated (Boutet et al, 1973; Rona and Bier, 1981).

Another theory which attempted to explain the mechanisms involved in the development of cardiotoxicity with catecholamines, especially with noradrenaline, is the theory of early sarcolemmal membrane permeability. According to this theory catecholamines mediate increases in sarcolemmal permeability contributing to the pathogenesis of myocardial injury (Boutet et al, 1973; Boutet et al, 1974).

Experimental observations carried out by Fleckenstein and colleagues supported the calcium overload theory for catecholamine induced cardiac toxicity (Fleckenstein 1971; Fleckenstein et al,1973). According to this theory there is enhanced calcium influx into the myocardial cells which in turn may cause calcium overload, cellular injury and impairment of the mitochondrial function (Waldenstrom et al, 1978). Recently Mann and co-workers have also shown that that cAMP-mediated calcium overload is the primary mechanism responsible for catecholamine-induced toxicity in cultured adult mammalian cardiocytes (Mann et al, 1992). This observation provides evidence that this is an important event in the genesis of cardiac injury.

Dhalla and co-workers have also developed another concept concerning the mechanism of catecholamine-induced myocardial injury (Dhalla et al, 1978). They postulated that not the catecholamines per se but rather their oxidation products, aminochomes, adrenochrome and noradrenochrome, are implicated in the pathogenesis of catecholamine toxicity.

This idea has been supported by the work of others who have suggested that the toxicity of aminochromes could at least be in part related to their ability to undergo redox cycling, in addition to extensive production of toxic oxygen free radicals (Bindoli et al, 1989). There are potential toxic metabolites of noradrenaline which might contribute to the injury to the myocardial cells and coronary endothelium and 6-hydroxydopamine is probably such a product (Malmfors and Sachs, 1968).

Potentiation of cateholamine-induced cardiotoxicity by the renin-angiotensin system

It has also been suggested that activation of the renin-angiotensin system may exert a deleterious effect on the heart and result in marked vasoconstriction (Tan et al, 1991). Furthermore, once formed, Angiotensin II may potentiate the effects of other vasoconstrictor hormones, like noradrenaline, by facilitating the central and peripheral effects of sympathetic nervous system and by enhancing the release of vasopressin from the pituitary (Hirsch et al, 1987). This may lead to a potentiating effect whereby, when systemic vasoconstriction is enhanced for whatever reason a further increased neurohumoral activity may occur.

Effect of circulating catecholamines on platelet aggregation

Buttrick and colleagues have shown that in vitro catecholamines in subaggregatory doses prevented PGI_2 induced inhibition of platelet aggregation, action which is of primary importance in the coronary circulation (Buttrick et al,1985).
Haft and colleagues reported that platelets aggregate in the small coronary arteries of sacrificed dogs after the infusion of noradrenaline (Haft et al, 1972).
In most of the vessels the endothelial surfaces appeared intact suggesting that the platelet aggregation was primary rather than secondary to vessel wall damage. In some of the vessels there were areas of vessel wall breakdown suggesting damage caused by lysosomal enzymes from the platelets (Mills et al, 1968).
High dose adrenaline infusion has a proaggregatory effect in vivo, which is mediated via alpha-adrenergic receptor activation (Larsson et al, 1992). Noradrenaline infusion has also been found to have a similar effect (Larsson et al, 1993).
It is noteworthy that insulin antagonises the harmful actions of noradrenaline on the heart muscle and vascular reactivity (Lee and Downing,1976) and that insulin also prevents the catecholamine triggered release of fatty acids and antagonises their action (Lee, 1978).

Possible role of catecholamines in the development of CAD in humans

Raab and colleagues advanced the view that catecholamines play an important role in the pathogenesis of CAD in humans. According to the authors, sympathetic hyperactivity can cause myocardial hypoxia and metabolic degeneration and is a key factor in the development of transient myocardial ischaemia, acute coronary insufficiency, angina and subendocardial myocardial infarction (Raab,1960; Raab et al, 1961). They suggested that these ischaemic developments might follow stressful conditions such as anxiety, exertion, postprandial state or exposure to cold. Furthermore, Raab and colleagues later postulated that sympathetic stimulation and the action of catecholamines is of particular importance in the presence of impaired coronary dilatability (Raab et al, 1962).

Catecholamine mediated cardiac toxicity may occur. However, to date, there is no consensus regarding the mechanism(s) responsible and the cardiotoxic effects in humans has definitely not been identified although its pathogenesis appears to be multifactorial (Mann et al,1992).

SECTION 3

Chapter 3.1 OBJECT

Chapter 3.2 METHODS

Chapter 3.3 RESULTS

Chapter 3.1. OBJECT OF THE PRESENT STUDIES

The objective of the present studies was to compare the effect of exercise on several biochemical parameters in patients with syndrome X versus a control group.
The biochemical markers were the catecholamines adrenaline and noradrenaline, lactate, potassium, bicarbonate and creatine kinase.

Chapter 3.2. METHODS

3.2.1. Patients

Study population.
Control group:
The group consisted of thirty apparently healthy, sex matched volunteers (18 men and 12 women) who were neither hospital staff (with the exception of two) nor medical students. Their age ranged from 27 to 66 with a mean of 43 years.
All of them were asymptomatic and gave no history of cardiac or pulmonary disease.
All had normal cardiac signs, normal resting electrocardiograms and normal m-mode and two-D echocardiograms.
None were trained athletes.
Sixteen subjects were current cigarette smokers and fourteen were non smokers.
Preliminary screening evaluation included clinical history and physical examination and a resting examination which was normal.
Subjects were informed of the research study protocol.

Syndrome X group :
The group consisted of thirty patients, 16 men and 14 women aged 38 to 72 years with a mean of 53 years. All had been referred to the Cardiology Department, The Middlesex Hospital, as in-patients, for evaluation of chest pain which was indistinguishable from myocardial ischaemia. All had a positive symptomatic and electrocardiographic response to a standard symptom-limited exercise test, using the Bruce protocol.
Coronary arteriography showed unobstructed epicardial coronary arteries and left ventricular angiograms were normal. Patients with coronary wall irregularities were excluded from the study.

A repeat treadmill exercise test was performed to confirm that the initial exercise test result was positive.

All patients had a normal physical examination.
Fourteen patients were current cigarette smokers and sixteen were non-smokers. None reported a history of 'Raynaud's' phenomenon.
The chest wall syndrome was considered to be unlikely on clinical grounds in all cases.
Oesophageal disturbances were also considered to be unlikely on clinical grounds, and in two doubtful cases endoscopy was carried out.
In all cases there was no suggestion of epicardial coronary artery spasm on the basis of the clinical history. There was no evidence of Prinzmetal angina or ST segment elevation. However, an ergonovine test was not carried out.
None of the subjects had hypertension (defined as a blood pressure of 165/95mm Hg or above) but two patients had borderline hypertension (defined as a blood pressure >140/90 mm Hg and <165/95 mm Hg).
None had evidence of myocardial hypertrophy, hypertrophic cardiomyopathy, primary myocardial disease, congestive heart failure, valvular heart disease and, in particular, mitral valve prolapse. Echocardiography was employed in all patients to assist in excluding the above conditions and any other structural abnormalities.
None had evidence of any significant systemic disorders, particularly diabetes mellitus.
It was decided that patients with chest pain and normal epicardial arteries associated with left bundle block might constitute a separate distinctive entity and therefore were excluded.
Subjects were required to be receiving no medications for at least seven days before the investigations aside from aspirin and paracetamol.
All subjects were informed of the investigatory nature of the study before entry and gave written informed consent for it which was approved by The Middlesex Hospital Ethical Committee.

3.2.2. Study Protocol

Exercise testing

All sixty subjects underwent formal symptom-limited treadmill exercise testing according to the Bruce protocol (Bruce et al, 1963).

Control subjects underwent two exercise tests. The first served as both a familiarisation procedure and also to establish that the test was normal.

The second exercise test was used for the purpose of this study.

The syndrome X patients also underwent two exercise tests.

The first exercise test was used to confirm that the test was positive.

The second test was used for the purpose of the present study.

Subjects were instructed to eat nothing on the morning of each study and to avoid caffeine and tobacco.

All studies were performed in the same laboratory, at the same time of the day, under identical conditions, by the same investigator, using the same equipment.

In the syndrome X group subjects discontinued because of general fatigue, breathlessness, leg fatigue or because the pain was severe enough for them not to be able to continue.

In the control group the test was discontinued when subjects were unable to continue because of general fatigue, leg fatigue or breathlessness.

The ST segment depression was quantitated by measuring the deviation from the baseline after 80 msec from the J point. This value is expressed in mms and a value exceeding 1 mm is taken as evidence of a positive electrocardiographic response to exercise.

Blood pressure was taken by an automatic sphygmomanometer. Application of the sphygmomanometer might alter circulating catecholamines; therefore blood pressure was monitored on the other arm and not on the one that blood was drawn from.

Twelve-lead electrocardiograms and blood pressure measurements were obtained at rest 20 min prior to exercing , at the end of each stage of exercise, immediately after exercise and at 1,2,3,4,5 and 20 minutes of recovery. Three leads were continuously monitored throughout the test and the recovery period. Heart rate and cardiac rhythm were continuously monitored from the ECG. The ST segment depression was determined in the lead with the most prominent ST segment depression by a computer assisted system (Marquette CASE 12).

3.2.3. Plasma catecholamine measurements

The subjects lay supine in a quiet room for 20 minutes.
Three venous blood samples were taken. The first, 20 minutes prior to exercising with the patient resting in the supine position, the second immediately after exercise with a fresh venepuncture, the last within one and a half minutes of stopping exercise with the patient in the supine position. It was decided to take the second blood sample, not at the peak of exercise, but immediately post-exercise with the subject resting supine.
It would have been inaccurate and misleading to compare pre-exercise resting catecholamine values with the subject lying down with values at the peak of exercise with the subject at the upright position. This is because upright position per se increases catecholamine values considerably (Osikowska and Sever,1976; Robertson et al,1979). The third sample was collected from a fresh venepuncture after 20 minutes in the recovery period. Plasma specimens were taken under the same conditions and great caution was exercised to treat them identically.

Each venous sample was promptly centrifuged, separated, transferred on dry ice and promptly stored at minus 70° C. The samples were coded and remained so until after the assay.
Noradrenaline and adrenaline were determined using the radioenzymatic method of Peuler and Johnson (Peuler and Johnson, 1977) and high performance liquid chromatography with electrochemical detection as described by May and colleagues (May et al, 1988).
Both assays were carried out at well established catecholamine laboratories.
All assays were done by the same technicians who are highly skilled in the performance of this procedure. The samples from each individual were assayed in one batch but the order of batches was random.
For both assays, the intraassay coefficient of variation were similar. For plasma adrenaline the intraassay coefficient is 7% with the radioenzymatic method whereas it is 8% with the high performance liquid chromatography method.
The interassay coefficient of variation are similar with the two techniques.
For plasma adrenaline, the interassay coefficient is 11% with the radioenzymatic method and 13% with the high performance liquid chromatography. For plasma noradrenaline, the interassay coefficient is 8% and 9% respectively. The differences between the two assay techniques are not statistically significant. The sensitivity of both assays is also in the range of 1 picogram per milliliter (pg/ml).

3.2.4. Metabolic measurements

Blood Lactate

Blood lactate measurements were made by using a Boehringer UV Kit (Cat No149993) modified from Noll.F (1974) p1475 of 'Methods of enzymatic analysis' 2nd edition (H.U Bergmeyer ed).
Lactate assay was performed on the Lotus Bio analyser (Hoffman-La Roche & Co Ltd).

Plasma Potassium

Plasma potassium was measured by an ion-selective electrode (indirect).

Plasma Bicarbonate

Plasma bicarbonate (Total CO2) was measured by the American Monitor Method Sheet 292720-04 11/86.

Plasma Creatine Kinase

Plasma creatine kinase was measured with the standard method of the determination of creatine kinase according to the recommendations of the German Society of Clinical Chemistry (A M Diagnostics CPK Method Sheet, 293782-01).

3.2.5. Statistical analysis

The Ryan-Joiner test for normality was performed on the distributions of the main variables prior to further analysis (Ryan and Joiner, 1976).
The distributions for the resting and exercise heart rates and blood pressures, and those for the duration of the exercise tests were not significantly different from normal at the 95% confidence level for both the control and syndrome X groups.
Thus, means with associated standard deviations have been quoted to describe these variable distributions. Also for further analysis of these variables, to test for significant differences between the control and syndrome X groups the two-sample t test was employed at the 95% confidence level.
The catecholamine, lactate, potassium, bicarbonate and creatine kinase distributions were also tested for normality with the Ryan-Joiner method but for both the control and syndrome X groups non-normal distributions were shown at the 95% confidence level.

Thus, medians along with the interquartile range have been quoted in order to summarise these variables distributions.

Also, in further analysis, to test for significant differences between the control and syndrome X groups as regards these biological variables the two-tailed, Mann-Whitney test was employed (Armitage and Berry,1987).

In order to establish whether there is a correlation between the delta values for the plasma adrenaline and noradrenaline increases from pre-exercise to immediately post exercise and ST segment depression, the Spearman Rank Correlation Coefficient was calculated for the two groups (Altman,1991). This was chosen because no obvious correlation between the two variables was apparent in the scatter diagram comparing one against the other. The correlation coefficient was used to obtain a P value in order to perform a hypothesis test as to whether a correlation exists between the variables.

The same analytical technique was used for the percentage increase in the plasma adrenaline and noradrenaline concentrations from pre-exercise to immediately post-exercise and ST segment depression.

Because the age distributions of the control and syndrome X groups happened to be slightly different, further analysis beyond the Mann-Whitney test was required in order to establish whether age could be a factor in explaining any of the differences between the two groups that were statistically significant. The delta values for the noradrenaline concentrations from pre-exercise to immediately post-exercise were statistically different between the control and syndrome X groups, so to check whether age was a factor in this difference the data were analysed in two ways.

Firstly, linear regression analyses were performed on the control and syndrome X groups separately using age as an independent variable to test whether either of the slopes of the separate regression lines were statistically different from zero.

Secondly, the data for the delta values with the corresponding age value for the control and syndrome X groups were combined and a linear regression performed on the combined data set. This tests whether the slope of the regression line, using age as the independent variable, is statistically significantly different from zero.

Using the combined data set yields a test of greater power than analysing each group separately but cannot be performed alone because combining the data sets might obscure the fact that the two groups might react differently to age.

Data were analysed using the statistical package MINITAB (MINITAB Reference Manual, Release 9, July 1993, 0-925636-15-0).

Chapter 3.3. RESULTS

3.3.1. Resting electrocardiographic and blood pressure data

Electrocardiograms

In the control group, the resting electrocardiogram was normal in 28 subjects and in two subjects showed minor non-specific T wave depression.

In the syndrome X group, the electrocardiogram was again normal in a greater percentage of patients, and only showed slight T wave depression in three.

The data values for the resting pre-exercise heart rates are shown in Table 1.

The mean resting heart rate in the control group was 72 beats/min (SD=10.3) and in the syndrome X group was 69 beats/min (SD=9.8).

There was no significant statistical difference between the resting heart rate distributions of the two groups (Two-sample t test, P=0.26).

A histogram showing the distribution of the two groups heart rates values is given in Figure 1.

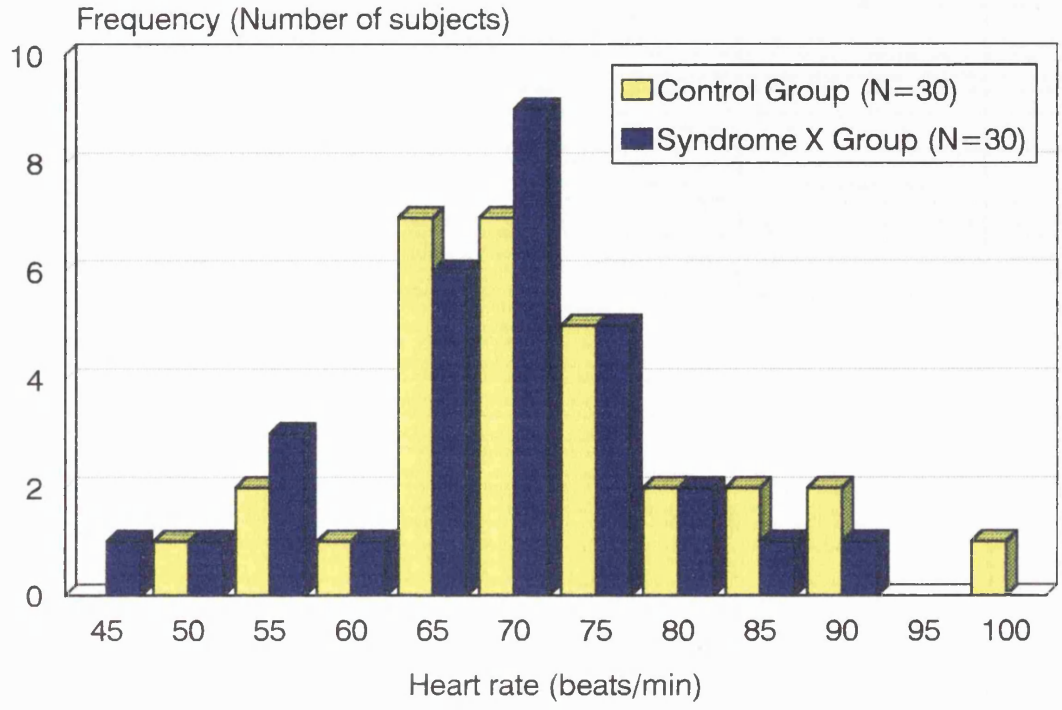
Blood pressures

Blood pressures were similar in both groups and are shown Table 1.

In the control group the mean resting blood pressure was 125/80 mmg (SD=13.9/8.8) and in the syndrome X group was again 125/80 mmHg (SD=11.3/9.0).

There was no significant statistical difference between systolic (Two-sample t test, P=0.99) and diastolic (Two-sample t test, P=0.77) blood pressures between the groups.

Figure 1.
Histogram of the pre-exercise resting heart rates for the control and syndrome X groups.



3.3.2. Exercise testing data

Duration of exercise tests

The duration of exercise tests was comparable in both control and syndrome X subjects allowing comparison of the various parameters studied.

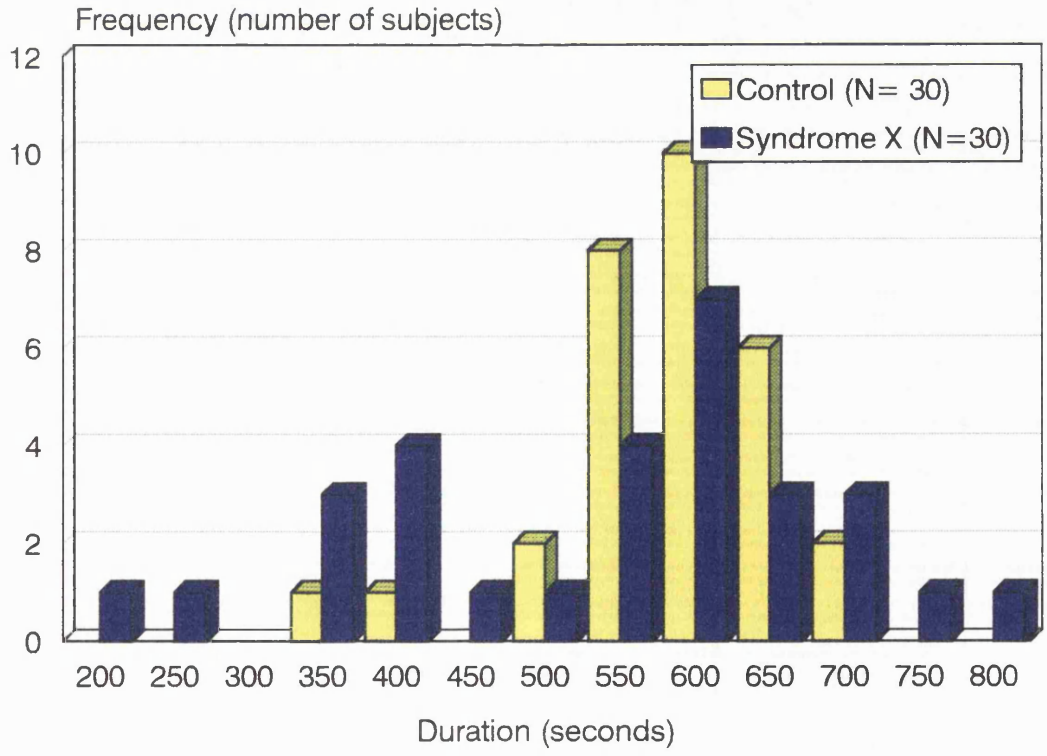
The data for the duration of exercise tests for both groups are shown in Table 2.

In the control group, the mean exercise test duration was 579 seconds (SD=80), whereas in the syndrome X group it was 539 seconds (SD=147).

There was no significant statistical difference in the duration of exercise tests between the two groups (Two-sample t test, P=0.2).

A histogram showing the distribution of the duration of the tests in the two groups is shown in Figure 2.

Figure 2.
Histogram of the duration of the exercise tests for the control and syndrome X groups.



Electrocardiograms

Heart rates:

The heart rate achieved immediately after exercise in both control and syndrome X subjects was comparable in both groups and is shown in Table 3.

In the control group the mean heart rate was 158 beats/min (SD=18) and in the syndrome X group was 155 beats/min (SD=18). There was no significant statistical difference between the two groups (Two-sample t test, P=0.46).

A histogram showing the distribution of the heart rates achieved immediately after exercise in both groups is shown in Figure 3.

Electrocardiographic changes:

In the control group the electrocardiograms were normal throughout the test.

Syndrome X patients showed varying degrees of ST segment depression immediately post-exercise which are shown in Table 3.

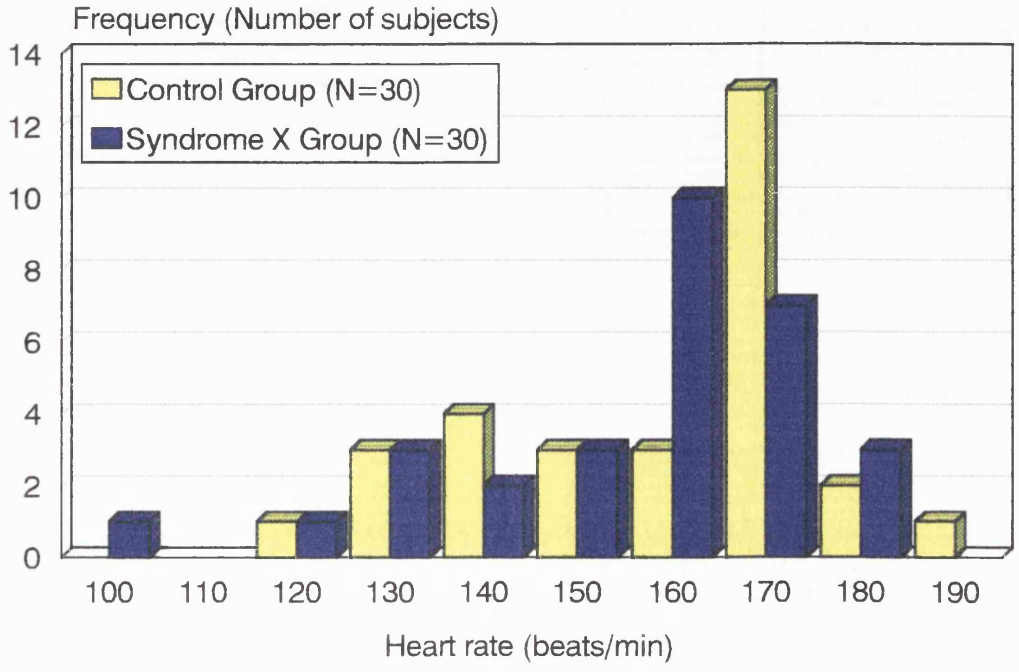
Blood pressures

The blood pressures achieved immediately after exercise in both control and syndrome X groups are shown in Table 3.

In the control group the mean blood pressure was 186/80 mm/Hg (SD=10.8/9.3) and in the syndrome X group was 188/80 mm/Hg (SD=11.4/10.0).

There was no significant statistical difference between the systolic (Two-sample t test, P=0.56) and diastolic (Two-sample t test, P=0.84) blood pressure distributions between the two groups.

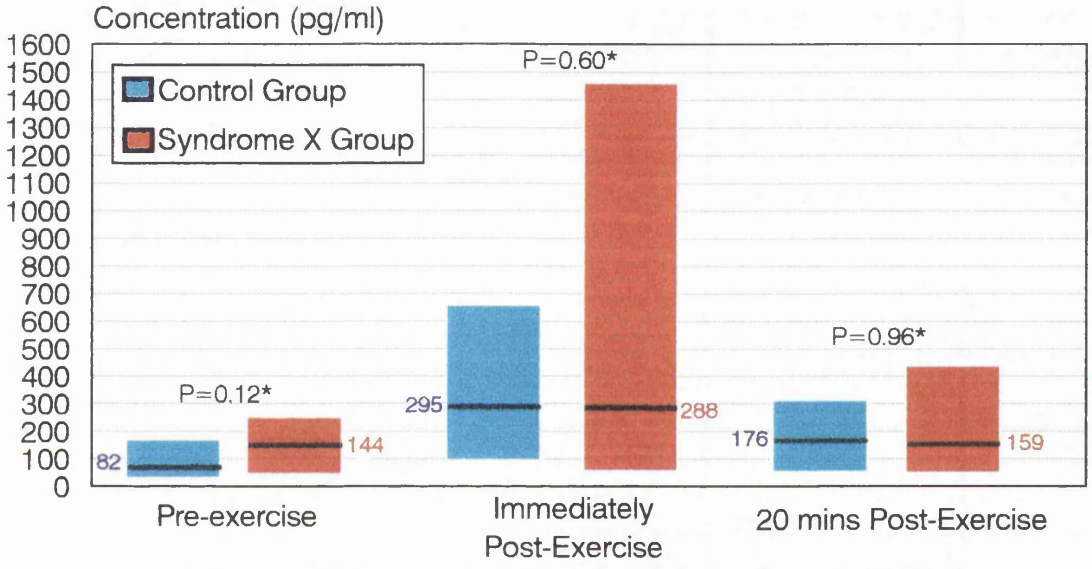
Figure 3.
Histogram of the immediately post-exercise heart rates for the control and syndrome X groups.



3.3.3. Catecholamine data at rest

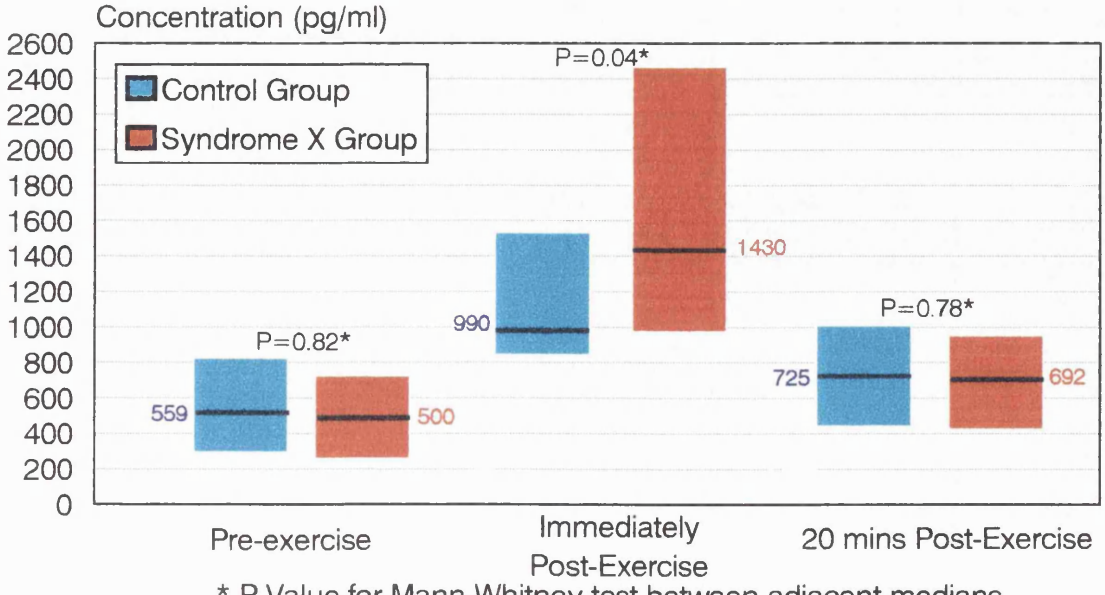
A bar chart illustrating how the median plasma adrenaline concentration for both the control and syndrome X groups vary over the course of the test is shown in Figure 4 and how plasma noradrenaline concentrations vary over the course of the test is shown in Figure 5.

Figure 4.
Median plasma adrenaline concentrations (with interquartile range) for the control and syndrome X groups over the course of the test.



* P Value for Mann-Whitney test between adjacent medians

Figure 5.
Median plasma noradrenaline concentrations (with interquartile range) for the control and syndrome X groups over the course of the test.



* P Value for Mann-Whitney test between adjacent medians

Resting, pre-exercise plasma catecholamine concentrations

Resting supine catecholamine plasma levels were similar in both control and syndrome X groups, there was no evidence of excess catecholamines in syndrome X (Table 4).
The median values, together with the interquartile range for both adrenaline and noradrenaline concentrations, are given in Table 4A.
In the control group, the median adrenaline concentration was 82(31,175) pg/ml and in the syndrome X group the median adrenaline concentration was144(49,249) pg/ml.
There was no significant statistical difference between the groups.
(Mann-Whitney, P=0.82)
In the control group the median noradrenaline concentration was 559(310,804) pg/ml and in the syndrome X group, the median noradrenaline concentration was 500 (262,769) pg/ml.
There was no significant statistical difference between the groups.
(Mann-Whitney, P= 0.11)

Resting plasma catecholamine concentrations during recovery

In the recovery period, 20 minutes after the cessation of exercise, plasma levels of both adrenaline and noradrenaline were slightly higher compared to the pre-exercise levels (Table 5).
The median values, together with the interquartile range for both adrenaline and noradrenaline are given in Table 5A.
In the control group the median plasma adrenaline concentration was 176(62,305) pg/ml and in the syndrome X group the median plasma adrenaline concentration was 159(52,430) pg/ml.
There was no significant statistical difference between the groups.
(Mann-Whitney, P=0.96)
In the control group the median plasma noradrenaline concentration was 725 (422,1000) pg/ml and in the syndrome X group the median noradrenaline concentration was 692 (409,964) pg/ml.
There was no significant statistical difference between the groups.
(Mann-Whitney, P=0.78)

3.3.4. Catecholamine data in response to exercise

With exercise adrenaline and noradrenaline plasma concentrations increased in both control and syndrome X groups and the actual plasma levels immediately post-exercise are shown in Table 6.

Adrenaline response to exercise:

The median values together with the interquartile range for the pre-exercise and immediately post-exercise plasma adrenaline concentrations are given in Table 6A.
In the control group, the median plasma adrenaline concentration increased from 82 (31,175) pg/ml at rest, to 295 (100,663) pg/ml immediately post exercise.
In the syndrome X group the median plasma adrenaline concentration increased from 144 (49,249) pg/ml to 288 (65,1457) pg/ml immediately after exercise.
Comparison of the two groups immediately after exercise showed that there was no significant statistical difference between them (Mann-Whitney, P=0.60).

Noradrenaline response to exercise:

The median values together with the interquartile range for the pre-exercise and immediately post-exercise plasma noradrenaline concentrations are given in Table 6A.
In the control group, the median plasma noradrenaline concentration increased from 559 (310,804) pg/ml at rest to 990 (857,1547) pg/ml immediately after exercise.
In the syndrome X group the median plasma noradrenaline concentration increased from 500 (262,769) pg/ml at rest to1430 (994,2448) pg/ml immediately after exercise.
Comparison of the two groups immediately after exercise showed that there was a significant statistical difference at a level of P=0.04 (Mann-Whitney).
Thus, at the 95% significance level, the data is compatible with there being a difference between the two immediately post-exercise plasma noradrenaline distributions.

Total catecholamine response to exercise

A bar chart illustrating how the median total (adrenaline + noradrenaline) plasma concentrations for both the control and syndrome X groups vary over the course of the test is shown in Figure 6.

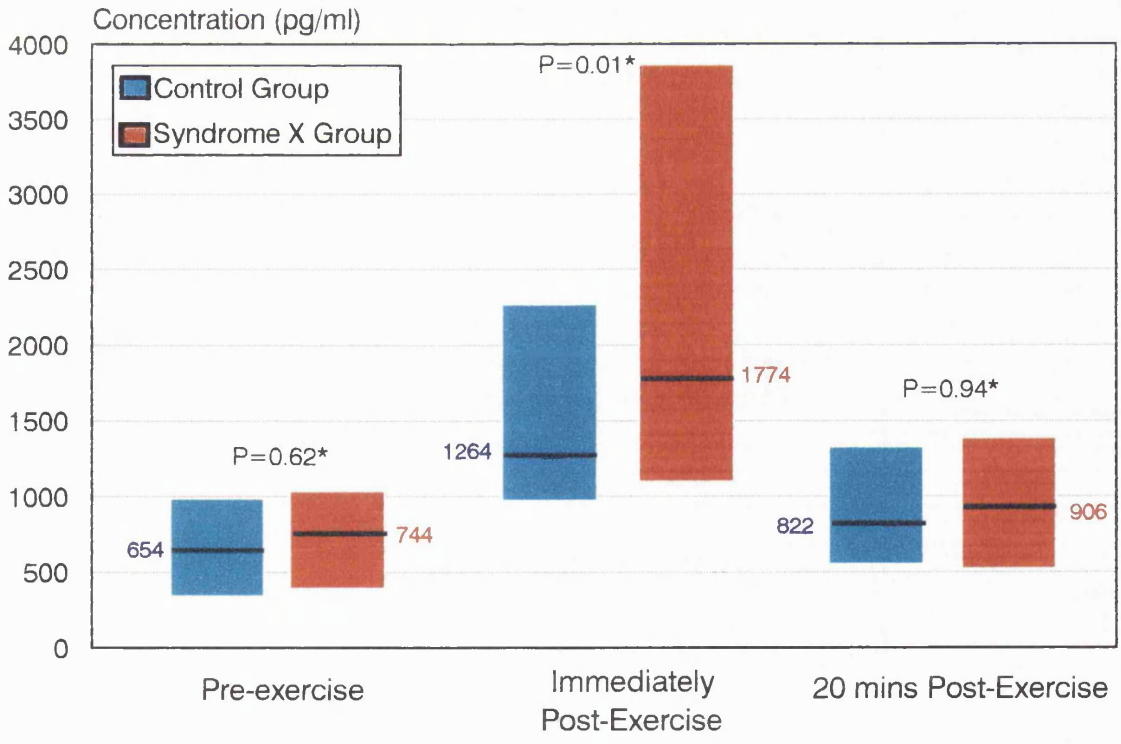
With exercise the total plasma catecholamine concentration increased in both groups. Resting, pre-exercise and immediately post-exercise values are shown in Table 7. The median values together with the interquartile range are given in Table 7A.

In the control group, the median total catecholamine concentration increased from 654 (357,953) pg/ml at rest, to1264 (965,2290) pg/ml immediately post-exercise.

In the syndrome X group the total catecholamine plasma concentration increased from 744 (407,1029) pg/ml at rest, to 1774 (1129,3857) pg/ml immediately post-exercise.

Comparison of the two groups immediately post-exercise showed that there was a highly significant statistical difference (Mann-Whitney, P=0.01).

Figure 6.
Median total plasma catecholamine concentrations (with interquartile range) for the control and syndrome X groups over the course of the test.



* P Value for Mann-Whitney test between adjacent medians

Plasma catecholamine concentration changes from pre-exercise to immediately post-exercise (delta values)

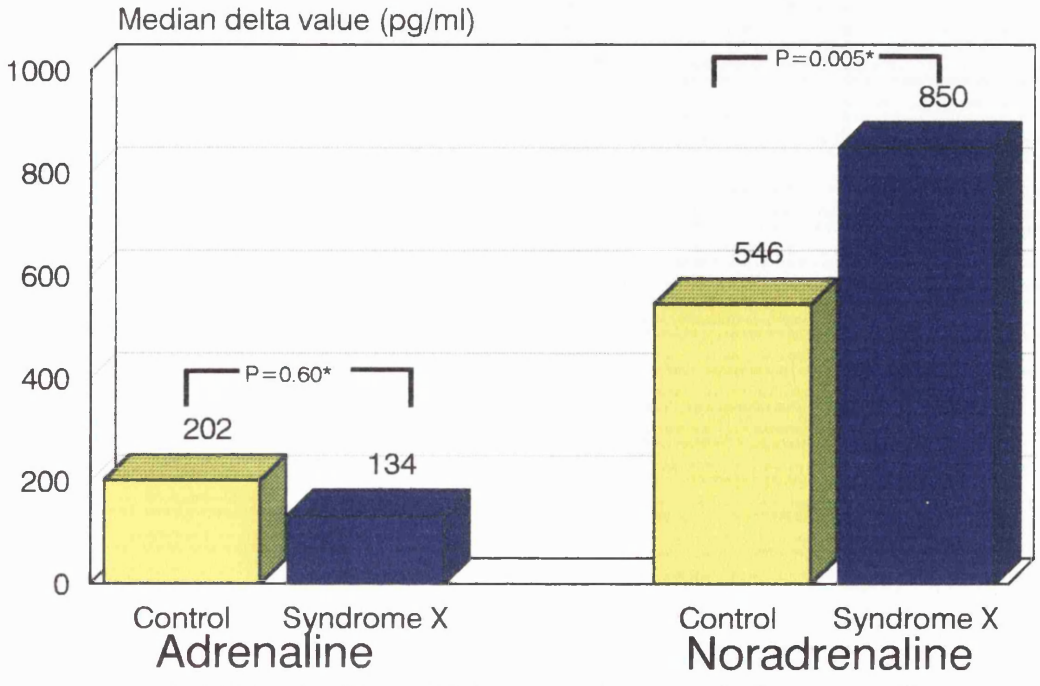
A box plot illustrating the median plasma adrenaline and noradrenaline concentration changes from pre-exercise to immediately post-exercise (delta values) is shown in Figure 7. This figure also lists the P values for the Mann-Whitney tests of significance between each of the two distributions at the pre-exercise and immediately post-exercise points.

The increases in the plasma catecholamine concentrations from pre-exercise to immediately post-exercise (delta values) for both the control and syndrome X subjects are shown in Table 8. The median delta values together with the interquartile range for the changes are given in Table 8A.

The median pre-exercise to immediately post-exercise change score for adrenaline was 202 (32,476) pg/ml for the control group and 134 (12,1233) pg/ml for the syndrome X groups. There was no statistical significant difference between the groups. (Mann-Whitney, P=0.60)

The median pre-exercise to immediately post-exercise change score for noradrenaline was 546 (260,901) pg/ml for the control group and 850 (520,1926) pg/ml for the syndrome X group. There was a highly significant statistical difference between the groups (P=0.005). Thus, at the 99% significance level, the data is compatible with there being a difference in delta noradrenaline values between the control and syndrome X groups.

Figure 7.
Median delta values for the plasma adrenaline and noradrenaline concentrations from pre-exercise to immediately post-exercise.



* P Value for Mann-Whitney test between indicated medians

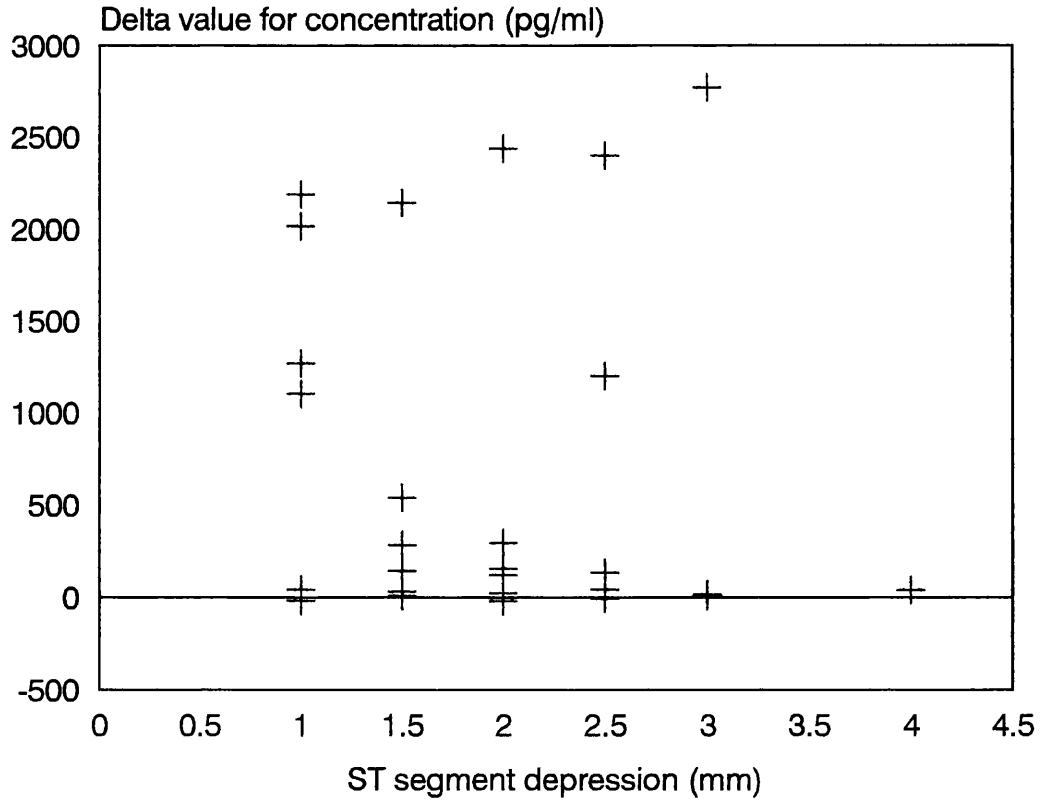
Relation between plasma catecholamine concentration changes from pre-exercise to immediately post-exercise (delta values) and immediately post-exercise ST segment depression in syndrome X patients

Adrenaline concentrations versus ST segment depression:

A graph illustrating the increase in the plasma adrenaline concentrations from pre-exercise to immediately post-exercise (delta values) versus ST segment depression immediately post-exercise in syndrome X patients is shown in Figure 8 .

From this scatter plot it is apparent that there is no correlation between the two parameters (The Spearman Rank Correlation Coefficient is - 0.094 which is not significant with a P value >0.2).

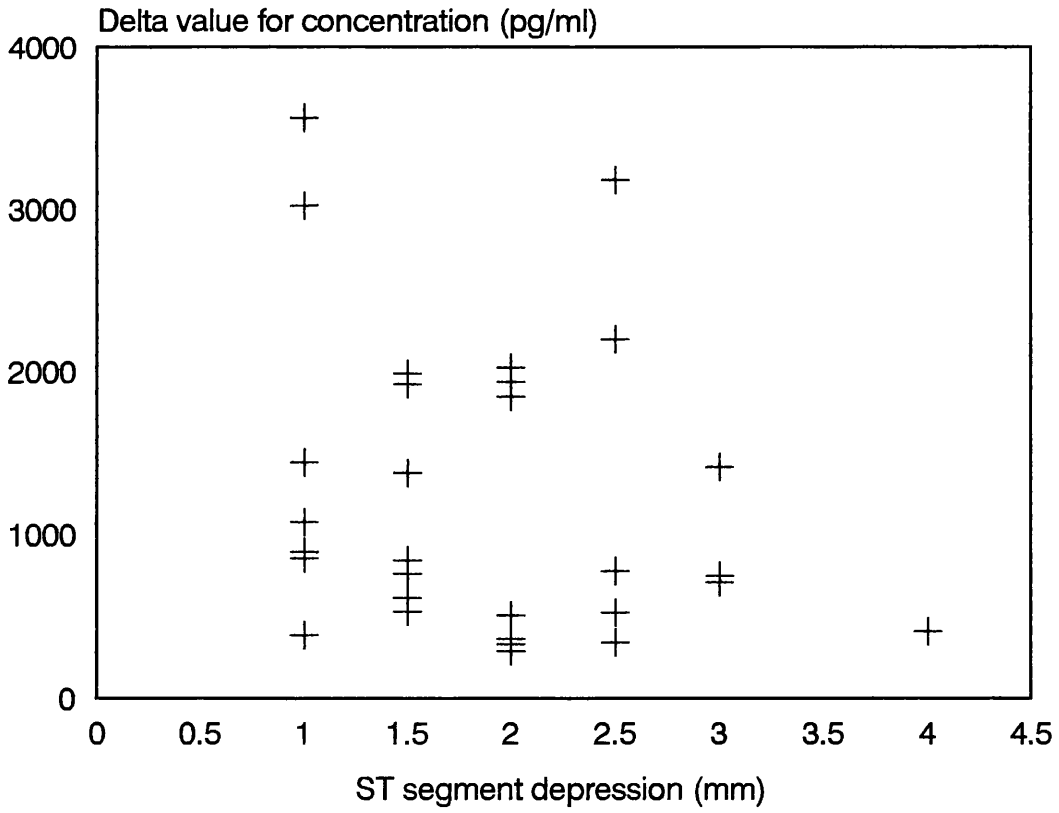
Figure 8.
Scatterplot of the delta values for the plasma adrenaline concentration from pre-exercise to immediately post-exercise versus ST segment depression for the syndrome X group.



Noradrenaline concentrations versus ST segment depression:

A graph illustrating the increase in the plasma noradrenaline concentrations from pre-exercise to immediately post-exercise (delta values) versus ST segment depression immediately post-exercise is shown in Figure 9.
From this scatter plot it is apparent that that there is no correlation between the two parameters (The Spearman Rank Correlation Coefficient is -0.244 which is not significant with a P value >0.1).

Figure 9.
Scatterplot of the delta values for the plasma noradrenaline concentration from pre-exercise to immediately post-exercise versus ST segment depression for the syndrome X group.



Percentage increase in the plasma concentration of catecholamines from pre-exercise to immediately post-exercise

The percentage increases in the median plasma catecholamine concentrations from pre-exercise to immediately post-exercise are illustrated in a bar chart in Figure 10. This Figure also lists the P values for the Mann-Whitney tests of significance for the percentage increases in adrenaline and noradrenaline serum concentrations.
The percentage increases in the adrenaline and noradrenaline median plasma concentrations are given in Table 9. The median percentage increase together with the interquartile range are given in Table 9A .

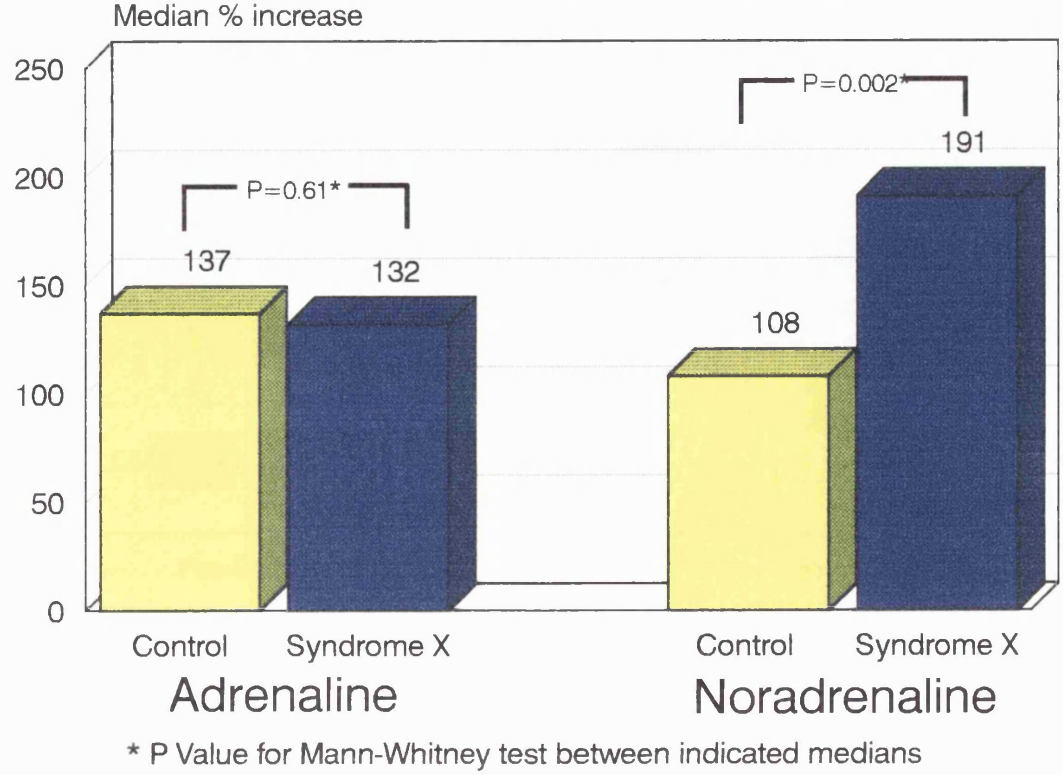
Plasma adrenaline:

In the control group the median plasma adrenaline percentage increase was 137% (55,498%) and in the syndrome X group was 132% (20,522%)
There was no significant difference between the groups (Mann-Whitney P=0.61).

Plasma noradrenaline:

In the control group the median plasma noradrenaline percentage increase was 108% (60,173%) and in the syndrome X group was 191% (109,313%). There was a highly significant statistical difference between the groups (Mann Whitney, P=0.002).
Thus, at the 99% significant level, the data are compatible with there being a difference between the two percentage increases in noradrenaline distributions.

Figure 10.
Median percentage increase in the plasma adrenaline and noradrenaline concentrations from pre-exercise to immediately post-exercise.



* P Value for Mann-Whitney test between indicated medians

3.3.5. Metabolic data

Blood lactate

A bar chart illustrating how the median blood lactate concentrations vary over the course of the test for both the control and syndrome X groups is shown in Figure 11. Blood lactate concentrations were similar at pre-exercise,immediately post-exercise and in the recovery period in both control and syndrome X groups and are shown in Table 10.The median values together with the interquartile range are given in Table 10A.

Resting pre-exercise blood lactate concentrations

In the control group the median lactate concentration was 1.2 (0.82,1.35) mmol/l and in the syndrome X group was 1.24 (0.83,2.28) mmol/l (Table 10A). There was no significant statistical difference between the two groups (Mann-Whitney, P=0.24).

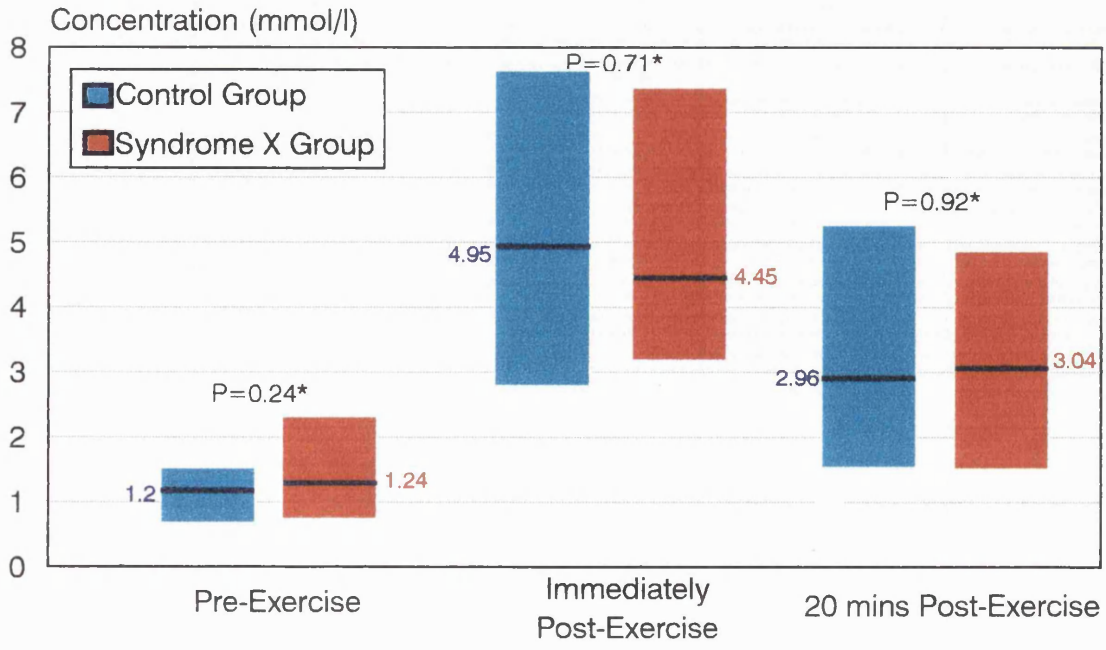
Immediately post exercise blood lactate concentrations

In the control group the median lactate concentration was 4.95 (2.93,7.73) mmol/l and in the syndrome X group was 4.45 (3.13,7.31) mmol/l (Table 10A). There was no significant statistical difference between the two groups (Mann-Whitney, P=0.71).

Blood lactate concentrations during recovery.

In the control group the median lactate concentration was 2.96(1.6,5.2) mmol/l and in the syndrome X group was 3.04(1.57,4.8) mmol/l (Table 10A). There was no significant statistical difference between the groups (Mann-Whitney, P=0.92).

Figure 11.
Median blood lactate concentrations (with interquartile range) for the control and syndrome X groups over the course of the test.



* P Value for Mann-Whitney test between adjacent medians

Plasma potassium

A bar chart illustrating how the median plasma potassium concentrations vary over the course of the test in both the control and syndrome X groups is shown in Figure 12. Plasma potassium levels were similar in both control and syndrome X groups at pre-exercise, immediately post-exercise and in the recovery period and are shown in Table 11. The median values together with the interquartile are shown in Table 11A.

Resting pre-exercise plasma potassium concentrations

In the control group the median plasma potassium concentration was 4.1 (3.85,4.4) mmol/l and in the syndrome X group was 4.0 (3.7,4.2) mmol/l (Table 11A). There was no significant statistical difference between the two groups (Mann-Whitney, P=0.16).

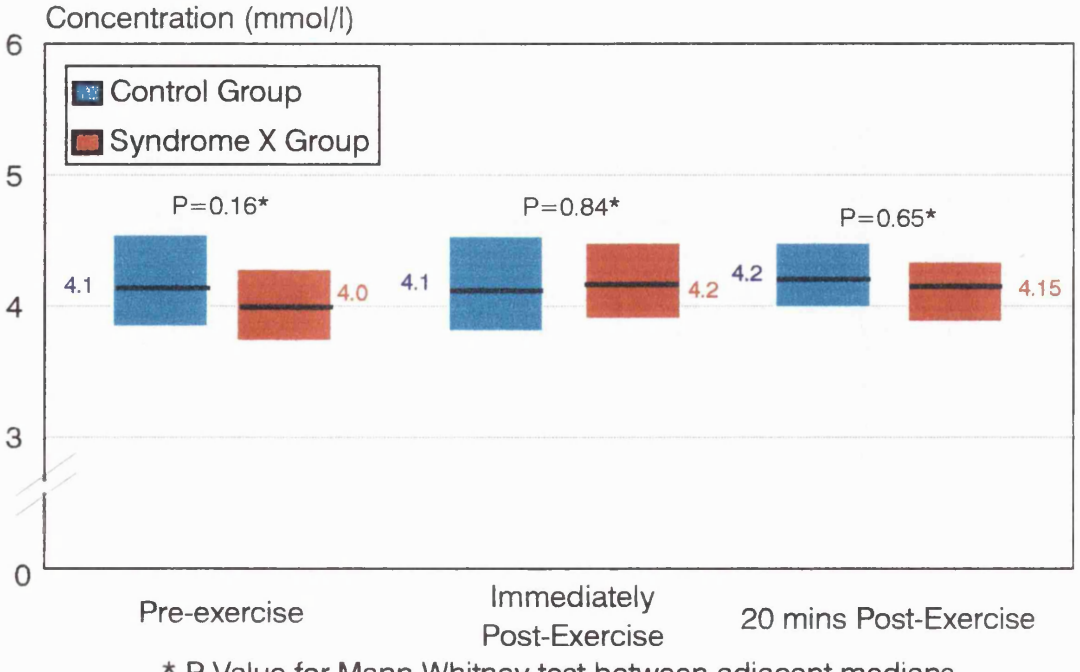
Immediate post-exercise plasma potassium concentrations

In the control group the median plasma potassium concentration was 4.1(3.8,4.4) mmol/l and in the syndrome X group was 4.2 (3.95,4.4) mmol/l (Table 11A).There was no significant statistical difference between the two groups (Mann-Whitney, P=0.84).

Plasma potassium concentrations during recovery.

In the control group the median plasma potassium concentration was 4.2(4.0,4.4) mmol/l and in the syndrome X group was 4.15 (3.9,4.3) mmol/l (Table 11A).There was no significant statistical difference between the two groups (Mann-Whitney, P=0.65).

Figure 12.
Median plasma potassium concentrations (with interquartile range) for the control and syndrome X groups over the course of the test.



* P Value for Mann-Whitney test between adjacent medians

Plasma bicarbonate

A bar chart illustrating how the median plasma bicarbonate concentrations vary over the course of the test for both the control and syndrome X groups is shown in Figure 13 Plasma bicarbonate levels were similar at pre-exercise, immediately post-exercise and in the recovery period and are shown in Table 12. The median values of plasma bicarbonate concentrations together with the interquartile range are given in Table 12A.

Resting pre-exercise plasma bicarbonate concentrations.

In the control group the median plasma bicarbonate concentration was 23.5(20.0,25.0) mmol/l and in the syndrome X group was 24.0 (21.5,25.5) mmol/l (Table 12A). There was no significant statistical difference between the two groups(Mann-Whitney,P=0.56).

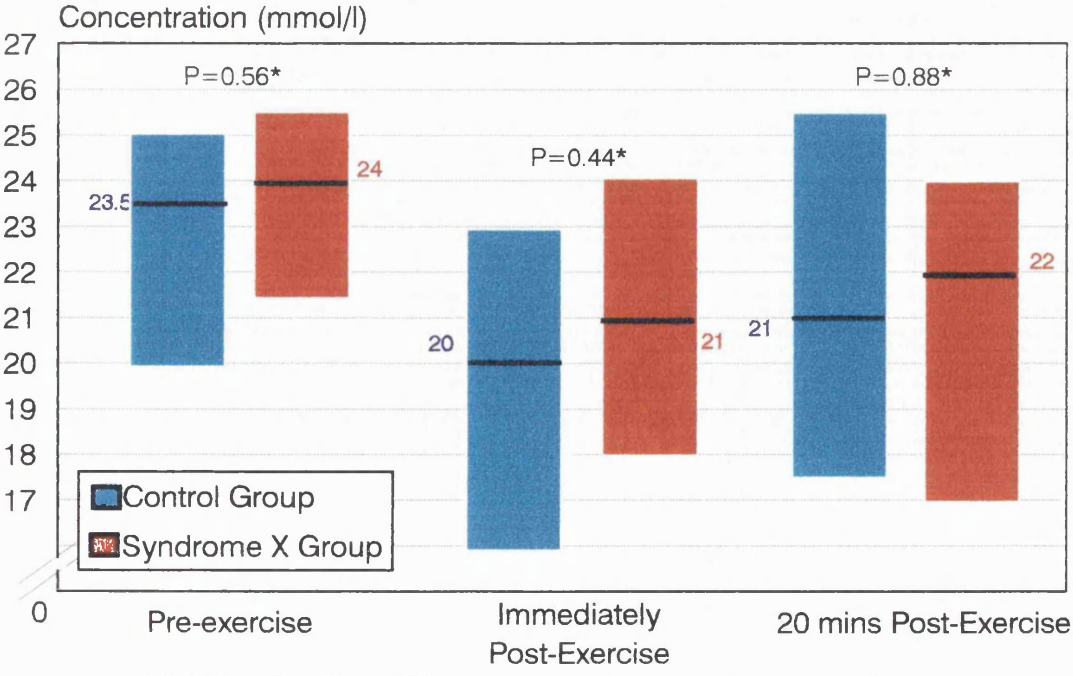
Immediate post-exercise plasma bicarbonate concentrations

In the control group the median plasma bicarbonate concentration was 20.0(16.0,23.0) mmol/l and in the syndrome X group was 21.0 (18.0,24.0) mmol/l (Table 12A). There was no significant statistical difference between the two groups (Mann-Whitney, P=0.4).

Plasma bicarbonate concentrations during recovery.

In the control group the median plasma bicarbonate concentration was 21.0(17.5,25.5) mmol/l and in the syndrome X group was 22.0 (17.0,24.0) mmol/l (Table 12A). There was no significant statistical difference between the two groups(Mann-Whitney,P=0.88).

Figure 13.
Median plasma bicarbonate concentrations (with interquartile range) for the control and syndrome X groups over the course of the test.



* P Value for Mann-Whitney test between adjacent medians

Plasma creatine kinase

A bar chart showing how the median plasma creatine kinase concentrations vary over the course of the test is shown in Figure 14.

Plasma creatine kinase levels were similar in both control and syndrome X groups at pre-exercise,immediately post-exercise and in the recovery period and are shown in Table13.The median values together with the interquartile range are shown inTable13A.

Resting, pre-exercise creatine kinase concentrations

In the control group the median plasma creatine kinase concentration was 88 (66.127) IU/L and in the syndrome X group was 99 (67,117) IU/L (Table 13A). There was no significant statistical difference between the two groups (Mann-Whitney, P=0.96).

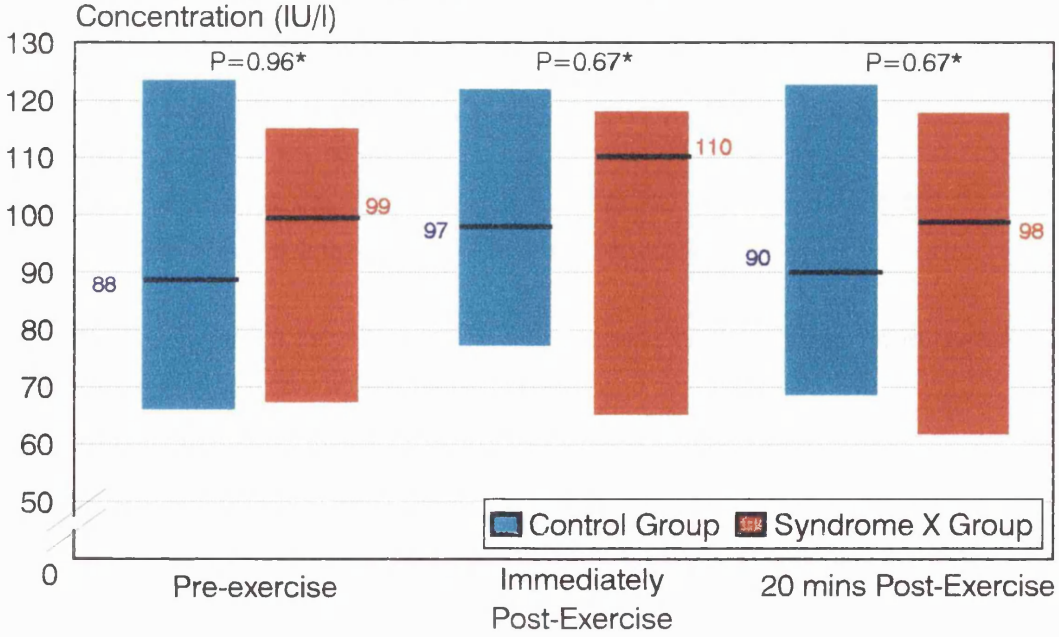
Immediately post-exercise creatine kinase concentrations

In the control group the median plasma creatine kinase concentration was 97 (76,122) IU/L and in the syndrome X group was 110 (64,119) IU/L (Table 13A). There was no significant statistical difference between the two groups (Mann-Whitney, P= 0.67).

Plasma creatine kinase concentrations during recovery

In the control group the median plasma creatine kinase concentration was 90 (69,124) IU/L and the syndrome X was 98 (62,118) IU/L (Table 13A). There was no significant statistical difference between the two groups (Mann-Whitney, P=0.67).

Figure 14.
Median plasma creatine kinase concentrations (with interquartile range) for the control and syndrome X groups over the course of the test.



* P Value for Mann-Whitney test between adjacent medians

3.3.6. Tables

List of Tables:

Note: In these Tables an asterisk indicates a missing value.

Table 1.

Resting, pre-exercise heart rates (beats/min) and blood pressures (mm/Hg) for the control and syndrome X groups.

Control		
ID No	Heart Rate	Blood Pressure
1	77	140/85
2	98	130/85
3	57	130/80
4	74	120/85
5	56	130/80
6	70	135/75
7	70	140/90
8	76	145/80
9	62	135/80
10	90	155/80
11	52	125/85
12	66	140/70
13	73	140/75
14	67	105/65
15	68	120/80
16	66	120/80
17	64	120/70
18	64	120/80
19	69	130/80
20	71	120/80
21	83	145/85
22	73	125/85
23	64	115/75
24	79	115/75
25	68	100/70
26	71	100/65
27	90	110/65
28	79	110/75
29	67	110/80
30	85	120/85

Syndrome X		
ID No	Heart Rate	Blood Pressure
1	69	120/80
2	72	110/85
3	69	125/75
4	71	100/70
5	71	105/75
6	91	120/80
7	63	120/80
8	47	120/80
9	59	125/85
10	77	135/75
11	76	145/90
12	70	120/80
13	64	130/85
14	70	120/70
15	51	130/75
16	79	135/80
17	67	115/65
18	74	130/75
19	75	140/80
20	57	140/85
21	74	130/85
22	57	135/90
23	57	120/65
24	82	140/80
25	64	115/70
26	87	125/85
27	64	125/80
28	64	115/70
29	72	145/75
30	68	115/85

Table 2.

Duration of exercise tests for the control and syndrome X groups (seconds).

ID No	Control	Syndrome X
1	600	600
2	600	618
3	710	218
4	540	720
5	530	530
6	400	420
7	600	360
8	635	390
9	540	720
10	480	470
11	720	540
12	540	420
13	600	660
14	620	580
15	660	600
16	660	390
17	360	750
18	540	270
19	540	540
20	480	660
21	600	720
22	600	360
23	630	780
24	630	660
25	540	360
26	600	540
27	540	600
28	600	480
29	600	600
30	660	600

Table 3.

Immediately post-exercise heart rates (beats/min), blood pressures (mm/Hg) and ST segment depressions (mm) for the control and syndrome X groups.

Control			
ID No	Heart Rate	Blood Pressure	ST Segment Depression
1	163	190/80	0
2	171	170/90	0
3	176	190/80	0
4	170	185/90	0
5	134	185/80	0
6	165	180/80	0
7	142	195/90	0
8	186	210/90	0
9	167	200/80	0
10	144	185/100	0
11	168	195/90	0
12	141	190/65	0
13	160	200/65	0
14	148	190/80	0
15	166	195/75	0
16	132	185/80	0
17	115	180/70	0
18	126	180/90	0
19	136	180/80	0
20	160	200/65	0
21	168	195/90	0
22	165	180/70	0
23	154	190/80	0
24	148	165/70	0
25	172	165/80	0
26	182	180/65	0
27	172	165/75	0
28	174	185/70	0
29	172	185/80	0
30	172	190/70	0

Syndrome X			
ID No	Heart Rate	Blood Pressure	ST Segment Depression
1	172	190/80	2
2	176	190/80	1.5
3	120	190/80	1.5
4	171	200/60	1.5
5	150	165/75	4
6	166	190/80	2
7	141	200/80	2.5
8	130	190/80	2.5
9	148	185/90	1
10	157	195/100	1.5
11	163	195/90	2.5
12	130	180/85	1
13	163	200/65	1
14	168	190/65	1.5
15	141	200/65	1
16	148	170/90	3
17	167	180/65	2
18	158	190/60	2
19	168	185/90	1
20	163	190/90	2.5
21	156	190/85	1
22	102	180/85	2
23	178	190/80	3
24	178	200/80	2
25	127	150/80	1.5
26	156	185/80	2
27	162	205/80	1
28	155	190/90	3
29	168	190/90	1.5
30	164	180/80	2.5

Table 4.

Resting, pre-exercise plasma catecholamine concentrations (pg/ml).

	Adrenaline		Noradrenaline		
ID No	Control	Syndrome X	ID No	Control	Syndrome X
1	250	101	1	1045	501
2	213	467	2	320	672
3	485	2190	3	801	499
4	20	115	4	129	147
5	79	13	5	685	750
6	118	170	6	358	682
7	99	414	7	148	1208
8	188	184	8	1174	563
9	95	240	9	720	383
10	23	274	10	684	467
11	58	466	11	811	852
12	86	354	12	1089	1476
13	294	35	13	1168	910
14	25	405	14	953	993
15	120	152	15	426	690
16	267	216	16	677	633
17	224	222	17	893	959
18	50	32	18	627	417
19	25	61	19	769	394
20	38	31	20	202	156
21	27	136	21	280	739
22	171	116	22	459	252
23	31	167	23	209	826
24	39	200	24	491	220
25	29	9	25	276	188
26	23	53	26	343	251
27	91	21	27	440	439
28	84	87	28	253	411
29	35	24	29	328	247
30	75	65	30	760	265

Table 4A.
Pre-exercise median plasma adrenaline and noradrenaline concentrations with interquartile range.

	Median Adrenaline Concentration (pg/ml)	Median Noradrenaline Concentration (pg/ml)
Control Group	82 (31, 175)	559 (310, 804)
Syndrome X Group	144 (49, 249)	500 (262, 769)

Table 5.

Resting plasma catecholamine concentrations during recovery (pg/ml).

	Adrenaline		Noradrenaline	
ID No	Control	Syndrome X	Control	Syndrome X
1	*	54	*	507
2	199	112	545	722
3	320	3769	1949	852
4	47	166	312	190
5	305	98	725	386
6	213	662	519	832
7	186	517	391	1347
8	162	528	1176	852
9	121	681	955	662
10	116	26	811	416
11	59	1134	890	1762
12	212	222	2167	776
13	430	186	1433	946
14	334	251	1034	1257
15	62	377	493	838
16	314	452	785	1036
17	277	423	1131	1128
18	408	40	1000	541
19	361	32	757	495
20	52	46	225	220
21	35	151	390	826
22	207	175	615	335
23	*	175	*	1092
24	54	136	530	344
25	36	13	422	118
26	117	32	359	556
27	176	9	478	496
28	87	68	271	1016
29	*	61	*	446
30	82	79	732	323

Table 5A.
Recovery median plasma adrenaline and noradrenaline concentrations with interquartile range.

	Median Adrenaline Concentration (pg/ml)	Median Noradrenaline Concentration (pg/ml)
Control Group	176 (62, 305)	725 (422, 1000)
Syndrome X Group	159 (52, 430)	692 (409, 964)

Table 6.

Plasma catecholamine concentrations immediately post-exercise (pg/ml).

	Adrenaline		Noradrenaline	
ID No	Control	Syndrome X	Control	Syndrome X
1	566	394	1825	1008
2	472	609	785	1202
3	980	*	1341	2422
4	275	397	680	763
5	526	51	1010	1159
6	657	288	1316	2528
7	569	1612	402	3406
8	684	318	3154	1088
9	173	2254	970	3406
10	764	814	2104	1309
11	92	2864	1047	4033
12	1058	2541	2475	5041
13	679	1303	2050	1806
14	974	2546	1398	2980
15	107	1253	922	2133
16	314	2987	939	1342
17	815	2658	1464	2983
18	341	26	1255	748
19	315	43	955	780
20	55	72	280	495
21	38	178	523	1596
22	234	269	881	541
23	102	183	348	2239
24	143	177	1896	583
25	49	16	767	950
26	47	74	917	2186
27	240	22	1408	1518
28	64	95	901	1159
29	17	55	893	1624
30	183	57	1797	1042

Table 6A.
Immediately post-exercise median plasma adrenaline and noradrenaline concentrations with interquartile range.

	Median Adrenaline Concentration (pg/ml)	Median Noradrenaline Concentration (pg/ml)
Control Group	295 (100, 663)	990 (857, 1547)
Syndrome X Group	288 (65, 1457)	1430 (994, 2448)

Table 7.

Pre-exercise total (adrenaline + noradrenaline) plasma catecholamine concentrations and immediately post-exercise total plasma catecholamine concentrations (pg/ml).

	Pre-exercise		Immediately post-exercise		
ID No	Control	Syndrome X	ID No	Control	Syndrome X
1	1295	602	1	2391	1402
2	533	1139	2	1257	1811
3	1286	2689	3	2321	*
4	149	262	4	955	1160
5	764	763	5	1536	1210
6	476	852	6	1973	2816
7	247	1622	7	971	5018
8	1362	747	8	3838	1406
9	815	623	9	1143	5660
10	707	741	10	2868	2123
11	869	1318	11	1139	6897
12	1175	1830	12	3533	7582
13	1462	945	13	2729	3109
14	978	1398	14	2372	5526
15	546	842	15	1029	3386
16	944	849	16	1253	4329
17	1117	1181	17	2279	5641
18	677	449	18	1596	774
19	794	455	19	1270	823
20	240	187	20	335	567
21	307	875	21	561	1774
22	630	368	22	1115	810
23	240	993	23	450	2422
24	530	420	24	2039	760
25	305	197	25	816	966
26	366	304	26	964	2260
27	531	460	27	1648	1540
28	337	498	28	965	1254
29	363	271	29	910	1679
30	835	330	30	1980	1099

Table 7A.

Pre-exercise and immediately post-exercise median total plasma catecholamine concentrations with interquartile range.

	Median Total Catecholamine Concentration (pg/ml) Pre-exercise	Median Total Catecholamine Concentration (pg/ml) Immediately post-exercise
Control Group	654 (357, 953)	1264 (965, 2290)
Syndrome X Group	744 (407, 1029)	1774 (1129, 3857)

Table 8.

Delta values for the plasma catecholamine concentrations from pre-exercise to immediately post-exercise (pg/ml).

	Adrenaline		Noradrenaline		
ID No	Control	Syndrome X	ID No	Control	Syndrome X
1	316	293	1	780	507
2	259	142	2	465	530
3	495	*	3	540	1923
4	255	282	4	551	616
5	447	38	5	325	409
6	539	118	6	958	1846
7	470	1198	7	254	2198
8	496	134	8	1980	525
9	78	2014	9	250	3023
10	741	540	10	1420	842
11	34	2398	11	236	3181
12	972	2187	12	1386	3565
13	385	1268	13	882	896
14	949	2141	14	445	1987
15	-13	1101	15	496	1443
16	47	2771	16	262	709
17	591	2436	17	571	2024
18	291	-6	18	628	331
19	290	-18	19	186	386
20	17	41	20	78	339
21	11	42	21	243	857
22	63	153	22	422	289
23	71	16	23	139	1413
24	104	-23	24	1405	363
25	20	7	25	491	762
26	24	21	26	574	1935
27	149	1	27	968	1079
28	-20	8	28	648	748
29	-18	31	29	565	1377
30	108	-8	30	1037	777

Table 8A.

Median delta values for the plasma adrenaline and noradrenaline concentrations from pre-exercise to immediately post-exercise with interquartile range.

	Median Delta Value for Adrenaline Concentration (pg/ml)	Median Delta Value for Noradrenaline Concentration (pg/ml)
Control Group	202 (32, 476)	546 (260, 901)
Syndrome X Group	134 (12, 1233)	850 (520, 1926)

Table 9.

Percentage increases in the plasma adrenaline and noradrenaline concentrations from pre-exercise to immediately post-exercise.

	Adrenaline		Noradrenaline		
ID No	Control	Syndrome X	ID No	Control	Syndrome X
1	126	290	1	75	101
2	121	30	2	145	79
3	102	*	3	67	385
4	1275	245	4	427	419
5	566	292	5	47	55
6	457	69	6	268	271
7	475	289	7	172	182
8	264	72	8	169	93
9	82	839	9	35	789
10	3222	197	10	208	180
11	59	514	11	29	373
12	1130	617	12	127	242
13	131	3622	13	76	98
14	3796	528	14	47	200
15	-11	724	15	116	209
16	18	1282	16	39	112
17	264	1097	17	64	211
18	582	-18	18	100	79
19	1160	-29	19	24	98
20	45	132	20	39	217
21	41	30	21	87	116
22	37	131	22	92	115
23	229	9	23	67	171
24	267	-11	24	286	165
25	69	77	25	178	405
26	104	39	26	167	771
27	164	4	27	220	246
28	-24	9	28	256	182
29	-51	129	29	172	887
30	144	-12	30	136	293

Table 9A.

Median percentage increase in the plasma adrenaline and noradrenaline concentrations from pre-exercise to immediately post-exercise (with interquartile range).

	Median % increase in the Adrenaline conc. from pre-exercise to immediately post-exercise	Median % increase in the Noradrenaline conc. from pre-exercise to immediately post-exercise
Control Group	137 (55, 498)	108 (60, 173)
Syndrome X Group	132 (20, 522)	191 (109, 313)

Table 10.

Blood lactate concentrations for pre-exercise, immediately post-exercise and 20 minute recovery (mmol/l).

	Pre-exercise		Immediately post-exercise		20 minute recovery	
ID No	Control	Syndrome X	Control	Syndrome X	Control	Syndrome X
1	6.2	2.2	7.2	3.5	1.6	2.9
2	0.74	3.4	3.55	4.6	*	4.1
3	1.49	2.2	6.06	2.9	5.68	3.5
4	1.26	3.4	4.59	4.6	2.07	4.1
5	0.6	1.8	2.65	6.7	1.65	7.7
6	1.35	6.2	4.22	12.9	2.74	6.6
7	0.59	1.1	2.92	7.8	1.9	5
8	0.84	*	6.38	*	4.72	*
9	1.23	0.7	13.7	4.8	5.33	1.9
10	1.22	2.16	4.53	5.37	2.96	3.43
11	*	2.3	8.34	10.2	5.07	6.6
12	1.79	1.21	2.37	1.57	1.67	1.16
13	0.75	0.8	14.07	3.93	2.96	1.48
14	1.27	1.32	7.89	4.15	7.54	2.76
15	0.91	0.6	1.05	1.57	1.77	1.05
16	1.53	0.71	5.73	4.31	4.7	2.64
17	1.42	1.13	1.84	3.01	0.52	1.57
18	0.82	1.27	0.8	3.58	0.69	1.56
19	1.2	*	2.94	*	*	*
20	0.56	0.61	10.66	6.3	1.18	4.6
21	1.07	1.09	1.9	2	1.08	0.79
22	0.63	3.3	5.56	6.05	9.43	1.77
23	1.23	2.58	17.94	10.71	13.29	5.15
24	*	0.51	*	8.71	*	3.68
25	*	0.54	*	1.54	*	1.01
26	1.05	0.9	5.31	2.34	4	1.58
27	1.6	1.67	7.25	3.8	3.97	2.99
28	1	0.91	4.5	4.3	1.1	3.08
29	1.3	1.15	3.7	8.52	*	4.9
30	1.19	2.37	10.64	7.51	5.49	5.57

Table 10A.

Pre-exercise, immediately post-exercise and recovery median blood lactate concentrations with interquartile range.

	Median Lactate Concentration (mmol/l) Pre-exercise	Median Lactate Concentration (mmol/l) Immediately post-exercise	Median Lactate Concentration (mmol/l) after 20 min. recovery
Control Group	1.2 (0.82, 1.35)	4.95 (2.93, 7.73)	2.96 (1.63, 5.2)
Syndrome X Group	1.24 (0.83, 2.28)	4.45 (3.13, 7.31)	3.04 (1.57, 4.83)

Table 11.

Plasma potassium concentrations for pre-exercise, immediately post-exercise and 20 minute recovery (mmol/l).

	Pre-exercise		Immediately post-exercise		20 minute recovery	
ID No	Control	Syndrome X	Control	Syndrome X	Control	Syndrome X
1	3.9	3.6	3.8	4.6	4.5	4
2	3.5	4.2	4.1	4.4	4.1	4.3
3	4	4.1	4.2	4	4.2	3.6
4	4.1	4.2	4	4.4	4	4.3
5	4.8	4.6	4.4	4.6	4.2	4.4
6	*	4.1	*	3.6	*	4.1
7	4.4	4.4	4.4	4.3	4.2	*
8	3.8	*	4	*	4.1	*
9	3.8	4.4	3.7	4	3.9	4.3
10	3.6	3.7	3.6	3.9	3.7	3.9
11	4.3	3.7	4.8	4.2	3.9	4.1
12	3.9	4	4.1	4.3	3.8	3.9
13	3.7	4	3.8	4.2	4.2	4.2
14	4.3	4.2	4	4.1	*	4.2
15	3.8	4.2	3.9	4.3	4	4.1
16	4.6	4.2	4.6	4.5	4.9	4.4
17	5.5	4	5.2	4.5	4.9	4.3
18	4.1	3.5	4.1	3.4	4.3	3.6
19	4.1	4.1	4	4.1	4.1	4.2
20	3.9	3.9	3.8	3.9	3.8	4.2
21	4.7	3.3	5	3.7	5.7	3.7
22	3.7	4.5	3.8	4.8	4.6	5
23	4.4	3.9	4.3	4.3	4.3	4.1
24	4.1	3.8	3.8	4.2	4	3.8
25	4.4	3.8	4.8	3.8	*	3.9
26	4.3	4.1	4.4	3.8	*	4.1
27	4.4	*	3.5	4	4.2	4.3
28	4.2	3.6	4.6	4	4.5	3.9
29	4.5	*	4.4	4	*	4.5
30	4	3.6	4	4.7	4.1	4.4

Table 11A.

Pre-exercise, immediately post-exercise and recovery median plasma potassium concentrations with interquartile range.

	Median Potassium Concentration (mmol/l) Pre-exercise	Median Potassium Concentration (mmol/l) Immediately post-exercise	Median Potassium Concentration (mmol/l) after 20 min. recovery
Control Group	4.1 (3.85, 4.4)	4.1 (3.8, 4.4)	4.2 (4.0, 4.4)
Syndrome X Group	4.0 (3.7, 4.2)	4.2 (3.95, 4.4)	4.15 (3.9, 4.3)

Table 12.
Plasma bicarbonate concentrations for pre-exercise, immediately post-exercise and 20 minute recovery (mmol/l).

	Pre-exercise		Immediately post-exercise		20 minute recovery	
ID No	Control	Syndrome X	Control	Syndrome X	Control	Syndrome X
1	25	26	22	24	18	24
2	24	23	19	21	21	17
3	19	24	17	24	23	24
4	*	23	*	21	*	17
5	28	29	27	24	30	28
6	*	24	*	15	*	16
7	25	20	22	17	20	16
8	16	*	23	*	19	*
9	25	20	16	18	25	24
10	28	24	21	23	23	19
11	18	22	16	18	18	19
12	22	25	21	27	22	26
13	23	26	13	22	17	25
14	24	19	16	16	*	16
15	24	21	28	23	29	22
16	25	24	16	24	26	23
17	25	23	25	21	26	20
18	29	24	27	20	28	23
19	22	23	24	18	25	20
20	*	*	*	*	*	*
21	*	*	*	*	*	*
22	*	*	*	*	*	*
23	*	*	*	*	*	*
24	20	*	16	*	17	*
25	19	*	15	*	15	*
26	11	27	16	27	*	27
27	20	*	14	20	19	22
28	26	26	23	22	15	22
29	20	*	22	7	*	11
30	20	19	10	16	14	22

Table 12A.
Pre-exercise, immediately post-exercise and recovery median plasma bicarbonate concentrations with interquartile range.

	Median Bicarbonate Concentration (mmol/l) Pre-exercise	Median Bicarbonate Concentration (mmol/l) Immediately post-exercise	Median Bicarbonate Concentration (mmol/l) after 20 min. recovery
Control Group	23.5 (20.0, 25.0)	20.0 (16.0, 23.0)	21.0 (17.5, 25.5)
Syndrome X Group	24.0 (21.5, 25.5)	21.0 (18.0, 24.0)	22.0 (17.0, 24.0)

Table 13.

Plasma creatine kinase concentrations for pre-exercise, immediately post-exercise and 20 minute recovery (IU/l).

	Pre-exercise		Immediately post-exercise		20 minute recovery	
ID No	Control	Syndrome X	Control	Syndrome X	Control	Syndrome X
1	212	117	217	117	247	117
2	101	40	108	54	102	48
3	108	117	97	117	99	116
4	132	40	127	54	122	48
5	120	67	115	65	119	71
6	74	110	91	119	77	106
7	182	178	175	192	157	184
8	134	*	117	*	127	*
9	89	139	96	121	78	138
10	137	71	122	78	125	72
11	82	108	80	118	69	106
12	119	35	120	24	114	55
13	77	99	80	102	73	98
14	96	78	97	69	110	65
15	86	110	85	117	95	105
16	68	80	68	82	66	80
17	59	77	60	86	60	76
18	76	77	74	53	69	40
19	60	132	78	132	69	134
20	113	34	123	33	*	35
21	269	116	284	113	275	119
22	193	129	215	118	202	114
23	52	44	64	73	57	38
24	69	109	72	110	84	102
25	125	192	130	301	131	285
26	36	87	44	161	*	98
27	6	*	114	119	62	119
28	72	65	76	63	80	58
29	52	*	56	37	61	70
30	50	171	79	121	17	127

Table 13A.

Pre-exercise, immediately post-exercise and recovery median plasma creatine kinase concentrations with interquartile range.

	Median Creatine Kinase Concentration (IU/l) Pre-exercise	Median Creatine Kinase Concentration (IU/l) Immediately post-exercise	Median Creatine Kinase Concentration (IU/l) after 20 min. recovery
Control Group	88 (66, 127)	97 (76, 122)	90 (69, 124)
Syndrome X Group	99 (67, 117)	110 (64, 119)	98 (62, 118)

SECTION 4

Chapter 4.1. GENERAL DISCUSSION

Defective control of vasomotor tone within the coronary microcirculation may be important in the pathogenesis of syndrome X.

As described in detail in the Introduction (Chapter 1.1) and in the chapter Proposed Pathophysiologic Mechanisms (Chapter 2.1), an attractive hypothetical mechanism concerns an abnormal interaction of vasoactive substances at the level of the coronary prearteriolar vessels. In particular, there may under certain circumstances be inappropriate vasoconstriction at this site, mediated by excess adrenergic drive (Cannon et al, 1987). Excess adrenergic vasoconstriction may occur on effort, so limiting the normal vasodilator response to exercise resulting in inducable ischaemia and chest pain.

For the purpose of the present study we have as a marker of such a mechanism the individual and total plasma catecholamine responses to exercise in a relatively large group of patients with syndrome X and have compared findings in these subjects with those of a matched group of healthy controls.

Results described above provide evidence to indicate that patients who fulfill the conventional diagnostic criteria for syndrome X show a relatively excessive noradrenaline response to exercise in comparison with controls.

Total plasma noradrenaline levels rose in both groups in response to standardised incremental treadmill exercise testing, but in those with syndrome X the noradrenaline response was exaggerated, while both groups showed similar resting and post-exercise noradrenaline levels.

Plasma adrenaline levels also rose as expected in response to exercise in both groups, there being no difference between them in this regard, and heart rate responses and blood pressure responses were likewise similar.

These findings are consistent with abnormally intense noradrenaline release during exercise in individuals with syndrome X.

As described in the Introduction, a number of theories have been advanced to explain the puzzling condition termed syndrome X, and more than one mechanism may be involved (Poole-Wilson and Crake, 1989; Maseri et al,1991(b); Cannon et al, 1992; Kaski et al,1995).

Of the several theories discussed in the Introduction and in the chapter Pathophysiologic Mechanisms, those involving the effects of sympathetic activity, the effects of intramyocardial adenosine and endothelial dysfunction have recently attracted interest.

4.1.1. Angina in patients with syndrome X

It is now recognised that the syndrome of patients with chest pain and normal coronary arteries encompasses different pathophysiological entities (Poole-Wilson and Crake, 1989; Maseri et al, 1991(b); Cannon et al,1992; Kaski et al, 1995).
Generally, patients with syndrome X present with chest pain which is difficult to differentiate clinically from that due to myocardial ischaemia caused by atheromatous coronary artery narrowing, and this is why they are being investigated.
The pain is usually typical of that due to CAD, i.e. has all the characteristics of genuine ischaemic pain. Furthermore, such a requirement, i.e. the 'typicality ' of the pain, is considered by many physicians as an absolute criterion in the definition of the syndrome, although others disagree and include patients with 'atypical' features.
It has been suggested that even when the pain is 'typical' there are occasionally a few distinguishing characteristics which may help to differentiate it from that due to coronary atherosclerosis, although it should be emphasised that these characteristics often are not obvious on initial examination of the patient. For example, it has been reported that the pain that syndrome X patients experience is often of prolonged duration, occasionally continuing for over 30 minutes after exercise or emotion (Maseri et al, 1991(b)). In some cases chest pain at rest is the predominant feature and there is a poor response to sublingual nitrates (Kaski et al, 1995). Nonetheless, this issue remains controversial.

The role of adenosine in the genesis of pain in syndrome X also, appears to be important (Maseri et al, 1991(b); Rosano and Crea, 1992) and this has been described in detail in the chapter Proposed Pathophysiologic Mechanisms (Chapter 2.1.14).
Another possibility for the explanation of the development of chest pain in these patients is that people with syndrome X might have a lower pain threshold and a lower tolerance to pain, compared to patients with CAD.
Shapiro and colleagues suggested that an enhanced perception of painful stimuli may be the underlying mechanism (Shapiro et al, 1988).

In another study, when dipyridamole, which increases extracellular concentration of adenosine, was given to syndrome X patients 68 - 95% of them reported chest pain, whereas when given to patients with CAD, chest pains were reported in only 40% of patients (Picano et al, 1987).
It has also been suggested that the threshold for the perception of chest pain is lower in female patients compared to males (Rosen et al,1994) but this view is controversial.
Turiel and colleagues found a lower threshold to peripheral painful somatic stimuli and a lower tolerance both to pain and to electrical skin stimulation but not to cold in women with syndrome X than those with CAD (Turiel et al,1987).
In a previous report Cannon and co-workers reported that in syndrome X patients, despite a higher pain sensitivity to catheter manipulation in the right side of the heart, the threshold for cutaneous pain stimulation was higher than in a group of patients with CAD (Cannon et al, 1990(c)). In this study the vast majority of patients were female and there was no stratification of the results according to sex.
Also, in another study by Shapiro and colleagues there was no indication as to the sex of the seven syndrome X patients that they studied (Shapiro et al,1988).

In the present study, syndrome X patients had typical anginal pain and there were no distinguishing characteristics.
To date, the actual trigger that causes the pain pathway to be activated in syndrome X patients and its pathogenesis remains to be elucidated.

4.1.2. The electrocardiogram in syndrome X

Resting ECG

The resting electrocardiogram of patients with syndrome X is usually normal.
However, some electrocardiographic abnormalities have long been recognised in this syndrome (Kemp et al, 1973(b)). These are usually T wave changes affecting mainly the inferior or lateral leads.
Henein and colleagues, also, recently carried out an electrocardiographic and echocardiographic study and reported that a significant percentage of the syndrome X group that they studied showed electrocardiographic abnormalities, consisting of absent septal Q waves in the lateral chest leads and abnormal T wave morphology (Heinein et al, 1994).
In the present study, 27 syndrome X patients had a normal ECG and only three showed slight T wave depression in the lateral leads.

Exercise ECG

Coronary arteriography currently represents the standard for detecting myocardial ischaemia due to coronary artery narrowing caused by atherosclerosis of the large epicardial coronary arteries. For this reason a positive ECG response to exercise in a patient with normal epicardial coronary is usually interpreted as a 'false' positive response.

However this approach raises questions.

Firstly, the coronary arteriography is not 100% sensitive in detecting atheromatic narrowings of the large coronary arteries.

Secondly, it only identifies disease of the large coronary vessels; it does not visualise lesions of the medium or small vessels. Furthermore, angiography is not a sensitive method for detection of early atherosclerosis. This has recently been proved by the use of intravascular ultrasound which has been validated as having significantly greater sensitivity than angiography for detecting coronary artery stenoses (Porter et al,1993). Furthermore, undetected atherosclerosis in angiographically smooth coronary arteries may also account for insufficient vasodilator response (Seiler et al, 1992).

Thirdly, it provides only anatomical information, not physiological information, regarding myocardial ischaem

It is conceivable that the 'false' positive response might be in fact a true positive one.

This is because either there is a degree of atheromatic coronary narrowing which has not been detected or the coronary arteries are unobstructed but there is functional myocardial ischaemia.

Is, therefore, the positive exercise test in syndrome X patients a 'true' or a 'false' positive one? What does it really represent?

There is now accumulating evidence to support the view that a large percentage of syndrome X patients, but not all, do in fact have 'true' positive exercise tests as a manifestation of genuine myocardial ischaemia (Cannon et al, 1983; Cannon et al, 1985(b); Epstein and Cannon, 1986; Cannon et al 1987). In these studies objective evidence of myocardial ischaemia was demonstrated by exercise-induced left ventricular dysfunction and patients showed inadequate coronary artery vasodilatory reserve by using cardiac pacing and radionuclide angiography.

These syndrome X patients, therefore, experience myocardial ischaemia probably caused by microvascular dysfunction, producing a truly ischaemic ECG response on exercise. Unfortunately, it is difficult to establish the exact percentage of syndrome X patients with 'true' positive or 'false' positive ECG response results for several reasons.

Patient selection criteria is of primary importance. Some investigators include patients in their studies exclusively if they have a positive ECG response to exercise, and therefore by definition all patients will have a positive exercise test (Poole-Wilson and Crake, 1989; Kaski et al,1995).

Others take the alternative view that a positive exercise test is not an absolute inclusion criterion and therefore a percentage of the syndrome X population studied would have a positive and a percentage would have a negative ECG response to exercise (Cannon and Epstein, 1988).

Some investigators include only patients with 'typical' angina, others are more liberal and include patients with 'atypical' features. It is generally considered that the more 'atypical' the pain the more probable the ECG response to exercise will be a truly 'false' positive one.

Some authors include in their studies patients with hypertension, myocardial hypertrophy or valvular problems, and in this case the exercise ECG response probably represents the perfusion state of these conditions and not of syndrome X (Cannon and Epstein, 1988; Poole Wilson and Crake, 1989).

A further difficulty surrounds the criteria for documenting the presence of 'true' ischaemia.

Therefore, the basis of Bayes' theorem the exercise test results will depend on patient inclusion and exclusion criteria (Epstein,1980) and also on the authors' conception of myocardial ischaemia.

Even in a highly homogeneous group of syndrome X patients, selected very carefully on very strict criteria, including a positive exercise test, and assuming that myocardial ischaemia exists in every single case studied, the sensitivity of the exercise ECG for detecting myocardial ischaemia cannot reach 100% levels. One of the reasons is that the distribution of myocardial ischaemia in some cases of syndrome X might be diffuse, so it obviates the development of an ischaemic electrical vector sufficient to be detected by the standard electrocardiogram. Such a diffuse pattern of ischaemia has been shown in thallium 201 scintigraphy studies performed in syndrome X (Meller et al, 1979; Dunn et al, 1981; Brown et al,1985).

Furthermore, in some cases myocardial ischaemia that develops on exercise might be so mild as not to be detected by the electrocardiogram. This might have been the case in some cases in the present study, in which syndrome X patients showed relatively short periods of chest pain and ischaemic ECG changes on exercise and also by the fact that the intensity of the pain experienced was not severe enough.

This view concurs with the theory of Maseri who suggested that the distribution of myocardial ischaemia is uneven in this condition and therefore it should be comparatively mild (Maseri et al, 1991(b)).
In some cases also, there is possibly an abnormal reaction to physical exercise of the distal epicardial coronary arteries, as reported by Bortone and colleagues (Bortone et al, 1989). In this case a positive ECG response to exercise might reflect the occurrence of genuine myocardial ischaemia.

Another possibility suggested by Holdright and co-workers from Poole-Wilson's group is that exercise-induced ST segment depression in these patients can be attributed simply to a localised increase in extracellular potassium due to an abnormality of potassium exchange (Holdright et al, 1992). They suggested that the significant proportion of a group of patients with syndrome X that they studied had a positive ECG response to exercise, which in fact was a 'false positive' one.

Recently Wiedermann and colleagues reported that most of the patients with syndrome X that they studied had abnormal epicardial coronary arteries by intravascular ultrasound and abnormal vasomotor response to exercise (Wiedermann et al, 1995).
The importance of this observation is still to be assessed. However, if these patients also have extensive microvascular disease, as the authors suggested, it would be theoretically possible to explain the presence of a positive exercise test in these patients.

In the present study all syndrome X patients had an abnormal ECG response to exercise as this was an absolute inclusion criterion.

4.1.3. Hypertension and syndrome X

Most studies of syndrome X specifically exclude patients with hypertension (Poole-Wilson and Crake, 1989). However, a significant percentage of patients with chest pain and normal coronary arteries also have hypertension at presentation and many authors do not exclude such patients when investigating this entity. In particular Cannon and colleagues reported a high prevalence of mild hypertension in patients with putative 'microvascular angina' (Cannon and Epstein, 1988).
Furthermore, syndrome X probably encompasses a subgroup of patients who are initially borderline hypertensive and who later develop overt hypertension.

Opherk and co-workers reported that from a subset of syndrome X patients that they studied, those with an increased sympathetic drive during exercise, a significant number developed hypertension during a 4 year follow-up period (Opherk et al, 1989). They suggested that analysis of heart rate and blood pressure response to exercise may help to identify patients with syndrome X who are borderline hypertensive.
Similarly, Romeo and co-workers found during long-term follow-up of patients initially diagnosed as having syndrome X that a subgroup of patients became clearly hypertensive with time (Romeo et al, 1993).
It is noteworthy that hypertension is an insulin resistant condition and that it has been linked with reduced activity of nitric oxide in both conduit and resistance vessels (Panza et al, 1990).
Recently it has been reported that some patients with a history of hypertension and hypercholesterolaemia are associated with impaired exercise-induced coronary artery dilatation of angiographically normal coronary arteries (Seiler et al, 1993). This has been supported by Egashira and colleagues in a recent study (Egashira et al, 1993(b)). Treasure and colleagues, also, have recently demonstrated that there is an association between hypertension and left ventricular hypertrophy with impaired endothelium mediated relaxation in human coronary resistance vessels (Treasure et al, 1993).

It has also been suggested that glucose intolerance and hyperinsulinaemia are common in hypertensive patients (Modan et al, 1985; Ferranini et al, 1987). Also, in patients with hypertension and normal coronary arteries abnormal coronary flow has been observed, suggesting an abnormality of the microcirculation (Brush et al, 1988).

4.1.4. Studies of coronary artery blood flow reserve

A large proportion of patients with syndrome X have limited coronary flow responses to pacing and pharmacological vasodilatation.
These abnormalities have been demonstrated by several different methodologies.
There are, however, quite a few patients with chest pain and normal coronary arteriograms who do not have any evidence of any coronary flow abnormality, therefore strengthening the conclusion reached by many authorities that syndrome X probably consists of more than one distinct pathophysiological entity.

Alternatively, if inappropriate prearteriolar coronary artery constriction existing proximal to those small coronary arteries responsible for the metabolic regulation of myocardial blood flow is unevenly distributed in syndrome X, it is reasonable to assume that myocardial perfusion, metabolism and function might be frequently found within normal limits. This might occur especially when evaluation is being done, using conventional diagnostic techniques that can only detect gross abnormalities occurring in probably larger myocardial regions.

Nuclear studies:

Nuclear studies have been used for more than 15 years for the investigation of this syndrome.

In the late seventies Green and colleagues and Meller and co-workers reported thallium-201 abnormalities occurring in patients with chest pain and normal coronary arteriograms (Green et al, 1978; Meller et al, 1979).

Later such perfusion defect abnormalities were confirmed by others (Dunn et al, 1981; Berger et al,1983).

By using exercise radionuclide angiography and thallium-201 scintigraphy and digital subtraction measurements, Legrand and colleagues reported the results before and after intracoronary contrast media in a group of syndrome X patients that they studied (Legrand et al,1985). Seven out of 18 patients with abnormal exercise radionuclide studies had lower regional coronary flow responses than the eleven with normal radionuclide results.

Kaul and colleagues observed reduced coronary blood flow, when compared with a normal control group, by using quantitative thallium imaging and suggested that myocardial ischaemia may occur with stress although epicardial coronary arteries are unobstructed (Kaul et al,1986).

Using gated blood pool scintigraphy Favaro and colleagues have found that a significant proportion of syndrome X patients have reduced left ventricular functional reserve during exercise, probably because of reduced coronary artery blood flow (Favaro et al, 1987).

Xenon-133 imaging has also been used in another study of syndrome X patients (Korhola et al, 1977). The authors observed regional myocardial perfusion abnormalities in these patients, suggesting reduced coronary artery blood flow.

Recently Tweddel and co-workers have reported that most of the syndrome X patients that they studied had abnormal thallium scans, although without any consistent pattern, whereas only 30% had a positive ECG response to exercise (Tweddel et al, 1992).

The authors suggested that a) inclusion of a positive exercise test as an absolute criterion may underestimate the true prevalence of syndrome X and b) that inducable myocardial dysfunction consistent with syndrome X may be much commoner than has been recognised by less sensitive tests.
However, some authors have not observed perfusion abnormalities in patients with angina pectoris and normal coronary arteriograms (Meller et al,1979).

Pharmacological studies - Dipyridamole:

Dipyridamole has been extensively used to evaluate coronary flow reserve and left ventricular function in this condition, usually in conjunction with pacing, nuclear studies or physical exercise.
Opherk and co-workers reported that in a syndrome X group of patients that they studied by argon washout measurements, there was a limited increase in coronary blood flow after dipyridamole administration (Opherk et al,1981).
Bortone and co-workers carried out coronary flow reserve studies after dipyridamole and reported epicardial coronary artery vasomotion during supine bicycle exercise in a group of patients with syndrome X (Bortone et al, 1989).
Coronary arteriography was carried out prior to exercising, two minutes into exercise, at peak exercise and post exercise. The coronary sinus flow response to dipyridamole was lower in the patients with exercise-induced distal coronary artery constriction than in those with exercise-induced epicardial coronary artery dilatation.
Cannon and co-workers also studied a group of patients with syndrome X with dipyridamole. In those patients with ergonovine-induced coronary vasoconstriction, they observed an abnormally small increase in coronary artery flow and suggested that this was due to functional abnormality at the level of the prearteriolar coronary vessels (Cannon et al, 1987).
Sutsch and colleagues evaluated both coronary and cutaneous blood flow reserve at rest and after coronary infusion with dipyridamole in a group of patients with syndrome X and a control group (Sutsch et al,1992). Their results showed an abnormal response of the coronary arteries to vasodilator stimuli, and they concluded that such a response is limited to the vessels of the heart and that there was no evidence from his study of a generalised involvement of the vasculature as was suggested by others (Sax et al, 1987).

Dipyridamole infusion has also been used with echocardiography to assess left ventricular function and showed that there were no regional left ventricular abnormalities in the syndrome X group of patients that were studied (Picano et al, 1987).
In a comparative study of the effects of dipyridamole, adenosine and papaverine on coronary vasodilatory reserve in patients with syndrome X, Holdright and colleagues found normal values for these patients whichever vasodilator was used (Holdright et al,1993).

Atrial pacing:

Atrial pacing has also been used extensively to assess coronary flow reserve and left ventricular function in this condition.
Several studies have shown that some patients with syndrome X develop chest pain and ST segment depression together with metabolic abnormalities consistent with myocardial ischaemia during rapid atrial pacing.
Arbogast and Bourassa were the first to report the development of these manifestations of the syndrome during pacing but there was no evidence of impairment of left ventricular function in the group of patients with chest pain and normal coronary arteries that they studied (Arbogast and Bourasssa 1973).
In a rather atypical group of syndrome X patients with a varying degree of chest pain threshold, Cannon and co-workers clearly demonstrated spontaneous chest pain associated with limitation in great cardiac vein flow, in response to atrial pacing and during ergonovine infusion (Cannon et al, 1983). After the initial pacing, ergonovine was administered with repeat flow measurements during pacing stress. Those patients who experienced chest pain during pacing and after ergonovine, increased great cardiac vein flow less from baseline than those who remained free of pain.
Crake and colleagues measured coronary artery oxygen saturation during pacing in patients with and without CAD or with syndrome X and demonstrated the presence of ischaemia (Crake et al,1987(b)).
Cannon and Epstein, based on the behaviour of coronary flow during pacing, hypothesised that a functional abnormality of resistance vessels co-exists with angiographically normal coronary arteries in this syndrome (Cannon and Epstein, 1988).

Camici and co-workers studied a carefully characterised syndrome X group of patients and a normal control group and evaluated, cardiac performance, myocardial metabolism and coronary haemodynamics (Camici et al, 1991). All of these patients developed anginal pain and significant ST segment depression during pacing and a lesser increase in blood flow in the great cardiac vein compared with normal controls. Oxygen extraction and lactate extraction were similar in both groups and global and regional left ventricular function was preserved in the syndrome X group.

Positron Emission Tomography:

Several studies have used positron emission tomography in investigating syndrome X and showed that many patients have an abnormal coronary artery flow reserve.
Camici and colleagues studied a group of syndrome X patients and measured myocardial blood flow and coronary vasodilatory reserve by means of positron emission tomography and ^{13}N-labeled ammonia (Camici et al, 1992). They found that myocardial blood flow values after dipyridamole were widely dispersed. Furthermore, they identified a subgroup of patients with lower coronary vasodilatory reserve, and hypothesised that there was increased adrenergic activity in this subgroup, suggesting that the limitation of the myocardial blood flow response to dipyridamole, observed in some patients, might be due to alpha$_1$-adrenrgic mediated coronary vasoconstriction. In this study syndrome X patients were not compared directly with matched normal control subjects.
These findings are in agreement with those of Geltman and co-workers (Geltman et al, 1990). In their study they investigated a group of patients with chest pain and normal or near-normal (coronary artery diameter < 50%) coronary arteriograms and a normal control group by positron emission tomography, using oxygen-15-labeled water as the flow tracer. There were no differences in myocardial perfusion after dipyridamole infusion between patients and normal control subjects. However, when the response to dipyridamole among patients was analysed with respect to normal responses (peak to rest myocardial perfusion ratio I > 2.5) half of the patients exhibited reduced coronary flow reserve(myocardial perfusion ratio of less than 2.5) compared with control subjects.
Kaski and colleagues measured coronary flow reserve by positron emission tomography with dipyridamole in a group of syndrome X patients and compared the results with a group of patients with documented CAD and a group of subjects with atypical anginal pain (Kaski et al, 1991).

Quantitative angiography was carried out before and after the administration of ergonovine and intracoronary isosorbide dinitrate. The results indicated that there were no differences between coronary diameters at baseline or after administering the drugs, supporting the view that conduit coronary vessels were not involved in the impairment of coronary reserve.

Galassi and colleagues also recently measured regional myocardial blood flow before and after intravenous dipyridamole, using continuous inhalation of oxygen-15-labeled carbon dioxide and positron emission tomography in a group of syndrome X patients, a group of patients with CAD and a normal control group (Galassi et al, 1993).

This study showed that in syndrome X patients there are probably clusters of myocardial regions with relatively higher flow during baseline and relatively lower flow during dipyridamole infusion. In other words, it showed a significantly greater heterogeneity of myocardial blood flow and patchy distribution in all anatomic regions in the syndrome X group compared to normal subjects and patients with CAD.

Rosen and colleagues investigated 29 syndrome X patients and 20 healthy volunteers with positron emission tomography and dipyridamole. The authors found a normal myocardial blood flow and distribution at rest, after the administration of dipyridamole and no difference compared to the control group and cast doubt on ischaemia as the basis for ischaemia occurring in the syndrome (Rosen et al,1994).

4.1.5. Left ventricular wall motion abnormalities

Regional left ventricular motion abnormalities have been reported in syndrome X by many authors (Schofield et al, 1986; Favaro et al, 1987; Picano et al, 1987).

In a recent study, Henein and colleagues showed objective evidence of regional wall motion abnormalities in some patients with syndrome X (Henein et al,1994).

Others, however, have come to different conclusions and found no evidence of exercise-induced regional wall motion abnormalities in syndrome X patients (Nadazdin et al, 1991; Nihoyannopoulos et al, 1991).

These inconsistent findings might be attributed to the fact that subtle wall motion abnormalities cannot always be readily detected from subjective inspection of cross sectional echocardiographic images, whereas cross sectional guided M mode echocardiography is ideal for precise left ventricular function evaluation.

Different inclusion criteria and patient selection may also explain some of these differences.

4.1.6 Limitations of the study and recommendations for future research

Definition of syndrome X

A recurrent weakness inherent in the literature of syndrome X relates to its definition. Therefore, in order to minimize the problem as much as possible, in this study the condition was precisely defined and strict inclusion and exclusion criteria were adopted in recruiting the patients in order to achieve as homogeneous a patient group as possible.

Control group characterisation

No subjects in the control group had coronary arteriography carried out.
However, all of the control group subjects were free from symptoms and had no abnormal signs; most of them were below the age of 50.
The prevalence of CAD in asymptomatic population is generally considered to be low, especially in the younger age groups.
It cannot be ruled out on clinical grounds, however, that one or two individuals from the control group might have CAD, but the majority of them probably have no significant coronary artery narrowing.

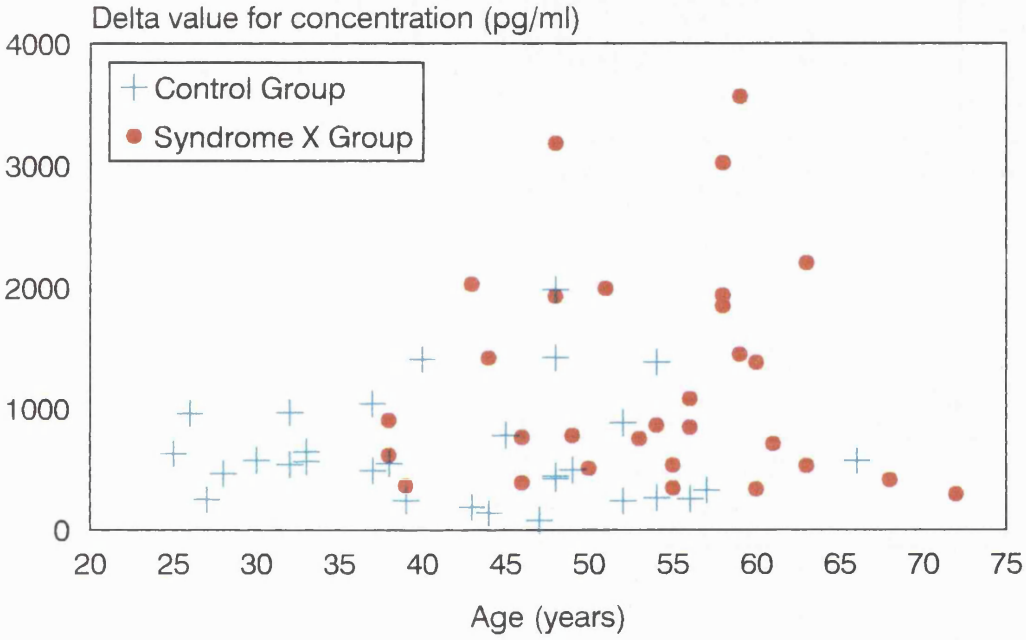
Age difference between control and syndrome X groups

Care has been taken to ensure that control and syndrome X subjects were matched as closely as possible.
However, because the syndrome X group contains a larger number of older patients than the control group, who were relatively younger, the question remains concerning whether some anomaly, other than the syndrome X characteristic, might explain the differences found between the two groups. Thus, a statistical analysis was carried out to consider whether age may be a factor behind the results.
This was achieved using linear regression analysis to determine whether age was a significant factor altering the characteristic under consideration.
The analysis showed that there is no statistical evidence for age having an effect on the parameters studied.

Details of the statistical analysis of the effect of age.

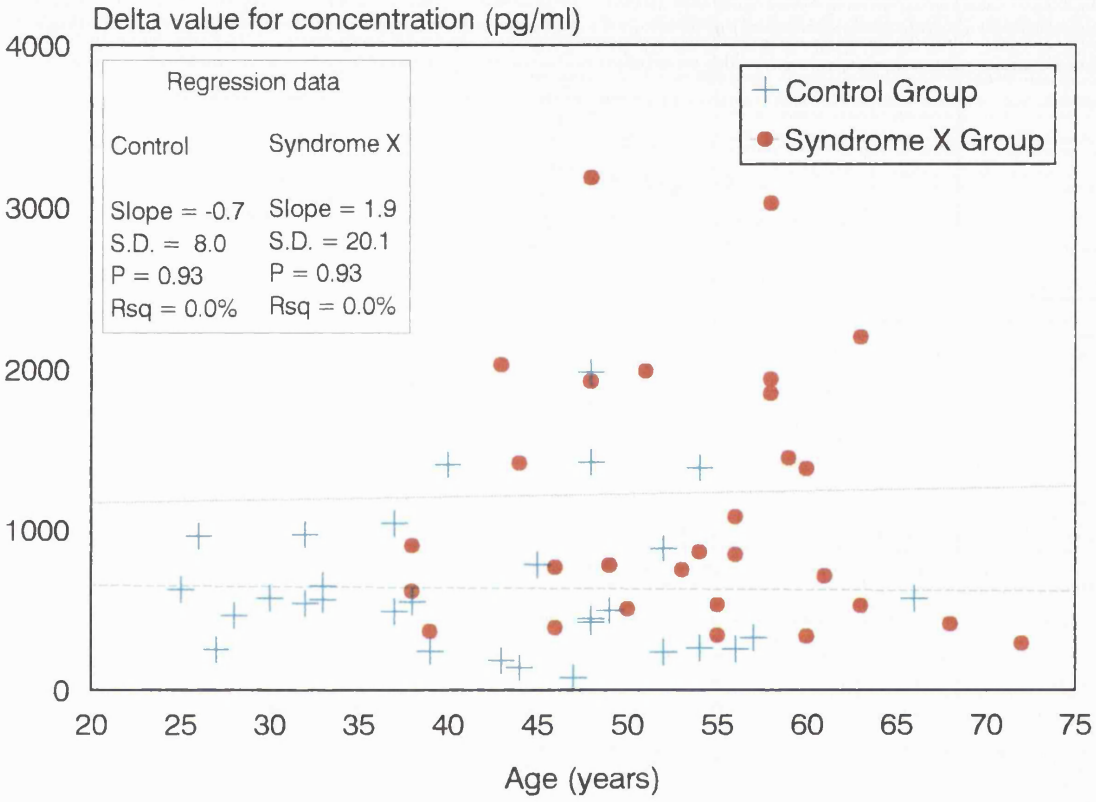
A scatter plot of the delta values in plasma noradrenaline concentrations from pre-exercise to immediately post-exercise versus age is shown in Figure 15.

Figure 15.
Scatterplot of the delta values for the plasma noradrenaline concentration from pre-exercise to immediately post-exercise versus age for the control and syndrome X groups.



The data were analysed in two manners, as described in the methodology section.
Firstly, two regression analyses were performed on the control and syndrome X groups separately, in which age in years was set as the independent variable and plasma noradrenaline delta values as the dependent variable.
The regression lines are shown in Figure 16.
The results of the linear regression showed that the slope of the regression lines were not statistically significantly different from zero (Control group P=0.93, syndrome X group P=0.93).
Thus, we have no evidence to suspect that age has any influence on the increase in noradrenaline serum concentration from pre-exercise to immediately post-exercise for either group.

Figure 16.
Scatterplot of the delta values for the plasma noradrenaline concentration from pre-exercise to immediately post-exercise versus age for the control and syndrome X groups. The regression lines for the two sets of data are also shown (N=30 in each case).

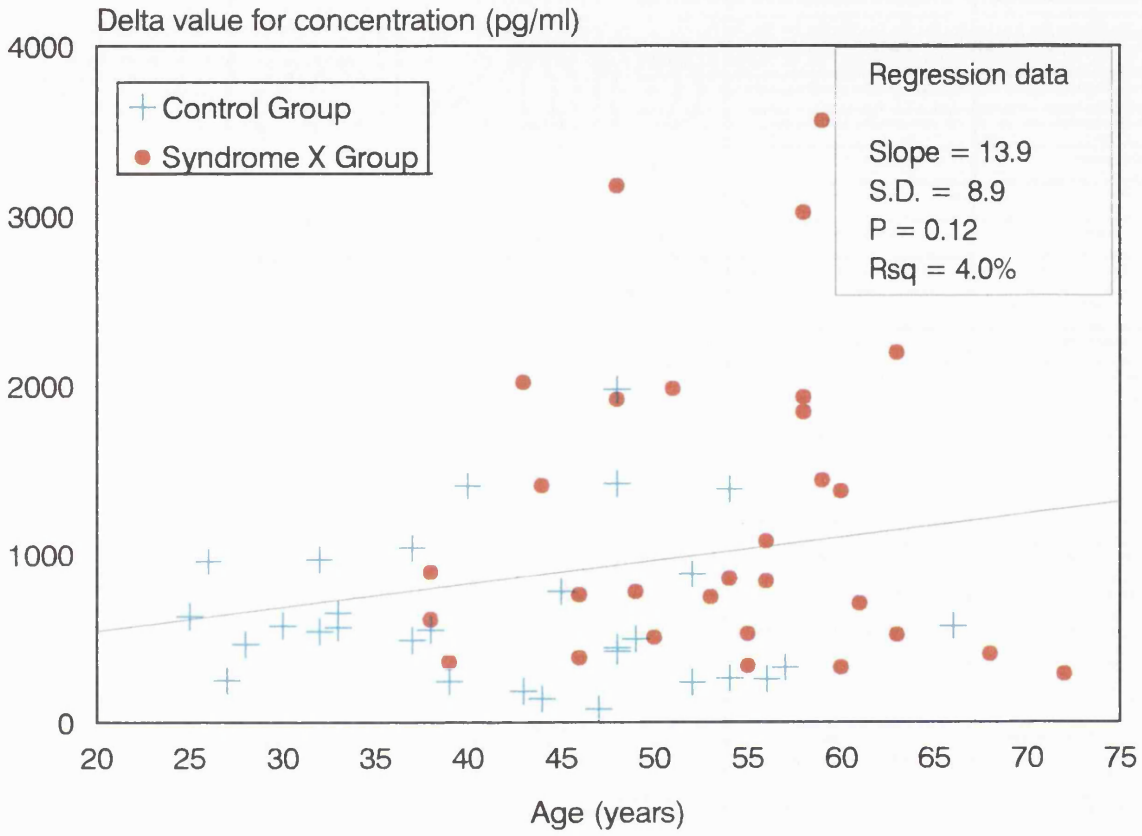


Secondly, the control and syndrome X groups were merged together and a linear regression performed on the joint data set with age as the independent variable and delta changes in noradrenaline from pre-exercise to immediately post-exercise as the dependent variable.

The regression line and data are shown in Figure 17.

Thus, with further analysis age was not found to be statistically significant in predicting the delta changes in plasma noradrenaline concentrations from pre-exercise to immediately post-exercise, returning a P value of P=0.12.

Figure 17.
Scatterplot of the delta values for the plasma noradrenaline concentration from pre-exercise to immediately post-exercise versus age for the control and syndrome X groups. The regression line for the combined data set is also shown (N=60).



Both the above analytical statistical techniques were applied to all the other parameters studied and showed no significant age effect.

The regression analyses performed on the combined data set for the delta values for the plasma noradrenaline percentage increase from pre-exercise to immediately post-exercise is shown in Appendix Figure 1, for the total plasma catecholamine in Appendix Figure 2 and for plasma adrenaline in Appendix Figure 3.

The P values are also given, obtained by the combined analytical technique, of lactate, potassium, bicarbonate and creatine kinase delta values which again showed no significant age effect (Lactate delta value, P=0.61;potassium delta value, P=0.08; bicarbonate delta value, P=0.63;creatine kinase delta value, P=0.58).

Possible methodological limitations

Methodological aspects also need consideration.
All subjects in this study were exercised to maximum and the second sample was taken within one and one half minutes after the cessation of exercise in all cases. However, the precise timing of venous sampling inevitably varied slightly from subject to subject and the possibility that this may have exerted a small influence on the results cannot be excluded.
This study utilises plasma catecholamine measurements as an index of sympathetic nerve activity. However, since plasma levels of noradrenaline probably represent a complex marker of such an activity there are possibly potential limitations of measurements.
Some of these limitations might be overcome by assessing cardiac and whole body spillovers by using radiotracer kinetic techniques (McCance, 1989).

Recommendations for future research

It is important to establish the catecholamine response to exercise of patients with documented CAD and find out whether there is any difference between this group and the syndrome X group.
Therefore a group of patients with significant (greater than 50%) coronary arterial stenoses on coronary arteriography is currently being investigated.

It is also important to investigate the catecholamine response to exercise in patients with chest pain, normal coronary arteries and a negative exercise test, a group that is considered by many investigators as representing syndrome X as well, but which was not included in the present study.
Such a group is also currently being investigated.

Chapter 4.2. HYPOTHETICAL MODEL OF PATHOGENESIS OF SYNDROME X

4.2.1. Disorder of coronary microvascular vasomotion

To date, there is accumulated evidence that at least in some patients with 'genuine' cardiac syndrome X, an abnormal coronary flow reserve in response to metabolic and pharmacologic vasodilator stimuli plays an important role in the pathogenesis of the syndrome.
The impaired coronary flow reserve may result from either abnormal vasomotion of coronary artery microcirculation or structural microvascular changes, or a combination. The mechanism(s) underlying this abnormal vasomotion may be due to either impaired endothelial function or inappropriate vasoconstriction, or both.

The preferential increase in plasma noradrenaline concentrations observed on exercise in patients with syndrome X in this study, compared to a control group, implies that there is in these subjects an enhanced level of cardiac sympathetic stimulation on exercise but not when at rest, due either to enhanced sympathetic neuronal noradrenaline discharge or to impaired neuronal noradrenaline re-uptake, or a combination of both during phases of increased sympathetic drive.
It is possible that noradrenaline clearance may be different in syndrome X patients, especially during physical exercise.
Noradrenaline may be taken up and released by terminal vesicles at high rates of sympathetic stimulation.
It appears possible that enhanced reactivity to physiological stimuli and/or impaired ability to limit or adjust the release of vasoactive substances on exercise may cause inappropriate vasoconstriction of prearteriolar coronary arteries.

Adenosine may also have a role in the pathophysiology of syndrome X, as described above, particularly in the production of chest pain on effort .
Chilian and Layne have observed that during severe hypoperfusion adenosine caused vasodilatation of small coronary arterioles <150 microns in diameter (Chilian and Layne, 1990). Maseri and colleagues postulated that a compensatory increase in adenosine concentration caused by constriction at the distal end of the coronary prearterioles in the presence of patchily distributed and sparse prearteriolar constriction might be responsible for the occurrence of pain even in the absence of true ischaemia (Maseri et al, 1991(b)).

This can occur if the local concentration of adenosine in the heart becomes sufficient to stimulate afferent nerves even in the absence of impairment in left ventricular function.
This theory is supported by Bertolet and colleagues who showed that adenosine induced chest pain is of cardiac origin and that cardiac afferent innervation is necessary for transmission of the sensation (Bertolet et al, 1993).
A likely trigger for adenosine release in syndrome X is increased resistance at the level of the prearteriolar coronary arteries due to local noradrenaline excess, when the role of adenosine would be to preserve myocardial blood flow (Romeo et al, 1988).
Otherwise, adenosine receptor dysfunction has been suggested as an alternative explanation for chest pain in the absence of myocardial ischaemia in this syndrome (Rosano and Crea,1992).

4.2.2. Initial stage

Possible effects of catecholamines on coronary artery endothelium

People with syndrome X may be different because they increase their plasma noradrenaline, and possibly other neurotransmitters, in response to exercise and other stimuli readily and excessively compared to 'normals', as the present study has shown.
On the basis of the data in the present study the hypothesis is advanced that altered sympathetic activity due to enhanced catecholamine response to exercise, over a period of time, may play an important role in the pathophysiology of the syndrome.

It is proposed that the critical factor in the development of this condition is the cardiotoxicity of noradrenaline and possibly other potentially vasoactive substances.
It is suggested that in this syndrome endothelial cells of the coronary arteries may be exposed, over a long period of time, to sudden bursts of substances with deleterious effect on coronary artery endothelium, resulting in altered endothelial function.
It might also be, that syndrome X patients may have a 'hypersensitive' coronary artery endothelium which is susceptible to the cardiotoxic effects of catecholamines and other similar substances.
A period of prolonged sympathetic adaptation may follow during which the manifestations of the condition are not apparent. During this time changes possibly take place in the function of the endothelium of the wall of the small coronary arteries.

With time, the inherent adaptation mechanisms of the coronary endothelium, which in these people might be deficient, may become overwhelmed and the endothelium 'injured.' Endothelial dysfunction may then further worsen by an increased sensitivity to the constrictor effects of catecholamines and other vasoactive substances.

Coronary artery dilator - coronary constrictor imbalance

Under normal circumstances, in the 'non-syndrome X' heart, during augmented sympathetic drive, competition between adrenergic coronary microvascular constriction and endothelium-dependent relaxation may limit the reduction in myocardial perfusion caused by adrenergic vasoconstriction.
In the 'syndrome X' heart, the adrenergic-mediated prearteriolar coronary vasoconstriction may be unopposed by the catecholamine 'damaged' endothelium and then the catecholamines themselves disproportionately accentuate microvascular constriction and result in impaired vasodilatation, or inappropriate vasoconstriction, of the coronary microvessels.

The 'damaged' endothelium may result in limited plasma levels of local nitric oxide and/or other vasodilating substances. It may also be that coronary arteries constrict rather than dilate during exercise.
Furthermore, it is suggested that coronary microvessels in patients with syndrome X have segments of disturbed endothelial function of variable degree.
This view is supported by the recent work of Wiedermann and colleagues who studied a large group of syndrome X patients using intravascular ultrasound imaging of the epicardial vessels to assess coronary morphology and the vasomotor response to exercise (Wiedermann et al, 1995). They identified three subgroups of syndrome X patients, one with 'true' normal coronary arteries and two with abnormal coronary arteries showing atherosclerotic plaques and marked intimal thickening. The group with the normal coronary arteries displayed a normal vasodilatory response to exercise; the other two groups showed an abnormal vasoconstrictive response to exercise consistent with dysfunctional endothelium. To complement the effects of minor coronary artery stenoses it was suggesed that the epicardial CAD may reflect the presence of more extensive coronary microvascular disease which may be of greater importance in view of its ability to restrict coronary flow reserve.

It is also inferred that acetylcholine under circumstances of altered endothelial vasoactivity, may well act as a vasoconstrictor agent potentiating the effect of noradrenaline and other vasoconstrictors, as was shown by the work of Motz and co-workers (Motz et al, 1991).

During this initial stage the above changes are probably minimal and intermittent; consequently the manifestations of the condition are not readily recognisable.
In the normal heart, there is an interaction and a dynamic balance between the various vasodilator and vasoconstrictor agents and the net result is an appropriate arteriolar coronary dilatation to meet the local metabolic myocardial demands.
At a certain moment and if the circumstances change, sympathetic constrictor effects are added to the basal coronary tone to achieve the appropriate coronary artery dilatation.
The balance is usually maintained predominantly by the state of functional normality of the coronary endothelium which plays an active role in regulating vessel structure and function.
The homeostatic balance between vasoconstrictors and vasodilators may no longer be in operation and the balance may shift to a new situation where vasoconstrictor substances become increasingly dominant and vasodilator substances become increasingly attenuated.

4.2.3. Emergence of classical pattern

In patients with syndrome X, should the exposure of the coronary microvessels to cardiotoxic agents like noradrenaline persist for some time, varying from patient to patient, and the endothelium become progressively susceptible to these agents, then its functional integrity may become permanently impaired.
It might also be that there is not only some loss of endothelial cells but that the remaining cells also lose their ability to respond to signals for vasodilatation and fail to release appropriate vasodilators. This may lead to a potentiating effect whereby superimposed altered sensitivity to circulating catecholamines may further contribute to further coronary vasoconstriction.
This probably explains why patients with syndrome X may exhibit manifestations of myocardial ischaemia even with 'normal' low levels of circulating catecholamines, as was shown in the present study.

Additionally, if the endothelium becomes sensitised and functionally altered, then at this stage, the coronary arteries of patients with this condition may constrict or inadequately dilate with the same concentrations of catecholamines that, in 'non-syndrome X' persons, cause no features of myocardial ischaemia.

However, this phenomenon is manifested in most of the cases, on exercise, because myocardial perfusion is only then compromised, as flow through the constricted coronary prearterioles cannot meet the increased demand. In contrast, at rest, the balance can be maintained, because the oxygen demand of the myocardium can be provided by appropriate vasodilatation of the prearteriolar vessels.
Even at this stage there may be some degree of reversibility of the endothelial dysfunction and consequently vasodilator-vasoconstrictor imbalance may not always be permanent. This might explain why the consistency and reproducibility of the ischaemic changes are not always related to the severity and chronicity of the disease process.

The exact mechanisms responsible for the pathogenesis of this intriguing phenomenon of chest pain and normal coronary arteries remain to be fully elucidated.
However, from the present study the idea that catecholamines may play an important role in the pathogenesis of syndrome X is strengthened.
Furthermore, the hypothesis is advanced that an enhanced catecholamine response to exercise over a period of time may have a deleterious effect on coronary artery endothelium, altering endothelial function and resulting, in some cases, in a susceptibility to true ischaemia during exercise.

APPENDICES

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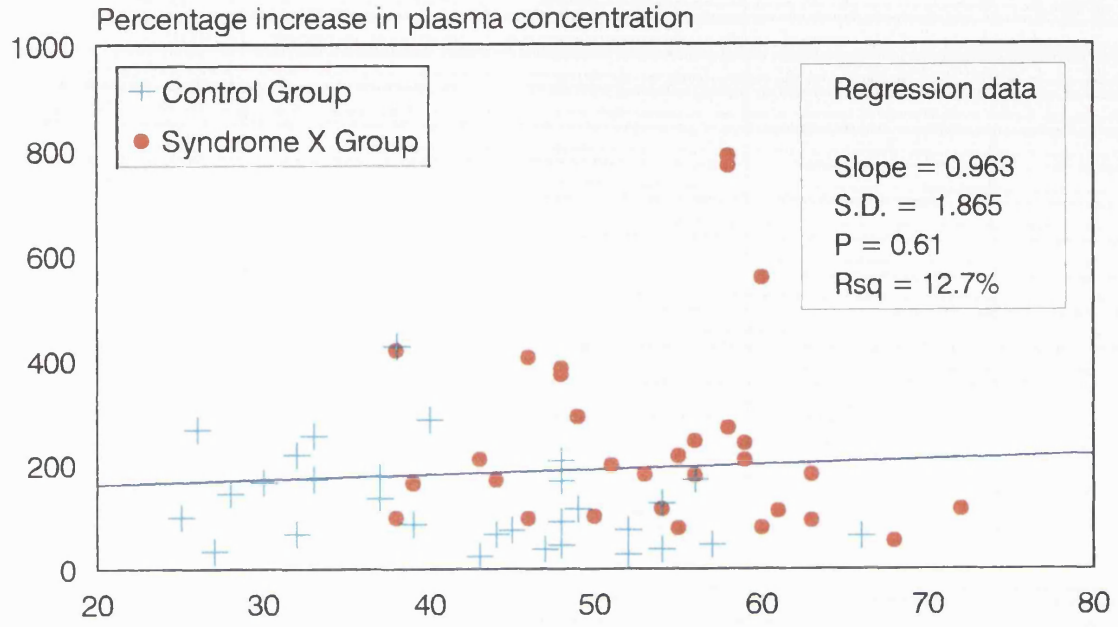
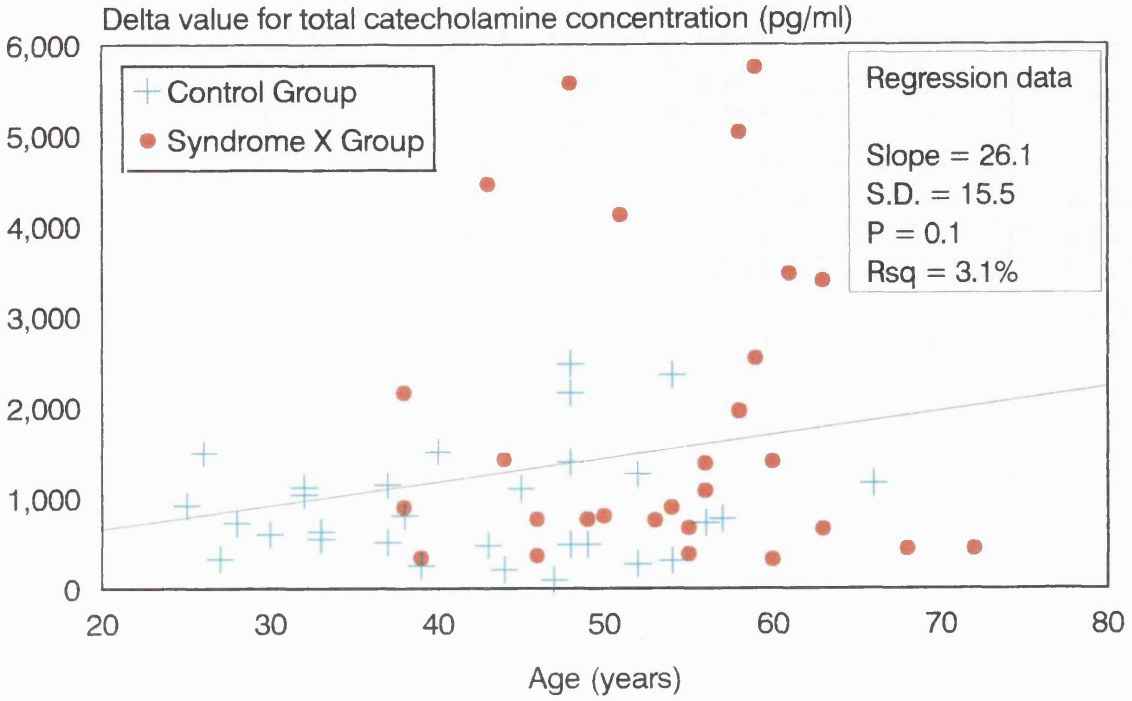
APPENDIX FIGURE 1

Scatterplot of the percentage increase in the plasma noradrenaline concentrations from pre-exercise to immediately post-exercise versus age for the control and syndrome X groups. The regression line for the combined data set is also shown (N=60).



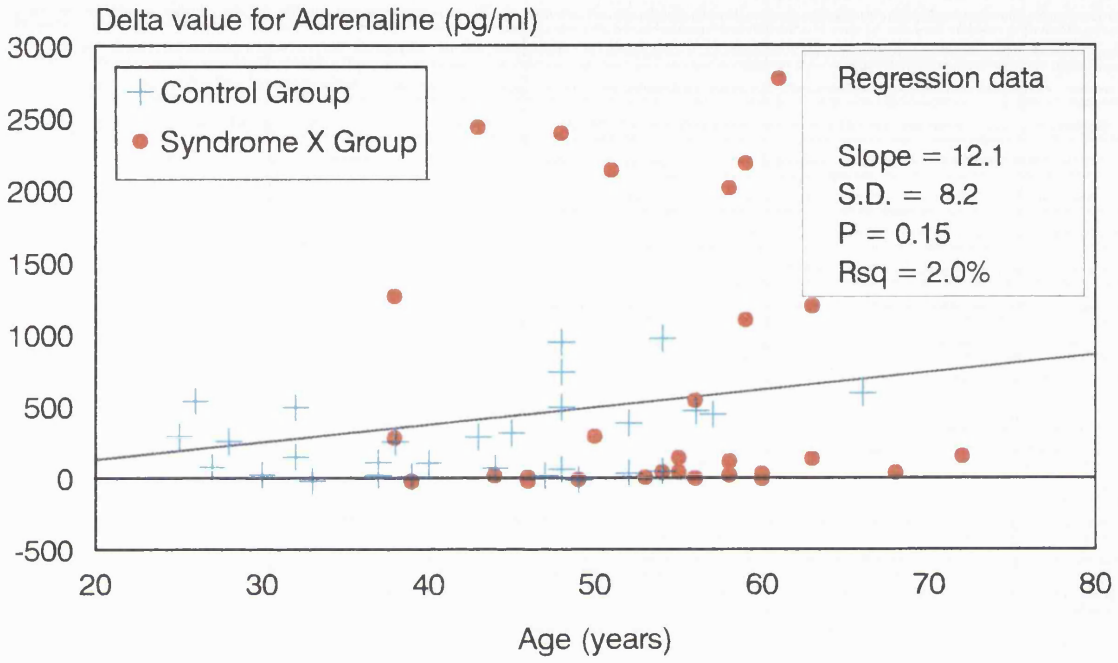
APPENDIX FIGURE 2

Scatterplot of the total plasma catecholamine concentrations delta values from pre-exercise to immediately post-exercise versus age for the control and syndrome X groups. The regression line for the combined data set is also shown (N=60).



APPENDIX FIGURE 3

Scatterplot of the delta values for the plasma adrenaline concentrations from pre-exercise to immediately post-exercise versus age for the control and syndrome X groups. The regression line for the combined data set is also shown (N=60).



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