# THE SYNDROME OF ANGINA PECTORIS WITH NORMAL CORONARY ANGIOGRAM

Per Albertsson


Göteborg 1996

University of Göteborg
Division of Cardiology, Sahlgrenska University Hospital
Göteborg, Sweden

# THE SYNDROME OF ANGINA PECTORIS WITH NORMAL CORONARY ANGIOGRAM

AKADEMISK AVHANDLING

SOM FÖR AVLÄGGANDE AV MEDICINE DOKTORSEXAMEN VID GÖTEBORGS UNIVERSITET,
OFFENTLIGEN FÖRSVARAS VID SAHLGRENSKA SJUKHUSET,
SAL F3, TORSDAGEN DEN 23 MAJ, 1996, KL.13.00

AV

Per Albertsson
leg. läkare

Avhandling baseras på följande delarbeten:

I Morbidity and use of medical resources in patients with chest pain and normal or near normal coronary arteries: Influences of the diagnostic angiogram.
*P Albertsson, H Emanuelsson, T Karlsson, C Lamm, W Sandén, G Lagerberg, J Herltiz.*
Submitted

II Quality of life in patients with chest pain and normal or near normal coronary angiograms.
*P Albertsson, I Wiklund, H Emanuelsson, M Haglid, T Karlsson, H Sjöland, J Herlitz.*
Submitted

III Coronary vasodilator capacity during atrial pacing and after adenosine administration in patients with syndrome X.
*P Albertsson, H Emanuelsson, C Lamm, F Waagstein.*
Submitted

IV Adenosine infusion - Provocation of left ventricular dysfunction in patients with syndrome X.
*P Albertsson, V Kujacic, D Jablonskiene, H Emanuelsson.*
Cor Europaeum 1994; 3:34-38.

V Forearm endothelial function and plasma nitrate are unaffected in patients with syndrome X and respond normally to transdermal estrogen.
*B Wall, P Albertsson, I Milsom, H Emanuelsson, Å Wennmalm.*
Submitted

VI Beneficial effect of treatment with transdermal estradiol-17-β on exercise induced angina and ST-segment depression in syndrome X.
*P Albertsson, H Emanuelsson, I Milsom*
Int J Cardiol. In press

VII Spinal cord stimulation in angina pectoris with normal coronary arteriograms.
*T Eliasson, P Albertsson, P Hårdhammar, H Emanuelsson, L-E Augustinsson, C Mannheimer.*
Coronary Artery Disease 1993;4:819-827

# ABSTRACT

**The syndrome of angina pectoris with normal coronary angiogram**

Six percent of 2639 patients performing coronary angiograms due to chest pain were found to have normal or near normal angiograms. Compared to patients with significant stenoses they were younger and more likely to be female (50 vs. 20%). The use of medical resources was reduced from a 66% percent need for hospitalisation two years prior to the angiography, compared to 35% during two years after the diagnostic procedure. Regarding self-estimated quality of life, this was considered significantly lower in patients with normal or near normal coronary arteries compared to patients with significant stenoses. This included score on Nottingham Health Profile I, Nottingham Health Profile II and Psychological General Well-Being Index.

Patients with angina pectoris, positive exercise test and normal coronary angiogram (syndrome X) were provoked with adenosine, rapid atrial pacing and intravenous ergonovine. Spasm was not induced in any patient. The flow increase after intracoronary adenosine was similar compared to a control group, but patients with syndrome X showed a lower flow increase after rapid atrial pacing. Four of 13 patients in the study group showed signs of lactate production during rapid atrial pacing compared to none in the control group.

After intravenous adenosine provocation, 14 of 20 patients with syndrome X were found to show signs of significant aggravation of left ventricle dysfunction as opposed to only 4 of 17 patients with atypical chest pain and none of 10 healthy subjects.

Intra-arterial administration of acetylcholine resulted in a dose-dependent increase in forearm blood flow that was similar in patients with syndrome X and in controls. The same was found for the endothelium independent vasodilator sodium nitroprusside.

Fifteen postmenopausal women with syndrome X were performing exercise tests during placebo treatment and during transdermal estrogen treatment. Time to angina increased significantly and so did total exercise time. The ST-segment depression on comparable workload was significantly reduced during active treatment.

Spinal cord stimulation during exercise test was investigated in 11 patients with syndrome X. Compared to the control situation, the rate pressure product and the maximal workload significantly increased and ST-segment depression in comparable workload was reduced from 1.5 to 1.0 mm .

In conclusion, patients with angina pectoris and normal coronary angiogram have an inferior quality of life compared to patients with coronary artery stenoses, but need for hospitalisation was reduced after the diagnostic angiogram. Patient with syndrome X have a reduced coronary flow reserve on rapid atrial pacing whereas flow reserve in the forearm was normal. Left ventricular dysfunction could be induced with adenosine. A beneficial treatment effect was shown with both estrogen treatment and spinal cord stimulation.

**Key words:** Angina pectoris, syndrome X, coronary circulation, endothelial function, estrogen, quality of life, morbidity, spinal cord stimulation.

*Göteborg 1996* ISBN: 91-628-2078-8

University of Göteborg
Division of Cardiology
Sahlgrenska University Hospital
Göteborg, Sweden

# THE SYNDROME OF ANGINA PECTORIS WITH NORMAL CORONARY ANGIOGRAM

Per Albertsson

Göteborg 1996

The syndrome of angina pectoris with normal coronary angiogram
By: Per Albertsson

Printed at Vasastadens Bokbinderi, Göteborg

ISBN 91-628-2078-8

*To my family*

# ABSTRACT


**The syndrome of angina pectoris with normal coronary angiogram**

Six percent of 2639 patients performing coronary angiograms due to chest pain were found to have normal or near normal angiograms. Compared to patients with significant stenoses they were younger and more likely to be female (50 vs. 20%). The use of medical resources was reduced from a 66% percent need for hospitalisation two years prior to the angiography, compared to 35% during two years after the diagnostic procedure. Regarding self-estimated quality of life, this was considered significantly lower in patients with normal or near normal coronary arteries compared to patients with significant stenoses. This included score on Nottingham Health Profile I, Nottingham Health Profile II and Psychological General Well-Being Index.

Patients with angina pectoris, positive exercise test and normal coronary angiogram (syndrome X) were provoked with adenosine, rapid atrial pacing and intravenous ergonovine. Spasm was not induced in any patient. The flow increase after intracoronary adenosine was similar compared to a control group, but patients with syndrome X showed a lower flow increase after rapid atrial pacing. Four of 13 patients in the study group showed signs of lactate production during rapid atrial pacing compared to none in the control group.

After intravenous adenosine provocation, 14 of 20 patients with syndrome X were found to show signs of significant aggravation of left ventricle dysfunction as opposed to only 4 of 17 patients with atypical chest pain and none of 10 healthy subjects.

Intra-arterial administration of acetylcholine resulted in a dose-dependent increase in forearm blood flow that was similar in patients with syndrome X and in controls. The same was found for the endothelium independent vasodilator sodium nitroprusside.

Fifteen postmenopausal women with syndrome X were performing exercise tests during placebo treatment and during transdermal estrogen treatment. Time to angina increased significantly and so did total exercise time. The ST-segment depression on comparable workload was significantly reduced during active treatment.

Spinal cord stimulation during exercise test was investigated in 11 patients with syndrome X. Compared to the control situation, the rate pressure product and the maximal workload significantly increased and ST-segment depression in comparable workload was reduced from 1.5 to 1.0 mm .

In conclusion, patients with angina pectoris and normal coronary angiogram have an inferior quality of life compared to patients with coronary artery stenoses, but need for hospitalisation was reduced after the diagnostic angiogram. Patient with syndrome X have a reduced coronary flow reserve on rapid atrial pacing whereas flow reserve in the forearm was normal. Left ventricular dysfunction could be induced with adenosine. A beneficial treatment effect was shown with both estrogen treatment and spinal cord stimulation.



**Key words:** Angina pectoris, syndrome X, coronary circulation, endothelial function, estrogen, quality of life, morbidity, spinal cord stimulation.

# LIST OF ORIGINAL PAPERS

This thesis is based on the following papers which are referred to by Roman numerals:

I Morbidity and use of medical resources in patients with chest pain and normal or near normal coronary arteries: Influences of the diagnostic angiogram.
*P Albertsson, H Emanuelsson, T Karlsson, C Lamm, W Sandén, G Lagerberg, J Herltiz.*
Submitted

II Quality of life in patients with chest pain and normal or near normal coronary angiograms.
*P Albertsson, I Wiklund, H Emanuelsson, M Haglid, T Karlsson, H Sjöland, J Herlitz.*
Submitted

III Coronary vasodilator capacity during atrial pacing and after adenosine administration in patients with syndrome X.
*P Albertsson, H Emanuelsson, C Lamm, F Waagstein.*
Submitted

IV Adenosine infusion - Provocation of left ventricular dysfunction in patients with syndrome X.
*P Albertsson, V Kujacic, D Jablonskiene, H Emanuelsson.*
Cor Europaeum 1994; 3:34-38.

V Forearm endothelial function and plasma nitrate are unaffected in patients with syndrome X and respond normally to transdermal estrogen.
*B Wall, P Albertsson, I Milsom, H Emanuelsson, Å Wennmalm.*
Submitted

VI Beneficial effect of treatment with transdermal estradiol-17-β on exercise induced angina and ST-segment depression in syndrome X.
*P Albertsson, H Emanuelsson, I Milsom*
Int J Cardiol. In press

VII Spinal cord stimulation in angina pectoris with normal coronary arteriograms.
*T Eliasson, P Albertsson, P Hårdhammar, H Emanuelsson, L-E Augustinsson, C Mannheimer.*
Coronary Artery Disease 1993;4:819-827

# TABLE OF CONTENTS

# INTRODUCTION

## Background

Soon after the advent in the early 60´s of coronary angiography, it became clear that among those patients reporting chest pain, some have normal coronary angiograms. The first report was published in 1967 (Likoff *et al* 1967) where 15 women with chest pain, ECG abnormalities, and normal coronary angiogram were described.

Soon thereafter a study was reported by Kemp regarding 50 patients with chest pain and normal coronary angiograms (Kemp *et al* 1967). In this series 62% of the patients were female and angina was considered typical in only 30%. These pioneer works addressed several important features that are still applicable today; the female predominance, severe chest pain which can often be atypical, and lack of efficacy with conventional pharmacological treatment. The term syndrome X was first used by Kemp in an Editorial comment accompanying an article by Arbogast and Bourassa in the American Journal of Cardiology in 1973, comparing a group of patients with angina and normal coronary arteries (group X) with a group of patients with angina and coronary artery stenosis. In this study, left ventricular function was normal during rapid atrial pacing in group X in spite of "ischemic" ST-segment depression. Kemp used the term "syndrome X" to denote the heterogenicity of the patients and the uncertainty of the ethiology behind the symptoms. More than twenty years later the term syndrome X is unfortunately still appropriate.

## Definition

There are no consensus how to properly define this syndrome, which leads to great difficulties regarding comparisons between different trials where different populations have been studied.

Except for angina pectoris and a normal coronary angiogram, signs of myocardial ischemia is most often required for the diagnosis of syndrome X.

Furthermore the absence of inducible spasm is often, but not always, desirable as is exclusion of patients with systemic hypertension, valvular heart disease, left ventricular hypertrophy and cardiomyopathy.

In this thesis the following criteria are used to define syndrome X;

1. *Exercise induced angina pectoris.*
2. *Normal coronary angiogram.*
3. *Normal left ventricular function at rest.*
4. *No signs of spasm angina.*
5. *Positive exercise test with >1mm horizontal or down-sloping ST-segment depression, 60 ms from the J-point.*

There are clear drawbacks with the use of exercise test as a marker for myocardial ischemia (discussed in more detail on p.46), but simply, it has a long tradition and is the most widely used provocation method.

## Incidence

The true incidence of syndrome X in a population with angina pectoris is not known. Since a normal coronary angiogram is mandatory for the diagnosis, it is plausible that only patients with

severe symptoms are properly diagnosed. In a sub-sample of middle-aged men, derived from the Primary Prevention Trial in Göteborg, however, the incidence of normal angiogram in cohorts with angina pectoris can be calculated (Hagman *et al* 1987). Two age-cohorts (47 and 48 years) of men living in Göteborg were investigated. Of 1432 subjects 70 (4.9%) were considered to have angina pectoris. Of these, coronary angiography was performed in 25 subjects of whom 15 had no significant stenoses (1 minor irregularity and 14 completely normal angiogram). This gives a maximal incidence of normal angiogram of 60% (15/25) and a minimal incidence of 21% (15/70).

In observational studies among patients performing coronary angiogram, 7-30% are reported to have normal coronary arteries (Proudfitt *et al* 1966, Likoff *et al* 1967, Pasternack *et al* 1980, Kemp *et al* 1986, Phibbs *et al* 1988), and reportedly 50% of these show positive exercise tests (Kemp *et al* 1973). There are, however, authors who believe the true incidence of syndrome X is substantially lower, and an ischemic origin of chest pain could be as low as 1% among patients with normal angiograms (Hutchinson *et al* 1988).

**"Proof" for ischemia.....**

The presence of chest pain and ST-segment changes are suggestive, but not conclusive evidence for an ischemic origin in syndrome X.

Since lactate is the end product of anaerobic glycolysis, its release to the coronary sinus has been regarded as one of the most important indications for ischemia. It is then natural that a demonstration of lactate production is considered to be one of the best evidence for presence of ischemia in syndrome X.

In different trials the proportion of lactate production varies between 10 and 40% among patients with syndrome X (Cannon *et al* 1987,1992, Opherk *et al* 1981, Greenberg *et al* 1987, Berland *et al* 1984, Virtanen 1984). In Cannons work where a reduced coronary flow was demonstrated on atrial pacing after ergonovine, lactate consumption was considerably lower in patients with a vasoconstrictor response and lactate production was seen in only 10% (Cannon *et al* 1987), and in Opherks work back in 1981, 5 of 21 patients can be identified as producing lactate during rapid atrial pacing. Already in one of the pioneer works, lactate metabolism investigation was undertaken and 9 of 29 patients were found to be lactate-producers. Simultaneous pacing did not induce left ventricular abnormality in this group of patients (Boudoulas *et al* 1974), which is rather conflicting since deterioration of left ventricular function represents another parameter indicative of myocardial ischemia. Numerous works have followed, some of which have shown a deterioration of left ventricular function during induction of ischemia (Berger *et al* 1981, Wieshammer *et al* 1986).

Cannon and co-workers demonstrated that during rapid atrial pacing after ergonovine administration, 26 of 33 patients showed a reduced coronary vasodilator capacity, and this group had a higher left ventricular end-diastolic pressure and reduced left ventricular ejection fraction during exercise, compared to the seven individuals with normal vasodilator capacity and a group

of 52 control patients (Cannon *et al* 1985).

In conclusion, both lactate production and left ventricular dysfunction have undoubtedly been demonstrated, at least in subgroups of patients with syndrome X. The discrepancy in these results could partly be explained by the variance of populations that have been investigated: For example, one study indicate that only female patients with syndrome X, and not men, have a fall in ejection fraction during exercise (Favaro *et al* 1987). In some investigations both patients with hypertension and diabetes mellitus have been included (Greenberg *et al* 1987), which also tends to confuse the issue.

### ...and doubts

The conflicting data that has been found regarding syndrome X has led to doubts about the aetiology of chest pain, and the hypothesis that syndrome X is a non-ischemic syndrome, is well in concordance with the excellent prognosis.

The described findings with myocardial lactate production and left ventricular dysfunction are, of course, challenged by investigators with contradictory results. Even in the first experimental work in this field (Arbogast and Bourassa 1973), the findings were obscure with ST-segment depression without left ventricular dysfunction after rapid atrial pacing, similar results have been reported by others (Gibbons *et al* 1981).

One of the most cited works that has been performed recently covered post-exercise echocardiography in 18 patients with syndrome X, which failed to demonstrate any disturbance in left ventricular function in spite of significant ECG-changes (Nihoyannopoulos *et al* 1991).

There are even findings suggesting that patients with syndrome X have left ventricular hypercontractility during exercise (Picano *et al* 1987, Tousoulis *et al* 1993).

Myocardial metabolism has recently been investigated in 12 women with "typical angina pectoris" and positive exercise test (Camici *et al* 1991), and the authors were not able to document any metabolic alterations indicative of ischemia and concluded; "in patients with syndrome X the symptoms, electrocardiographic signs and impairment in the increase in great cardiac vein flow during pacing co-exist with preserved global and regional left ventricular function and myocardial energy efficiency".

Support that only a small fraction of patients with syndrome X have myocardial ischemia was found in a study by Crake and co-workers (Crake *et al* 1988). When coronary sinus oxygen saturation was measured continuously during incremental pacing, patients with coronary artery disease (CAD) responded with a fall in saturation which was not normalised until pacing was discontinued. Ten patients with syndrome X responded in a very heterogeneous way. Six of ten had ST-segment depression but only two had a fall in coronary sinus saturation in a manner similar to CAD patients. In five patients the saturation was unchanged (as in healthy controls) and in three the saturation gradually *increased* throughout the procedure, in spite of the presence of ST-segment depression. The authors interpret these findings as such that only a small proportion of patients

with syndrome X really have an ischemic heart condition.

A very interesting hypothesis has been introduced by Philip Poole-Wilson: Potassium is released from the myocardium when the heart rate is increased, and on cessation of the tachycardia the small net loss of potassium is replaced. If patients with syndrome X have a deterioration in release (to much) or uptake (to slow) of potassium, it would be retained in the myocardium. The retention of potassium would explain both the chest pain and the ST-segment depression (Poole-Wilson 1984, 1989, Webb *et al* 1986, 1987).

This hypothesis has, in a way, been supported by Waldenström and coworkers discovery of metabolic derangement in muscle biopsies from patients with chest pain and abnormal 201-thallium scan. They demonstrated a low energy charge with an inverse or an equalised ATP/ADP ratio. Low ATP could be explained by an ischemic condition, but on biopsy specimens taken during resting conditions and during ischemia, ATP levels were higher than ADP levels. A suggestion is that an excessive ion pumping is present in order to restore the transmembrane gradients of K+ ions. The elevated lactate levels that were found could reflect enhanced K+ pumping due to increased leakage (Waldenström *et al* 1992).

The discussion whether syndrome X is an ischemic or non-ischemic condition will probably continue. A reasonable prediction is that "both sides" will eventually be proven correct. We have to realise that syndrome X is not *one* disease, but a syndrome consisting of different populations with several different mechanisms behind the symptoms.

**Coronary circulation**

Since the heart never rests it needs large quantities of energy, mostly in form of oxidative metabolism which generates ATP (adenosine triphosphate). The myocardium is almost totally dependent on aerobic metabolism. Oxygen-independent glycolysis, during anoxia, contributes to no more than approximately 7% of ATP formation (Neely *et al* 1974). Therefore, in steady state, determination of the rate of myocardial oxygen consumption ($MVO^2$) constitutes an accurate measurement of the total metabolism.

The principal determinants of $MVO^2$ are heart rate, contractility, and wall stress [volume x chamber pressure divided by wall thickness] (Graham *et al* 1968). Additional important factors are the direct metabolic effect of cathecolamines and properties to utilize fatty acids.

Myocardial ischemia occurs when $MVO^2$ exceeds the coronary arteries capacity to deliver oxygen. Induced myocardial ischemia leads to anaerobic glycolysis in the tissue, resulting in a release of lactate, contrary to the normal perfused heart which extracts lactate. The strong correlation between myocardial blood flow, ischemia and regional myocardial function has been demonstrated especially regarding subendocardial blood flow (Downey 1976).

Coronary flow is phasic with the preponderance of flow occurring during diastole (Chilian *et al* 1982), and the flow is determined by the driving pressure (aortic pressure) and the coronary resistance.

The coronary resistance is an additive quantity of vascular and extravascular forces. An increased resistance during systole (due to twisting and shearing of the vessels during heart contractions), represents a small part of the total resistance. The predominant element in extravascular resistance is the intraventricular diastolic pressure which is transmitted mostly to the subendocardium to a greater extent than to the subepicardium. This can lead to limited subendocardial flow in the presence of an elevated left ventricular end diastolic pressure.

The major epicardial coronary vessels act primarily as conductance vessels, and in the absence of atherosclerotic stenoses, they offer little or no resistance to myocardial flow. Small intramyocardial arteries (penetrating the myocardium approximately at right angles) and arterioles (with a size of 10-140 μm in diameter - below the resolution of coronary angiography) are the major source of coronary vascular resistance, together with the somewhat larger (100-250μm) pre-arteriolar arteries. These vessels have well-developed media, and with increasing vascular tone they profoundly alter the resistance to coronary blood flow.

The coronary circulation is under neural regulation with sympathetic innervation (from superior, middle, and inferior ganglia and the thoracic sympathetic ganglia I-IV), and from parasympathetic tone via branches of the vagus nerve. Specifically, the sympathetic tone plays a role in vasoregulation of the heart, but metabolic autoregulation overrides, for example, the constrictive effect of nor-epinephrine (McRaven *et al* 1971).

**Coronary flow reserve**

Coronary flow reserve is the ratio between maximum blood flow during hyperaemia and blood flow during autoregulation. (Fig 1).

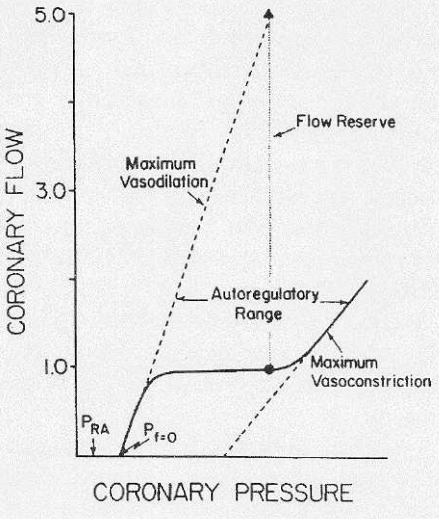



**Figure 1** Steady-state relationship between coronary flow and coronary arterial pressure in the left ventricle. The solid line depicts the normal relationship. At a constant level of myocardial metabolic demand, coronary flow is maintained constant over a wide range of coronary pressure, between the bounds of maximum coronary vasodilatation and constriction (dashed lines). The solid circle represents the normal operating point under basal conditions: the solid triangle is the flow observed at the same pressure during maximum vasodilatation. Flow reserve, the ratio of flow during vasodilatation to that measured before vasodilation, is in this case 5.0 $P_{RA}$ = right atrial pressure: $P_{f=0}$ = "back pressure" opposing coronary flow.
*Klocke; Circulation:1987;:76:1184*

The dynamic alterations in arteriolar vascular tone in response to the oxygen demand of the myocardium, is the fundamental principle behind auto-regulation. When there is a lumen-narrowing lesion in the large epicardial vessels which affects coronary flow, autoregulatory influences alter arterial resistance to maintain an appropriate relation between myocardial oxygen demand and coronary flow. Once the vasodilator reserve capacity of the arterioles is reached, flow can no longer increase (unless the driving pressure increases), and the resistance of the epicardial vessels becomes flow-limiting (Mates *et al* 1978).

Hence, $pO^2$ may be the initial metabolic stimulus for autoregulation, the following cascades of action is more complex.

Several different mechanisms and pathways have been investigated. Among others adenosine (Schrader *et al 1977)*, prostaglandins (Moretti *et al 1978*) and potassium (Olsson *et al* 1987) have been suggested as mediators, and during the last years an increased appreciation for the role of the vascular endothelium has developed.

Since the pioneer observations by Opherk and co-workers (Opherk *et al* 1981), there are confirmations in several studies that patients with syndrome X exhibit a reduced coronary flow reserve (Table 1). It is important to highlight that the investigated subjects have been very heterogeneous in the different trials.

Far from all investigators use the classical definition based on objective signs of ischemia. Opherk characterised patients as syndrome X if they had "typical stress-induced angina pectoris promptly relieved by nitro-glycerine".

Only 12 of 21 experienced a positive exercise test. In their now classical work, Cannon and co-workers (Cannon *et al* 1985) evaluated 50 patients with "chest pain syndromes but with normal epicardial coronary arteries". Only two had a positive exercise test. During atrial pacing 24 subject experienced chest pain and this group of patients were found to have a significant reduction in coronary flow reserve, compared to the subjects who did not report pain. Because of the assumption that the increased coronary resistance originated from vessels smaller than the resolution of coronary angiography, the term "microvascular angina" was introduced to denote this syndrome. These and later observations emphasise that a cardiac origin of chest pain cannot be excluded in patients who fail to develop ECG changes during exercise test.

A weakness in invasive investigations is the problem of finding an adequate control group. Due to the invasive nature of trials concerning coronary flow, it is impossible to include healthy subjects, and control patients have often experienced symptoms justifying a diagnostic coronary angiogram.

**Table 1 Myocardial blood flow reserve in patients with syndrome X and controls**

| Author | Method | Provocation | Patients | Flow Reserve |
|---|---|---|---|---|
| Opherk 1981 | Argon washout | Dipyridamole intravenous | 21 SX (12+ET) | 2.0 |
| | | | 15 Control | 3.8 |
| | | | 10 CAD | 1.9 |
| Geltman 1990 | PET Oxygen-15-labelled water | Dipyridamole intravenous | 17 SX (4+ET) | 1.4 |
| | | | 16 controls | 3.7 |
| Galassi 1993 | PET Oxygen-15-labelled water | Dipyridamole intravenous | 13 SX (13+ET) | 2.4 |
| | | | 7 Control | 3.9 |
| | | | 8 CAD (1-VD) | 3.2 normal vessel |
| | | | | 1.7 stenotic vessel |
| Camici 1990 | PET Nitrogen-13-labelled ammonia | Dipyridamole intravenous | 22 SX (22+ET) | 2.0 |
| | | | 15 Control | 2.9 |
| Cannon 1985 | Coronary sinus thermodilution | Atrial pacing | 24 SX* (2+ET) | 1.4 |
| | | | 26 Control* | 1.8 |
| Greenberg 1987 | Coronary sinus thermodilution | Atrial pacing | 10 SX** | 1.5 |
| | | | 17 control** | 1.8 |
| Camici 1991 | Coronary sinus thermodilution | Atrial pacing | 15 SX (15+ET) | 1.6 |
| | | | 10 Control | 2.0 |
| Chauan 1994 | Intracoronary doppler | Papaverin intracoronary | 53 SX (53+ET) | 2.7 |
| | | | 26 Control | 5.2 |

PET = Positron Emission Tomography
Flow reserve = Maximal flow induced divided by basal flow
SX = Syndrome X (in this table the authors study group. Different definitions - not necessarily including positive exercise test)
* Patients were grouped whether they experienced chest pain during pacing (SX) or not (Control).
** Patients were grouped whether they produced lactate during pacing (SX) or not (Control)
+ET = Positive exercise test
CAD = Coronary artery disease
1-VD = One-vessel disease

## Pathophysiology behind reduced coronary flow reserve-Hypotheses

It is still unknown whether the nature of increased vascular resistance is structural (vascular wall hypertrophy) or functional (vasoconstriction or lack of vasodilatation), but interesting theories have been presented regarding possible mechanisms.

*Pre-arteriolar coronary constriction.*

The proximal compartment of resistive vessels are the prearterioles, the distal compartments are composed of the arterioles. The arterioles vasomotor tone is influenced mainly by autoregulation, but pre-arterioles whose main purpose is to maintain an optimal perfusion pressure at the origin of the arterioles, are regulated by both neural, hormonal and local vasoactive factors.

It is impossible to exactly determine the site (arteriole or pre-arteriole) responsible for an increased coronary resistance with methods currently available. A theoretical concept, based on observations that dipyridamole induces pain and ischemia in the presence of increased myocardial flow, may provide insight into this issue (Epstein *et al* 1986). The localisation of flow impediment must, in this model, be located in the small pre-arteriolar vessels prior to the branching point of the sub*epi*cardial arterioles, to induce coronary transmural blood flow steal from the sub*endo*cardial region.

A more general model has been proposed by Maseri (1991). He suggested that there is a patchy distribution of abnormal constriction of pre-arterioli vessels. An increased resistance in these vessels can explain the reduced coronary vasodilative response observed, even when the small arterioles are supposed to dilate maximally. A localised compensatory increase of adenosine release can cause angina even in the absence of ischemia, since adenosine, except for being a potent vasodilator, also has algogenic properties and is even considered to be the mediator of pain in angina pectoris (Sylvén *et al* 1986). The speculation of patchy distribution of impaired coronary flow reserve was confirmed in a study employing PET (Positron Emission Tomography) and 15-oxygen-labelled water (Galassi *et al* 1993). Patients with syndrome X had higher resting perfusion than both normal subjects and patients with one-vessel disease. After dipyridamole infusion small areas of hypoperfusion were irregularly distributed in all anatomic regions, whereas in patients with coronary artery disease, the hypoperfused areas were clustered in the region supplied by the stenotic artery.

*Neurohumoral control*

There are studies indicating that patients with syndrome X may have increased sympathetic activity, since they have been found to have a higher mean heart rate (Galassi *et al* 1991), an increased coronary artery tone and higher plasma levels of cathecolamines during exercise (Ishihara *et al* 1990). Frøbert and co-workers found that patients with micro-vascular angina but normal exercise tests, demonstrated signs of a general elevated sympathetic activation with a higher heart rate and a decreased heart rate variability (Frøbert *et al* 1995). On the other hand the patients with micro-vascular angina and a positive exercise

test did not exhibit signs of autonomic dysfunction.

Endogenous peptides (i.e. Neuropetide Y and endothelin) may also play an important pathogenetic role since they can cause a distal vasoconstriction potent enough to overpower autoregulation (Larkin *et al* 1989).

Intracoronary infusion of Neuropeptide Y to patients with syndrome X induces chest pain and ECG changes but no lumen changes in the epicardial coronary arteries (Clarke *et al* 1987), while at the same time contrast medium run-off is lengthened indicating constriction of small coronary vessels (Kaski 1992). This implies that coronary hyperreactivity to constrictor neuropeptides *may* be present in patients with syndrome X. A finding not supporting a pathophysiologic impact of increased sympathetic tone is the lack of efficacy for treatment with alpha-blocking agents, which fails to improve exercise-induced symptoms and ischemia if given to patients with syndrome X (Galassi *et al* 1989).

*Role of epicardial vessels.*

In contradiction to the general assumption that the target for the impaired coronary flow reserve in syndrome X is at pre-arteriolar or arteriolar level, a study has been presented which identifies a subgroup of patients with a vasoconstrictor response that involves the epicardial branches (Montorsi *et al* 1991). A similar result was achieved by Bugiardini and co-workers who found a constrictor response with increased vascular tone in the microcirculation *and* the epicardial vessels, suggesting a disorder involving the entire coronary tree (Bugiardini *et al* 1993).

*Endothelial dysfunction.*

The vascular endothelium lines the entire circulatory system. It is evident that the endothelium itself has a relaxing effect on the smooth muscle (Furchgott *et al* 1980). Many stimulus have been shown to induce endothelium-dependent dilatation, among others endogenous and pharmacological agents such as acetylcholine, substance P and bradykinin, as well as mechanical stimuli like flow (shear stress). Furchgott proposed that the action was mediated via a substance, an "Endothelium Derived Relaxing Factor, EDRF". It later became clear that this substance was identical to nitric oxide, NO (Palmer *et al* 1987). The research group lead by Moncada a year later identified the amino acid L-arginine as the biological precursor to NO (Palmer *et al* 1988) which, for conversion, is dependent on a family of enzymes, nitric oxide synthase, "NOS" (Bredt *et al* 1991).

In the investigational situation acetylcholine has shown to be the agent best suited for evaluation of endothelium function, since it dilates the vessel in presence of intact endothelium, a response which will be reversed to constriction when the endothelium is defect.

Theoretically an impaired endothelial function is a very pleasing mechanism behind coronary flow impedance in patients with syndrome X and evidence has been sought.

Flow-response after acetylcholine and dipyridamole were measured in 23 patients (Motz *et al* 1991). Eight patients did not show increased flow after acetylcholine, whereas coronary blood flow increased after dipyridamole. In six patients, neither acetylcholine nor-

dipyridamole were followed by increased flow. Interpretation of this study should nevertheless be performed with care, since fourteen of the patients had a history of arterial hypertension and five had negative exercise test.

Lagerqvist provoked 20 patients with angina pectoris, pathologic thallium scintigram and normal coronary angiography with intracoronary infusion of acetylcholine (Lagerqvist *et al* 1991). There were unfortunately no consistent findings in the response in this group of patients.

Vrints *et al* infused high doses of acetylcholine intracoronary in 24 patients with normal coronary angiograms (Vrints *et al* 1992). Twelve patients with typical angina pectoris responded with constriction, even more pronounced than in patients with documented coronary artery disease. No coronary flow measurements were made, leaving endothelial function at microvascular level as speculative.

The strongest evidence for a relationship between syndrome X and impaired endothelial function was found in a recent study by Egashira and coworkers. They demonstrated, with intracoronary doppler measurements, reduced coronary flow after acetylcholine administration in nine patients with syndrome X compared to controls (Egashira *et al* 1993). This difference was not present when provocation was repeated with nitrate and papaverine. This observation is today the strongest evidence that endothelial function is abnormal in patients with syndrome X.

**Mechanisms of pain and pain perception**

Pain induced by cardiac ischemia can be regarded as a warning signal, and is probably generated by the stimulation of cardiac polymodal receptors, which respond to both mechanical and chemical stimuli. Adenosine, bradykinin and K+ are all considered as possible mediators of ischemic pain (Sylwén *et al* 1986, Maseri *et al* 1992).

Following sensory receptor stimulation, the nociceptive impulses are transmitted in slow C-fibres or the faster Að-fibres.

These fibres project on dorsal horn neurones that also receive impulses from somatic fibres in the same dermatome. The transmission of nociceptive messages is modulated in the dorsal horn spinal neurones according to the "gate theory of pain control", proposed by Melzack and Wall (1969). This leads to that nociceptive inputs from distant areas can inhibit the activity of the convergent neurones.

The projection is transmitted from the dorsal horn along the spinothalamic tract to the thalamus. The target for the ascendant pathways beyond thalamus is cortex and the cingulate gyrus, but there is probably not a specific localised "pain-centre" present.

Following recent research, abnormal pain perception has been suggested as a mechanism behind chest pain in syndrome X.

Pain is provoked in a substantially higher proportion of patients with microvascular angina compared to patients with coronary stenosis when right ventricular pacing is performed (Cannon *et al* 1990). Similarly in patients fulfilling the criteria for syndrome X

their typical chest pain was provoked by catheter movement within the right atrium and by intra-atrial boluses of saline (Shapiro *et al* 1988, Chauhan *et al* 1994).

Finally has it been reported that patients with syndrome X report chest pain on a lower dose of adenosine compared to healthy volunteers (Lagerqvist *et al* 1992).

**Role of estrogen**

A marked sex difference with a majority of males in the risk zone for developing coronary heart disease has long been recognised (Glendy *et al* 1930). This is in contradiction to syndrome X where there is a female predominance (Kemp *et al* 1967 and 1986). The first appearance of the disease is often in relation to menopause and a high prevalence of hysterosalpingo-oophorectomy has been noted prior to the onset of symptoms (Sarrel *et al* 1992, Rosano *et al* 1992). This has led to the assumption that estrogen-deficiency may play an important role behind the pathogenesis of syndrome X.

There is now an abundance of research reporting that estrogen has vasodilator properties. The classical model of steroid action is diffusion into the target cell where it binds to a receptor, and the hormone-receptor complex binds to specific DNA sequences, resulting in altered transcription of specific mRNA and subsequent protein synthesis (Farhat *et al* 1995). This genomic pathway can be detected within an hour after hormone administration. Estrogen also clearly acts with responses that are non-genomic and these vascular effects can be observed within minutes or even seconds after administration. Jiang demonstrated that 17-ß-estradiol induce relaxation in both female and male rabbit coronary arteries (Jiang *et al* 1991), and they subsequently demonstrated that this effect was in concordance with calcium-blocking agents (Jiang *et al* 1992). Williams reported that acute administration of estrogen attenuates the coronary vasoconstrictor response to acetylcholine in atherosclerotic ovariectomized cynomolgus monkeys (Williams *et al* 1992), a response that earlier had been demonstrated with chronic treatment (Williams *et al* 1990). These observations suggest that estrogen plays a fundamental role in the normal regulation of vascular tone. In humans it has been demonstrated that women with early coronary disease who are treated with estrogen replacement therapy (ERT) show a vasodilator response to acetylcholine infusion, while women not receiving ERT show a vasoconstrictor response on acetylcholine. Gilligan showed that intracoronary infusion of physiological levels of estradiol-17-beta prevented epicardial constriction induced by acetylcholin, leading to increased coronary flow (Gilligan *et al* 1994).

Randomised trials have now been presented regarding estrogen replacement therapy. Rosano *et al* demonstrated in a placebo-controlled trial with exercise tests in eleven female patients with coronary artery disease (CAD), that 17-ß-estradiol improved time to 1mm ST-segment depression and total exercise time (Rosano *et al* 1993).

In patients with syndrome X, ERT has been demonstrated to improve symptoms in form of reduced chest pain, and

cessation of hot flushes, as well as improvement of the hyperaemic response of post-occlusion blood flow (Sarrel *et al* 1992). This implies a possible relationship between estrogen deficiency and chest pain in at least a subset of women with syndrome X.

**Extracardiac manifestations**

It is not unusual that patients with syndrome X simultaneously demonstrate symptoms from non-cardiac organs. For example, migraine headache and Raynaud phenomena have been found in a high prevalence.

Airway hyperesponsiveness has also been demonstrated in patients with microvascular angina (Cannon *et al* 1990), these findings being consistent with the hypothesis that syndrome X may represent a more generalised abnormality of vascular and non-vascular smooth muscle function. This was first proposed when a reduced forearm vasodilator reserve was demonstrated by Sax and co-workers, who investigated hyperaemic responses to forearm ischemia with plethysmography in 16 patients compared with normal controls (Sax *et al* 1987).

Diabetes mellitus is most often considered as an exclusion criteria when investigations are performed regarding syndrome X. The reason for this is avoidance of inclusion of patients with structural small vessel diseases. In a series of eleven patients without overt diabetes mellitus, stimulated hyperinsulinaemia was found (Dean *et al* 1991), this was later confirmed by Chauhan *et al* 1994. Further information was achieved by Bøtker and co-workers who, applying the technique of glucose turnover during a 2 hour hyperinsulinaemic clamp, found that patients with syndrome X had substantial insulin resistance (Bøtker *et al* 1993). This suggests that there could be a connection between the "cardiologic syndrome X" and the "metabolic syndrome X" (=insulin resistance, hypertension, hyperlipidaemi and central obesity). Reaven introduced this term, probably unaware of the existence, since 15 years, of the "cardiologic syndrome X", which has led to a great deal of confusion. In Bøtker and co-workers study, no other features of metabolic syndrome X was found, this is in contrast to a recent work were non-obese men with chest pain and normal coronary angiogram were insulin resistant, hyperinsulinaemic and had increased levels of triglycerides (Swan *et al* 1994).

There is by some colleagues an apprehension that patients with syndrome X are a group of hyperchondriacs and neurotics. This could in part be explained by the fact that these patients are often misunderstood and regarded as simulates when the findings of normal angiograms are evident. However, employing accepted research methods with interviews before the diagnostic angiograms has revealed a high co-existence, up to 40%, with psychiatric morbidity (Waxler *et al* 1971, Bass *et al* 1984). Anxiety neurosis is the most common psychiatric diagnosis and it is often accompanied by unexplained breathlessness (Bass *et al* 1983). These figures appear extremely high, but one should keep in mind that this association consisted of patient with normal coronary arteries and objective signs of ischemia were not required. In

comparison 23% of patients with coronary artery disease (Bass *et al* 1984) and 27% of patients in general medical clinics (Davies 1964) have also signs of psychiatric morbidity.

**Differential diagnosis**

A complete history is usually important in the search for the correct diagnosis. There are some clinical characteristics typical for syndrome X, for example pain at rest, general fatigue, dyspnea and prolonged pain, often >30 minutes in duration (Kaski 1994). Still, it is important to rule out other diagnosis before the patient can be regarded as having syndrome X.

*Cardiac Chest Pain*

Spasm angina has some features in common with syndrome X, and efforts should be made to rule this out since spasm angina is a different disease with a different pathogenetic background, and show often a good response to pharmacological treatment (calcium channel blockers and nitroglycerine). There are possibilities that spasm can co-exist with syndrome X but in patients with "angina-like pain" only 5% had signs of spasm (Heupler *et al* 1973), and 4 of 58 patients with exercise induced angina, normal coronary arteries and a high proportion of lactate production, responded with spasm on methergine provocation (Bertrand *et al* 1982).

It is often wise to include an echo-cardiography in the arsenal of investigative analysis of angina and normal coronary angiogram, since it can reveal heart conditions often associated with chest pain e.g. aortic regurgitation, aortic stenosis, mitral valve prolapse, hypertrophic cardiomyopathy and dilated cardiomyopathy (Nitenberg *et al* 1988, Cannon *et al* 1985, Opherk *et al* 1983).

*Non-cardiac chest pain*

In some clinical reviews >50% of patients with chest pain with normal coronary arteriograms are believed to have symptoms that originate from the musculoskeletal system (Urschel *et al* 1973), but since this is very common even in the general population it could simply be an innocent bystander.

Pain arising from the oesophagus is clinically often difficult to differentiate from pain of cardiac origin. Abnormal refluxes have been found in a high proportion of patients with chest pain and normal coronary arteries. (DeMeester *et al* 1982). Another explanation could be elevated distal oesophageal pressure with normal peristaltic consistent with "nutcracker oesophagus" (Richter *et al* 1988).

A complicating factor is that oesophageal dysfunction and coronary heart disease often co-exist. It is possible that there is even a link between the two conditions, "linked angina". Oesophageal acid stimulation has been demonstrated to reduce coronary blood-flow in syndrome X, suggesting the presence of a cardio-oesophageal reflex (Chauan *et al* 1993). This implies that oesophageal reflux really can induce angina pectoris!

Other conditions that can mimic angina pectoris are peptic ulceration and gall bladder pain (Hamton *et al* 1959).

## Treatment

Patients with syndrome X are considered to respond poorly to conventional pharmacological treatment. There are different regimens which have been tried and found effective, and some studies are presented below.

Sublingual nitrates are effective in relieving chest pain in approximately 50-60% of the patients (Kemp *et al* 1973, Romeo *et al* 1993).

Treatment with alpha-blocking agents (prazosin or clonidin) have been given in an attempt to reduce alpha-adrenergic stimulation to the micro-circulation (Galassi *et al* 1989). No significant changes were seen in exercise duration, heart rate-blood pressure product or ST-segment shift on ECG.

Imipramin has been shown to reduce the frequency of anginal attacks (Cannon *et al* 1993). The authors believe this to be related to the drugs' visceral analgetic effect, and not to the anti-depressive effect.

The adenosine inhibitor, theophylline has been demonstrated to improve exercise capacity in patients with ischemic heart disease (Crea *et al* 1989). This has also been repeated in patients with syndrome X were intravenous infusion of aminophylline in eight patients abolished the ECG changes and increased effort tolerance in presence of an increase in rate-pressure product (Emdin *et al* 1989).

The ACE-inhibitor enalapril has also been tried in syndrome X (Kaski *et al* 1994). Ten patients with syndrome X and a reduced coronary flow reserve underwent exercise tests after two weeks of treatment with enalapril 10mg/day or placebo. Total exercise duration and time to angina was prolonged, and magnitude of ST segment depression was decreased during active treatment. The authors speculate that the effect is mediated by a direct modulation of microvascular tone, resulting in an increased myocardial oxygen supply.

In a double-blind placebo-controlled trial, consumption of nitroglycerin was reduced and exercise duration was prolonged after one month of treatment with verapamil or nifedipin (Cannon *et al* 1985). However, there were no differences in ECG-changes or in rate-pressure product.

Betablocking agents has been compared to calcium channel blockers (verapamil vs acebutolol). In fifteen patients verapamil were superior to both placebo and acebutalol, and in the remaining fifteen both verapamil and acebutolol revealed a significant prolonged exercise duration (Romeo *et al* 1988).

In our personal experience the beneficial effect of pharmacological administration is not always maintained during long-term treatment, but in the clinical situation we often start with calcium channel blockers and short acting nitroglycerin, and when ineffective, other regimens are prescribed in a "trial and error" way.

## Prognosis

Long-term follow up studies have shown an excellent outcome regarding cardiac death and myocardial infarction in patients with chest pain and a normal coronary angiogram (Table 2).

**Table 2** Outcome of patients with angina and normal or near-normal coronary angiogram in different trials

| Author | No of patients | Mean follow-up (months) | Population (degree of stenoses) | Non-fatal myocardial infarction (%) | Mortality Cardiac | Total |
|---|---|---|---|---|---|---|
| Waxler 1971 | 86 | 15 | N | 0 | 0 | 0 |
| Kemp 1973 | 200 | 36 | <10% | 0 | 2 | 3 |
| Bemiller 1973 | 37 | 49 | N | 0 | 2.7 | 2.7 |
| Bruschke 1973 | 342 | 60-88 | N | 0.9 | 0.6 | 5.2 |
| | 101 | | <30% | 4 | 4 | - |
| | 57 | | 30-50% | 3.5 | 5.3 | - |
| Pasternack 1980 | 159 | 43 | 0-30% | 0.6 | 0 | 0 |
| Proudfit 1980 | 357 | 120 | N | 0.8 | 0.8 | - |
| | 101 | | <30% | 7.9 | 2 | 6.4 |
| | 63 | | 30-50% | 6.3 | 15 | 16.5 |
| Ockene 1980 | 57 | 16 | N | 0 | 0 | 0 |
| Kemp 1986 | 3136 | 84 | N | - | 0.4 | 1.3 |
| | 915 | | <50% | - | 1.9 | 4.8 |
| Papanicolau 1986 | 1491 | 60 | 0-25% | 1 | - | 2 |
| | 486 | | 25-50% | 3 | - | 2 |
| Romeo 1993 | 30 | 60 | N | 0 | 0 | 0 |
| Radici 1995 | 30 | 146 | N | 0 | 0 | 3.3 |
| Lichtlen 1995 | 176 | 147 | N | 2.3 | 1.1 | 2.3 |
| Kaski 1995 | 99 | 84 | N | 0 | 0 | 0 |

* = Cardiac death includes sudden death of unknown reason
- = Data not available in article
N = Completely normal angiogram

Hence, there seems to be reasons to differentiate between patients with mild disease and patients with completely normal angiograms. Bruschke demonstrated that patients with entirely normal angio-grams had an incidence of myocardial infarction and cardiac death of only 0.9% and 0.6%, respectively, during a 5-year follow-up period (Bruschke *et al* 1973). In the presence of mild disease the incidence of myocardial infarction increased to 5.3% and cardiac death to 3.5%. A similar result was found by Proudfit, with cardiac mortality being 0.6% with normal angiography, increasing to 1.9% in the presence of <30% stenosis, and 15.9% in patients with 30-50% stenosis during a 10-year follow-up period (Proudfit *et al* 1980).

It seems moreover reasonable to believe that the two groups constitute at least two different populations, probably with different mechanisms behind the pain.

In spite of the good prognosis regarding mortality and risk for development of myocardial infarction, a high proportion of the patients continue to have chest pain, which has been described in a frequency of 20-80% (Kemp *et al* 1973, Proudfit *et al* 1980, Bemiller *et al* 1973, Isner *et al* 1981). Once again the discrepancy between trials can be explained by different populations being investigated.

A subgroup with a worse prognosis may be patients with constant or rate-dependent left bundle branch block. In this subgroup, a deterioration in left ventricular function has been described, with an increase in exercise pulmonary artery pressure and a decrease in ejection fraction (both at rest and during exercise) when these investigations were repeated after four years (Opherk *et al* 1989). It is possible that "syndrome X with left bundle branch block" may be an early form of dilated cardiomyopathy (Kübler *et al* 1992). There are some similar features and a reduced coronary vasodilator capacity has also been described in patients with cardiomyopathy (Opherk *et al* 1983). This reduction in the dilatory capacity is probably explained by hemodynamic alterations, e.g. increased diastolic wall stress, and there is no data that support an identical mechanism behind increased coronary vascular resistance as in syndrome X.

# AIMS OF THE PRESENT STUDY.

1. To asses the incidence of normal coronary angiogram in a population performing coronary angiogram.

2. To study the morbidity in terms of demographic background data and utilisation of medical resources in patients with normal and near normal coronary angiogram.

3. To asses self-estimated "quality of life" among patients with chest pain and normal or near normal coronary angiograms.

4. To study the coronary hemodynamic patterns in patients with syndrome X.

5. To study myocardial metabolism and evidence for ischemia during atrial pacing and adenosine administration in patients with syndrome X.

6. To explore the value of a new non-invasive method in the diagnosis of syndrome X.

7. To evaluate the endothelium dependent and independent flow response in the peripheral circulation in syndrome X.

8. To examine the value of estrogen replacement treatment to postmenopausal women with syndrome X.

9. To examine the value of Spinal Cord Stimulation in patients with syndrome X.

# METHODS

## Study designs

*Paper I and Paper II.*
In these papers an open prospective design was employed to register all patients who performed coronary angiography during the period May 88 - May 91. Estimation of hospitalisation and utilisation of medical resources were performed in a retrospective analysis in Paper I.

*Paper III.*
Carefully selected patients with chest pain and and normal coronary angiogram were recruited to this open labelled designed trial.

*Paper IV.*
This is an open labelled designed trial without use of placebo where the influence of adenosine infusion on left ventricular function was studied. Analysis of the recorded echocardiographic investigations were performed by two independent investigators not familiar with the result of the exercise tests.

*Paper V.*
Study 1 in Paper V is an open-designed trial where the study drugs were given in a randomised order. In Study 2 in the same paper a randomised placebo-controlled cross-over design was employed.

*Paper VI.*
A randomised placebo-controlled cross-over design was used in this paper.

*Paper VII.*
This is an open trial where the order of treatment and control exercise tests could not be randomised since we lacked knowledge of the long-term effects of spinal cord stimulation.

## Patients

In Papers I and II all patients in a population with chest pain and a normal coronary angiogram were studied. The remaining five papers are experimental trials and the patients were carefully selected. Some patients participated in more than one study (See Table 3 for further information). In general, patients were recruited to the study groups (syndrome X) if they had typical exertional angina, a positive exercise test and a completely normal coronary angiogram. The chest pain was typical and was suspected of originating from an ischemic heart condition. Papers III and IV include control patients who had performed coronary angiography.

## Table 3 Syndrome X patients in investigational trials (Paper III-VII)

| Subj. | age | Gender | # Cath. | # Echo | ADO Echo | #Cath perif | # E-Perif. | # E-Ex | # ESES | Ex 3 Watt | Ex 3 ST | Ex4 Watt | Ex4 ST | Ex6 Watt | Ex6 ST | Ex7 Watt | Ex7 ST |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MK | 72 | F | 1 | | | 1 | 1 | | | 80 | 1.2 | | | | | | |
| RA | 55-60 | F | 2 | | | 10 | 10 | 11 | 1 | 80 | 1.4 | | | 80 | 0.5 | 103 | 1.0 |
| BS | 44-45 | M | 3 | 15 | Pos | 2 | 2 | | | 120 | 1.9 | 140 | 1.8 | | | | |
| UW | 68 | F | 4 | | | | | | | 60 | 1.9 | | | | | | |
| MN | 60.64 | F | 5 | 16 | Neg | 7 | 7 | 2 | 5 | 90 | 1.2 | 100 | 1.5 | 90 | 1.0 | 90 | 1.0 |
| EL | 55-61 | F | 6 | 5 | Pos | 3 | 3 | 6 | | 80 | 1.1 | 80 | 4.0 | 50 | 0.4 | | |
| LL | 58-59 | M | 7 | 12 | Pos | 5 | 5 | | 8 | 180 | 2.0 | 160 | 1.0 | | | 143 | 2.0 |
| BH | 60-63 | F | 8 | 19 | Pos | | | 3 | | 90 | 2.8 | 120 | 2.0 | 80 | 2.8 | | |
| BD | 60 | F | 9 | 17 | Pos | | | | | 70 | 1.8 | 40 | 1.2 | | | | |
| SD | 58-60 | M | 10 | 14 | Pos | 9 | 9 | | 7 | 120 | 2.0 | 140 | 1.5 | | | 120 | 1.3 |
| RA | 62-67 | F | 11 | 3 | Pos | | | 7 | 2 | 130 | 1.5 | 130 | 1.5 | 110 | 2.9 | 80 | 2.0 |
| EK | 62 | F | 12 | | | | | | | 110 | 1.1 | | | | | | |
| BK | 60-61 | F | 13 | | | 6 | 6 | | | 100 | 1.9 | | | | | | |
| SY | 60-71 | M | *** | | | 4 | 4 | | | | | | | | | | |
| AD | 72-74 | M | | 1 | Pos | | | | 4 | | | 100 | 1.0 | | | 90 | 0.8 |
| SU | 50-54 | F | | 2 | Pos | | | 4 | | | | 100 | 1.5 | 90 | 2.8 | | |
| RE | 59 | M | | 4 | Neg | | | | | | | 110 | 1.2 | | | | |
| AN | 56-58 | M | *** | 6 | Pos | 8 | 8 | | 11 | | | 130 | 4.0 | | | 87 | 0 |
| MS | 67-71 | F | *** | 7 | Pos | | | 1 | 3 | | | 80 | 2.5 | 80 | 1.6 | 60 | 2.5 |
| IP | 44 | F | | 8 | Pos | | | | | | | 100 | 1.0 | | | | |
| NE | 48 | F | | 9 | Neg | | | | | | | 90 | 1.7 | | | | |
| I-LH | 58 | F | | 11 | Neg | | | | | | | 120 | 1.2 | | | | |
| RT | 63 | M | | 10 | Neg | | | | | | | 110 | 2.0 | | | | |
| KE | 51 | M | | 13 | Pos | | | | | | | 120 | 2.0 | | | | |
| AS | 51 | M | | 18 | Pos | | | 7 | | | | 140 | 4.5 | 90 | 2.5 | | |
| BR | 50 | F | | 20 | Neg | | | | | | | 80 | 1.5 | | | | |
| BO-E | 48-51 | F | *** | | | | | 8 | 6 | | | | | 100 | 1.9 | 90 | 1.7 |
| LR | 61 | F | | | | | | | 9 | | | | | | | 90 | 1.5 |
| GB | 64 | F | | | | | | | 10 | | | | | | | 103 | 1.2 |
| EN | 63 | F | | | | | | | 12 | | | | | | | 90 | 0.7 |
| MT | 57 | F | | | | | | 9 | | | | | | 90 | 2.6 | | |
| LP | 53 | F | | | | | | 10 | | | | | | 80 | 1.7 | | |
| I-LN | 57 | F | | | | | | 12 | | | | | | 100 | 1.5 | | |
| IS | 54 | F | | | | | | 13 | | | | | | 90 | 1.0 | | |
| I-LB | 61 | F | | | | | | 14 | | | | | | 110 | 1.2 | | |
| KK | 53 | F | | | | | | 15 | | | | | | 90 | 1.3 | | |

Age = age at time when study was performed. # Cath = Referring to patient number in table 1-4, paper III. # Echo = Referring to patient number in table 2, paper IV. ADO-echo = Result on adenosine echocardiography, paper IV (pos/neg = presence respectively abscence of segmental left ventricular dysfunction during adenosine infusion). #Cath-perif = individuals included in paper V, study I. # Echo-Perif = Individuals included in paper V, study 2. . # E-Ex = Individuls included in paper VI. # ESES = Referring to patient number in table 1-5, paper VII. Ex 3= Exercise tests in relation to catheterisation., paper III Ex 4 = Exercise test in relation to echocradiography, paper IV. Ex 6 = exercise test during placebo treatment, paper VI. Ex7 = Mean value of three run in exercise test without spinal cord stiumlation treatment, paper VII . ST = ST segment depression in mm. Watt= Maximal workload in watt.
*** Catheterisation performed, but patients not included in trial.

*Paper I and Paper II.*
All patients performing coronary angiography at Sahlgenska University Hospital, Östra University Hospital and Skövde Community Hospital during the period May 88 - May 91 were registered. At the time of registration these three centres performed all the coronary angiograms in western Sweden (population 1.5 million). Four hundred and twenty-one patients were excluded since background data and indication for the coronary angiogram were incompletely registered. Patients who had previously performed CABG (n=280) or PTCA (n=182) were also excluded as were patients with concomitant valvular disease (n=636) and patients with indications other than angina pectoris being the indication for angiography, e.g. arrhythmias, congestive heart failure, cardiac tumours etc. (n=424). The remaining population of 2639 performed angiography due to chest pain suspected to originate from coronary artery disease and since CABG or PTCA had not been performed the presence or absence of coronary stenoses was not known. These patients constitute the investigated population in Papers I and II.

*Paper III.*
Thirteen patients with syndrome X (10 females, mean age 60 years) were compared with 9 patients (4 females, mean age 52 years) with atypical chest pain, negative exercise test and a normal coronary angiogram. The indications for coronary angiogram had been chest pain but this was atypical, the exercise tests were negative and the chest pain was *not* suspected to originate from an ischemic heart condition.

*Paper IV.*
20 patients (11 women) with syndrome X constituted the study group. Mean age was 56 years. They were compared with two separate control groups. One consisted of 17 patients (11 women) with atypical chest pain, negative exercise test and a normal coronary angiogram.

A second control group consisted of 10 completely healthy males who had not performed coronary angiogram. Their mean age was 29 years.

*Paper V.*
This paper is based on two studies. The first study included 10 patients with syndrome X (5 females) with a mean age of 60 years and 9 healthy controls (5 females) with a mean age of 55 years.

The second study included 11 postmenopausal women with syndrome X, mean age 59 years and the control group constituted of 8 postmenopausal healthy women with a mean age of 58 years.

*Paper VI.*
15 natural postmenopausal women with syndrome X with a mean age of 58 years were compared with eight healthy postmenopausal women with a mean age of 58 years (same control group as in Paper V, Study 2).

*Paper VII.*
Twelve patients (eight females) with exercise induced chest pain, positive exercise test and a normal coronary angiogram with a mean age of 61 years were studied. They had all been treated with spinal cord stimulation (for a mean time of eight month) and responded well to the treatment.

### Estimation of hospitalisation

All patients with insignificant coronary artery stenoses in Paper I were approached with a questionnaire more than two years after the diagnostic angiogram, asking if and where they had been hospitalised during four years (two years prior to and two years after the diagnostic angiogram). Furthermore all medical files from all 15 hospitals in western Sweden were collected. The main diagnosis given at each time of hospitalisation is presented in the analysis.

### Quality of Life

Questionnaires for self-administration of quality of life were mailed to all patients before the diagnostic coronary angiogram in Paper II. Three different questionnaires were completed by the patients; the *Physical Activity Score*, the *Nottingham Health Profile* and the *Psychological General Well Being Index*.

The *Physical Activity Score* contains six questions, an extract from an angina-specific questionnaire, (*Angina Pectoris Quality of Life Questionnaire*), for self-estimation of physical abilities (Wilson *et al* 1991). Each item is graded from 1-6 and the mean value for all items are calculated, the higher the total value, the greater is the disability.

The *Nottingham Health Profile* is used to assess health-related Quality of Life (QL) and constitutes two parts where the respondent are expected to answer *Yes* or *No* (Hunt *et al* 1980). The first part includes 38 statements which reflects limitations of activity or aspects of distress in six separate dimensions: physical mobility, energy, pain, sleep, social isolation and emotional reactions. A total score of 100 can be obtained from each dimension, the higher the score - the greater limitation of activity or level of distress. The second part reflects seven aspects of social life that is related to the patients state of health; occupation, ability to perform tasks around the house, social life, home relationships, sexual life, hobbies and holidays.

The *Psychological General Well Being Index* constitutes 22 questions, dealing with six different aspects of well-being; anxiety, depression, vitality, general health, self-control and well-being (16). A score from 1-6 should be given for each item, giving a total score rate of 22-132, with the highest score corresponding to superior well-being.

### Exercise tests

All tests were performed on bicycle and a 12-lead ECG was recorded according to standardised technique.

In Papers I and II all subjects but one had undergone exercise tests. The tests were analysed retrospectively.

The exercise tests in Papers III-VII were performed prospectively on an automatically braked bicycle (Corival 400 LODE, Groningen, The Netherlands, Papers V and VI or Rodby, Siemens Elema, Solna, Sweden, Papers III, IV and VII). The ST-segment depression 60ms after the J-point in the lead showing most change from baseline was measured after signal-averaging with use of a computer-assisted system (Case 15 Marquette, Milwaukee, Wis USA, Papers III-VI) or analysed "manually" with a conventional system (Marquette Mac 1, Milwaukee, Wis USA, Paper VII).

The repeated exercise tests in Paper VI and in Paper VII were performed on the same bicycle, during equal conditions at the same time of day.

### Rapid atrial pacing

Atrial pacing was performed via a coronary sinus thermodilution catheter (Paper III). Pacing was initiated at a heart rate of 100 bpm, increasing with 10 bpm every second minute to a target heart rate of 160. Premature termination of pacing was allowed if chest pain rated at least 5 on the ten grade Borg-scale (Borg 1982).

### Blood sample analysis

In Paper III, blood oxygen saturation was determined with an OSM 2 Hemoximeter (Radiometer, Copenhagen, Denmark). Oxygen consumption ($MVO^2$) was computed as; *(arterial-coronary sinus $O^2$ content) x coronary blood flow.*

Lactic acid concentration was assayed by enzymatic method (Lactate Analyser 640, Roche Bio Electronics, Basle, Switzerland). Myocardial lactate extraction ratio was computed as; *100(arterial-coronary sinus lactate concentration)/ arterial lactate concentration.*

Serum estradiol in Papers V and VI was assessed by radioimmunoassay (The Abbot Imx® Estradiol Assay, Diagnostic Division Abbot Park, USA).

Nitrate, the main metabolite of nitric oxide was analysed using gas chromatography and mass spectrometry (Wennmalm *et al* 1993)

### Coronary sinus flow measurements

A thermodilution catheter (Wilton-Webster Laboratory, Altadena, Ca. USA) was introduced into the right atrium via the right internal jugular vein. The great cardiac vein was cannulated and position was verified with contrast injection. The position was kept constant in relation to "bony" landmarks. Coronary sinus blood flow was deter-mined by the continuous infusion thermodilution method with the catheter attached to a Wheatstone bridge. Changes in resistance were recorded on a Siemens-Elema Mingograph (Siemens-Elema, Solna, Sweden), and coronary sinus blood flow (CSF) was calculated according to the formula; $CSF=FIx\ k\ [(TB-TI/TB-TM)-1]$ where $FI$= infusion rate, $TB$= temperature of blood, $TI$= temperature of injectate and $TM$= temperature of mixture of blood and injectate, and $k$ = a constant derived from the density and specific heat of saline solution and blood.

### Adenosine provocation

In the first four patients in Paper III, adenosine 11.3 mmol/l (3.0mg/ml; Hässle AB, Mölndal, Sweden) was given as a continuous infusion in the right atrium, starting with a dose of 50µg/kg Bw/min, increasing with 10µg/kg every second minute to a maximal dose of 100µg/kg. In the remaining 18 subjects adenosine was administered as an intracoronary bolus in the left coronary ostium. The starting dose was 0.1 mg and thereafter 0.3, 0.6, 1.2, 3.0, and 6.0 mg were given at two minutes intervals if dose increment was tolerated.

In Paper IV adenosine was given as an intravenous infusion with a starting dose of 60µg/kg bw/min to a maximal dose of 200µg/kg/min.

**Cardiac echocardiographic examination**

Cardiac echocardiography was performed with a Hewlett Packard Ultrasound Computerised Sonographic equipment with a 3.5 MHz sector transducer. Total ejection fraction was calculated from 2 and 4 chamber view using single plane ellipse formula (SP-EL). Wall motion was analysed in a 9-segment model and the segments were as follows: apex, proximal anterior, distal anterior, proximal lateral, distal lateral, proximal posterior, lateral posterior, proximal septal and distal septal wall. Wall motion was interpreted visually and graded as follows: 1= normal, 2=hypokinesia, 3=akinesia, 4=dyskinesia. A total sum of 9 represents normal function and higher sum implies dysfunction. To interpret the test as clearly positive an increase from rest to provocation in a total sum of at least 3 was required. LVSI (Left Ventricular Score Index) was calculated as total score divided by number of analysed segments, and an increase of at least 0.3 was regarded as positive.

**Estimation of forearm endothelial function**

An intra-arterial catheter was inserted into the left brachial artery. Forearm blood-flow was measured in the left arm with venous occlusion plethysmography (strain-gauge). An infusion of either acetylcholine (10, 20, 30, 40, 50, and 60 µg/kg/min) or sodium nitro-prusside (1, 2, 3, 4, 5 and 6 µg/kg/min) was administered in a random order. Each drug was infused for 4 minutes per dose phase with measurements taken of blood flow during the final minute. In another study design, high resolution ultrasound (7.0 mHz transducer and a 128XP/10 system, Acuson, Mountain View, Ca. USA) was used for measurement of the diameter of the right brachial artery during resting situation and following reactive hyperaemia. This was induced by inflation of a pneumatic tourniquet to a pressure of 240-250 mmHg for five minutes.

**Spinal Cord Stimulation**

The stimulation equipment (Medtronic, Minneapolis, Min. USA) was surgically implanted under local anaesthesia. An electrode tip was placed epidurally in mid-line at level Th 1- Th 2. The system was tested and adjusted so that paraesthesiae covered the area of the anginal pain. The generator was placed in a subcutaneous pouch below the left costal arch and a connection-lead was tunnulated to the stimulation electrode. The pulse generator is controlled with an external magnet, and the patients are able to turn it on and off. In Paper VII the stimulation was initiated 15 minutes before exercise tests #4 and #5, and maintained during exercise and recovery. The last 15 seconds of every minute, the system was turned off to avoid interference with the ECG.

**Statistics**

For comparisons between groups in Papers 1 and 2 Fischers exact test was used for dichotomous variables and Wilcoxon´s rank sum test for continuous or ordinal variables. In Paper I the Sign test was used to test for differences of proportions prior to and after angiography. For number of days in hospital Wilcoxon´s signed rank test was used. A stratum adjusted Kruskal-Wallis test, using the Cochran-Mantel-Haenszel

statistic was used for comparison of quality of life scores when adjusting for differences for sex and age in Paper II. In Paper III Fisher´s permutation test was used to test for differences between groups. Data before and after provocation were compared using analysis of variance (ANOVA) in Paper IV.

In Study 1 in Paper V the correlation coefficient (Spearman rank order correlation) between the doses of drugs and the resulting flow was calculated separately in each subject. The resulting correlation coefficients for either drug were then compared between groups using the non-parametric Mann-Whitney U test. In Study 2 in Paper V Student's *t*-test for paired or unpaired data was used. Also in Paper VI Student's *t*-test was carried out to compare placebo versus estradiol treatment. In Paper VII Fisher´s non-parametric test for paired comparison (Bradley) with two-sided test was carried out.

# RESULTS

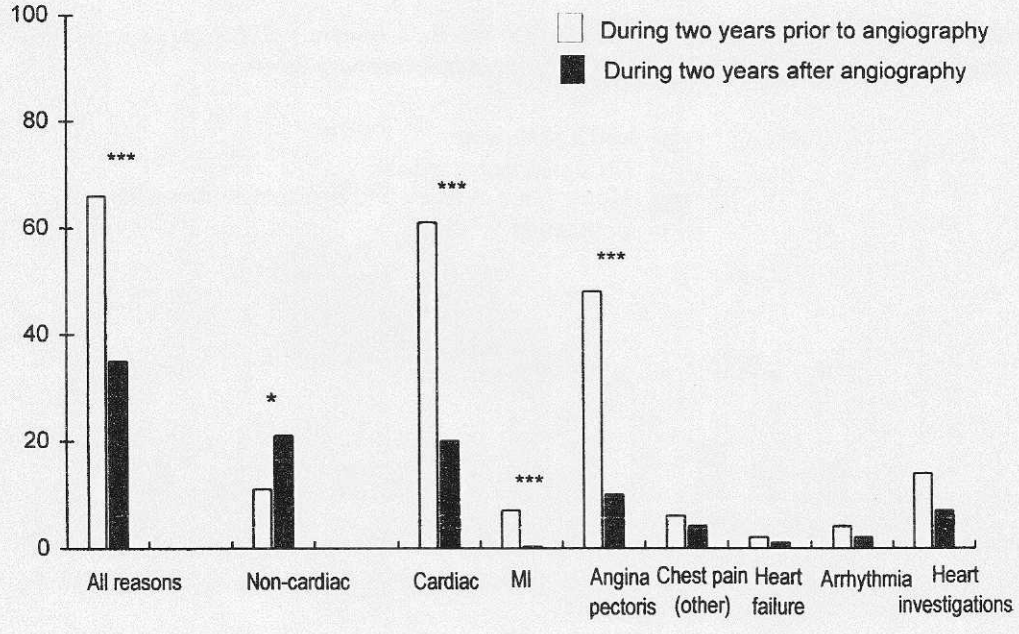
*Paper I*

Of 2639 patients performing coronary angiography, 163 (6%) were found to have normal (n=113) or near normal (n=50) coronary angiogram. They were compared to patients with significant coronary artery stenoses, younger and more likely to be female (50 vs 20%). Patients with coronary artery stenoses suffered more often from previous myocardial infarction, congestive heart failure, cerebrovascular disease and were more likely to be diabetic.

Sixtysix percent of the patients with normal or near normal coronary angiograms had been hospitalised during two years prior to the diagnostic angiography compared to 35% during two years after (Fig I:I).

The reduction of utilisation of medical resources was mainly due to curtailed hospitalisation for cardiac reasons, which was reduced from 6.6 days to 2.8 days in hospital ($p<0.001$).

**Figure I:I Percentage of patients with normal or near normal coronary angiogram requiring hospitalisation during two years prior to and two years after angiography.**

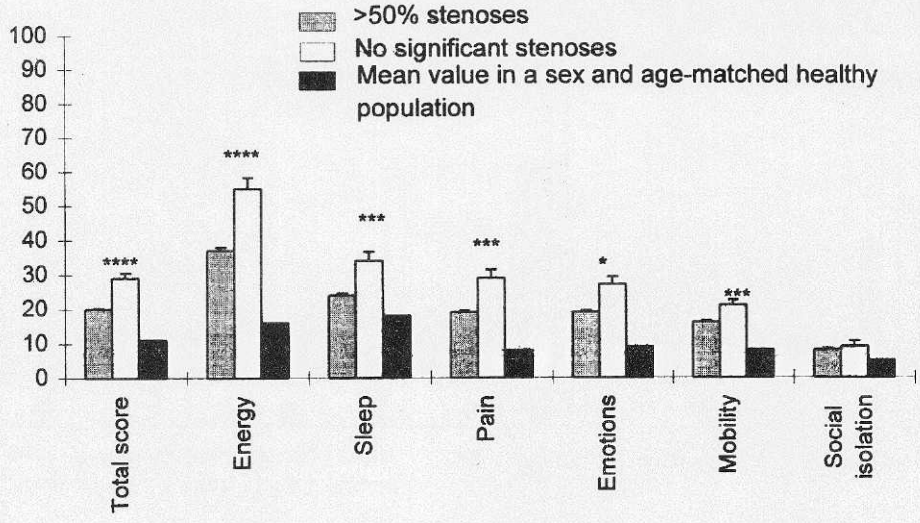


*Paper II*

Approx. 85-86% of the patients with normal or near normal coronary angiogram responded to the different questionnaires regarding self-estimated *Quality of Life* (QoL). The corresponding number in the group with significant coronary artery stenoses was 70-72%. Unexpectedly, patients with coronary artery stenoses reported superior quality of life even when adjusted for sex and age. This was apparent in both the Nottingham Health Profile (NHP) and the Psychological General Well Being Index (PGWB) Fig. II:I and Fig. II:II.

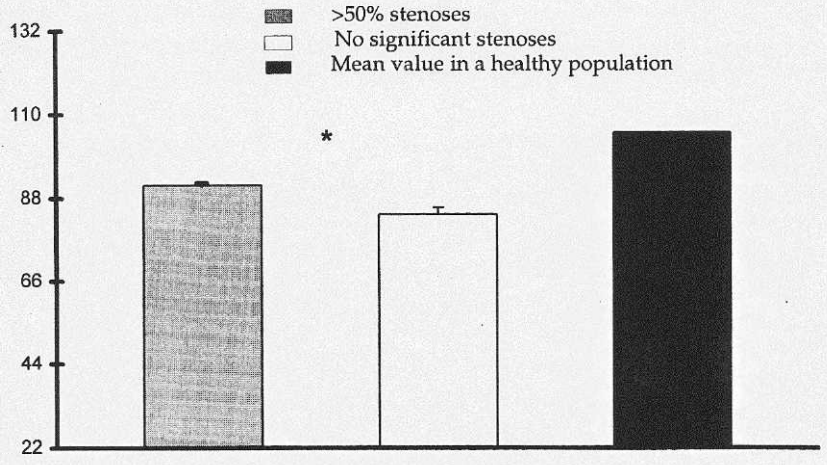
The lower QoL in patients without significant stenoses included the NHP subscales concerning energy ($p<0.0001$), pain ($p<0.001$), mobility ($p<0.001$) sleep ($p<0.001$) and emotions ($p<0.05$). Regarding PGWB, patients with normal or near normal coronary angiograms reported inferior QoL in subscales related to vitality ($p<0.0001$), anxiety ($p<0.05$) and well-being ($p<0.05$). There were however no significant difference in score of the more angina-specific questionnaire Physical Activity Score. With regards to patients without significant stenoses there were no major differences between patients with mild (<50%) stenoses and completely normal angiogram. There where also very similar scores when comparing patients with positive and negative exercise tests.

**Figure II:I Score on Nottingham Health Profile I (mean + SEM) in patients with coronary artery disease and normal or near normal coronary arteries.**




* = p<0.05, *** = p<0.001, **** = p<0.0001*

**Figure II:II Psychological General Well-Being Index. Total score (mean + SEM). A higher score indicates superior well-being.**




* = P<0.05

**Table II:I NHP I, PGWB and PAS. Comparison between patients with completely normal angiogram and mild stenoses, and comparison between patients with positive and negative exercise tests.**

| | Mild stenoses (n=50) | No stenoses (n=113) | p | Positive exercise test (n=78) | Negative exercise test (n=84) | p |
|---|---|---|---|---|---|---|
| NHP I | 28 | 30 | NS | 28 | 31 | NS |
| PGWB | 86 | 83 | NS | 85 | 83 | NS |
| PAS | 4.2 | 4.1 | NS | 4.2 | 4.1 | NS |

NHP I = Total Score in Nottingham Health Profile 1
PGWB = Total score in Psychological General Well-Being Index
PAS = Physical Activity Score.

*Paper III*

During atrial pacing an insignificantly higher heart rate was achieved in control patients compared to patients with syndrome X. Patients with syndrome X reported more severe chest pain and they also demonstrated more pronounced ST-segment depression. The baseline coronary flow was higher in patients with syndrome X, but the relative flow increase on maximal atrial pacing was higher among controls, which was in contradiction to flow increase after adenosine administration which was equally high in the two groups (Fig. III:I).

Ergonovine administration was not accompanied by differences in coronary flow changes in any of the two groups. ECG changes and pain reaction was similar in patients with syndrome X and in controls.

Myocardial lactate extraction was lower during pacing in patients with syndrome X but the difference was not significant. Lactate production was achieved in four patients with syndrome X during atrial pacing but in none in the control group. On the other hand lactate production was demonstrated in two control patients after adenosine administration and in one patient with syndrome X. There were no significant differences in arterio venous oxygen difference after pacing, adenosine, or ergonovine provocation when comparing control patients and subjects with syndrome X. There was a lower $MVO^2$ during rest in patients with syndrome X, but in spite of a reduced flow reserve, and a higher incidence of lactate production during atrial pacing, there was no differences in $MVO^2$ during atrial pacing

**Figure III:I Coronary flow increase after pacing and intracoronary adenosine**

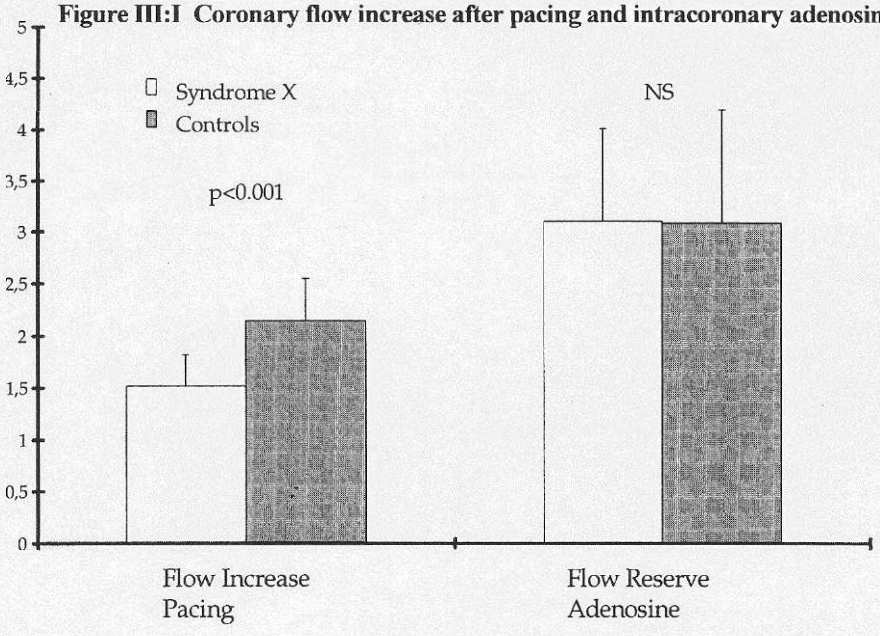


**Table III:I Myocardial Lactate Extraction**

| Patient No. | Rest | Pacing | Rest | Adenosine | Rest | Ergonovine |
|---|---|---|---|---|---|---|
| 1 | 16,5 | -7,1 | 16,9 | 1,6 | . | . |
| 2 | 8,3 | 11,3 | 12,9 | 8,5 | . | . |
| 3 | 27,4 | 24,6 | 12,7 | -4,3 | . | 16,1 |
| 4 | 21,2 | 7,7 | . | . | . | . |
| 5 | 1,6 | -7,9 | 3 | 4,7 | 6,1 | 4,9 |
| 6 | 2,1 | 7,8 | . | . | 5 | 9,1 |
| 7 | 53,2 | 5,8 | 8,5 | 32,8 | 10,2 | 36,7 |
| 8 | . | . | . | . | . | . |
| 9 | 20 | -4,3 | . | . | . | . |
| 10 | 2,3 | 4,5 | 10,9 | 8 | 12,5 | 25,5 |
| 11 | 41,5 | -3,1 | 13,2 | 15 | . | 13,9 |
| 12 | . | . | . | . | . | . |
| 13 | 25 | . | . | . | . | 10 |
| **mean ± SD** | **20±17** | **4±10** | **11±4 **** | **9±12** | **8±4** | **17±11** |
| 14 | . | . | . | . | . | . |
| 15 | 31,5 | 7,9 | . | . | 17,1 | 20 |
| 16 | 14,5 | 25,9 | 20,8 | 3,4 | 9,3 | 35,8 |
| 17 | 32,7 | 10,9 | 23,9 | -4,3 | 17 | 34,7 |
| 18 | 8,2 | 11,3 | . | . | . | . |
| 19 | 28,8 | 35,5 | 34,4 | 18,1 | 22,8 | 28,6 |
| 20 | . | 11,1 | . | . | . | . |
| 21 | 4,7 | 10,7 | 16,7 | -5,6 | 5,4 | 24,2 |
| 22 | 0 | 0 | . | . | -7,5 | -5,8 |
| **mean ± SD** | **17±14** | **14±11** | **24±8 **** | **3±11** | **11±11** | **23±15** |

** = p<0,01, syndrome X versus controls
Lactate extraction = myocardial lactate extraction ratio. "-" indicates lactate production

*Paper IV*

After adenosine provocation both patients with syndrome X and patients with atypical chest pain and normal exercise tests demonstrated a higher heart rate compared to healthy controls. There was also differences in diastolic blood pressure after provocation which was also lower in healthy subjects. During adenosine provocation four patients with syndrome X demonstrated significant ST-depression compared to only one subject with typical chest pain and none of the healthy controls.

Three of ten healthy controls, on the other hand, developed AV-block II or III which forced the infusion to be haltered (which resulted in a normal conduction in 10, 13 and 25 seconds respectively).

During adenosine infusion, 14 of 20 patients demonstrated signs of significant aggravation of left ventricular dysfunction compared to only 4 of 17 patients with atypical chest pain and none of the healthy controls (Table IV:I)

**Table IV:I Echocardiographic changes during adenosine provocation**

| | Healthy controls | Atypical chest pain | Syndrome X |
|---|---|---|---|
| LVSI rest | 1,0 | 1,0 | 1,2 |
| LVSI adenosine | 1,0 | 1,2 | 1,7* |
| No of patients with regional dysfunction (score increase >3) | 0 | 4 | 14* |

LVSI = Left ventricular score index
(An increase from baseline with 0,3 or more is considered positive)
* = $p<0.05$

*Paper V*

This paper is divided into two sub-studies. In the first study was it demonstrated that intra-arterial administration of acetylcholine resulted in a dose-dependent increase in forearm blood flow in both patients with syndrome X and in controls. The mean basal flow was 2,3 ± 0,3 and 3,0 ± 0,3 ml/min per 100 ml tissue, respectively. The flow response to the maximal dose of acetylcholine was in syndrome X patients 5,5 ± 0,8 and in controls 7,3 ± 1,8 ml/min per 100 ml tissue, NS (Fig. V:I). The forearm blood flow response to the endothelium-*in*dependent vasodilator sodium nitroprusside was 11,2 ± 1,7 in syndrome X patients and 11,2 ± 1,9 ml/min per 100 ml tissue in controls (NS), (Fig V:II).

In the second study transdermal estrogen (estradiol 17-β, 100μg/24 tim) was shown to result in a significant increase in plasma estradiol levels in both patients with syndrome X and in healthy controls (from 25 ± 22 to 106 ± 49 and from 33 ± 14 to 101 ± 55 pg/ml respectively).

During treatment with placebo the mean resting brachial artery diameter was 3,34 ± 0,11 mm in patients with syndrome X and 3,29 ± 0,11 mm in controls.

The post-occlusive diameter increased to 3,52 ± 0,14 mm in patients and 3,51 ± 0,12 mm in controls (a flow mediated dilatation of 5,4 and 6,7 % respectively).

Following 24 hours of transdermal estradiol treatment, the mean brachial artery diameter was, in patients with syndrome X, 3,23 ± 0,12 and in controls 3,21 ± 0,06. The mean post-occlusive diameter increased to 3,54 ± 0,15 and 3,58 ± 0,08, corresponding to flow-mediated dilatation of 9,6 and 11,5% respectively. Estradiol treatment augmented the flow-mediated dilatation of the brachial artery to 9.6 vs 5.4% compared to placebo in patients with syndrome X (p=0.026). Also in the placebo group the flow mediated dilatation was larger after estradiol treatment (11.5 vs. 6.7%) but this difference did not reach significance (p=0.054), (Fig V:III). However, the brachial artery diameter response to estrogen was not significantly larger for the syndrome X patients than that seen in the control group.

Plasma nitrate levels were 53 ± 5 and 50 ± 6 μmol/l during placebo in patients and controls respectively, and were not significantly affected by estradiol treatment (55 ± 7 and 53 ± 5 μmol/l).

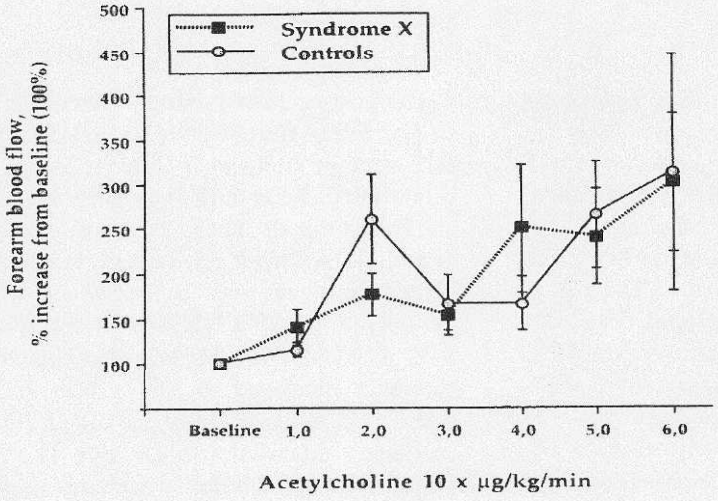



**Figure V:I** Increase in forearm blood flow induced by i.a. infusion of acetylcholine (10-60 µg/kg/min) in patients with syndrome X (closed boxes) and controls (open circles). Values given as mean ± SEM and expressed as a percentage of the baseline flow. There was no difference in response to acetylcholine in syndrome X and controls

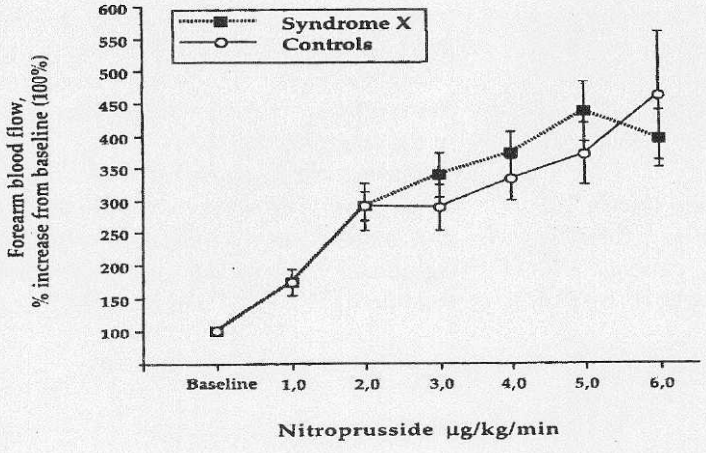



**Figure V:II** Increase in forearm blood flow induced by i.a. infusion of sodium nitroprusside (1-6 µg/kg/min) in patients with syndrome X (closed boxes) and controls (open circles). Values given as mean ± SEM and expressed as a percentage of the baseline flow. There was no difference in response to sodium nitroprusside in syndome X and controls.

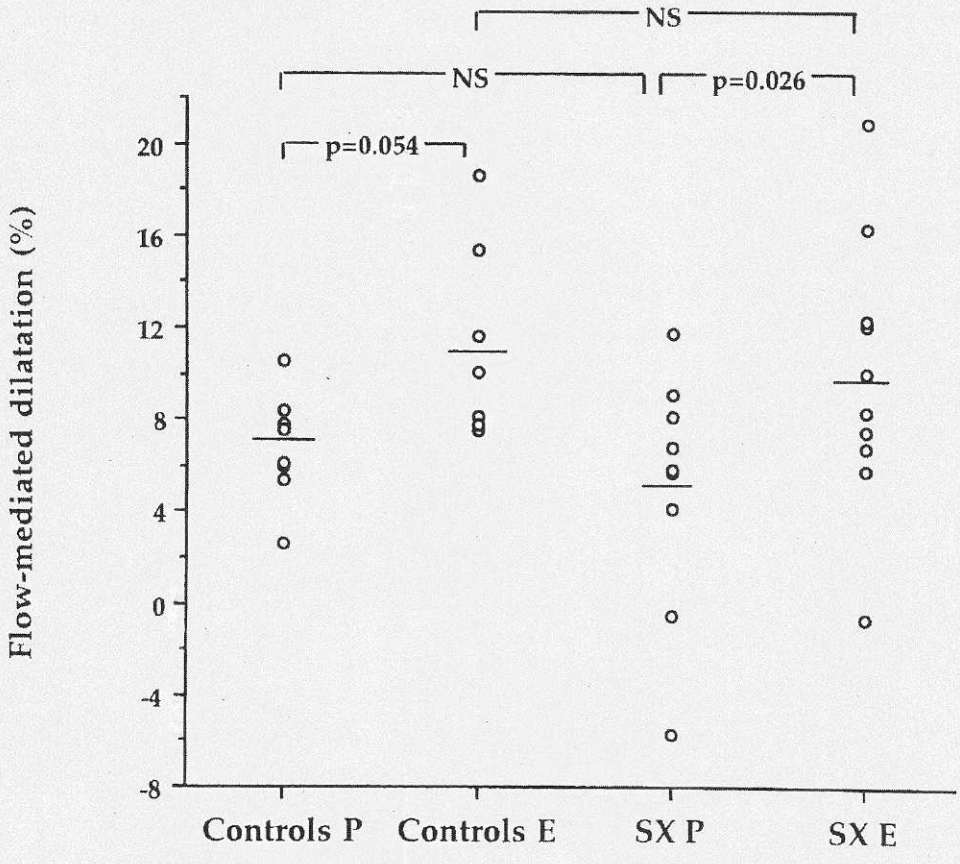



**Figure V:III** Flow-mediated dilatation of the brachial artery following release of proximal artery occlusion, expressed as a percentage of the basal (pre-occlusive) vessel diameter. "Control P" and "Control E" indicate flow-mediated dilatation in healthy subjects after treatment with placebo and estrogen, respectively and "SX P" and "SX E" indicate flow-mediated dilatation in patients with syndrome X following similar treatments. Open circles represent individual observations and horizontal lines indicate mean values. Levels of significance given in the upper part of the figure.

*Paper VI*

Healthy post-menopausal women did not respond with chest pain or ST-segment depression at exercise, and there was no difference in working capacity after estradiol treatment compared to placebo.

Of fifteen postmenopausal women with syndrome X, twelve had their typical chest pain during exercise on placebo treatment compared to eight on estradiol treatment.

Time to 1mm ST-segment depression increased from 187 ± 43 to 257 ± 38 seconds ($p<0.05$), time to angina increased from 233 ± 21 to 323 ± 29 seconds ($p<0.01$), total exercise time increased from 323 ± 22 to 364 ± 27 seconds ($p<0.05$), and recovery time from angina was reduced from 202 ± 43 to 150 ± 46 seconds ($p<0.05$) when comparing estradiol treatment with placebo. The difference in ST-segment depression on maximal workload was not significant. However, a higher workload was achieved on estradiol treatment (Fig VI:I) and when analysing ST-segment changes on comparable workload, a significant reduced ST-segment depression was noticed during estradiol treatment compared with placebo (Fig VI:II).

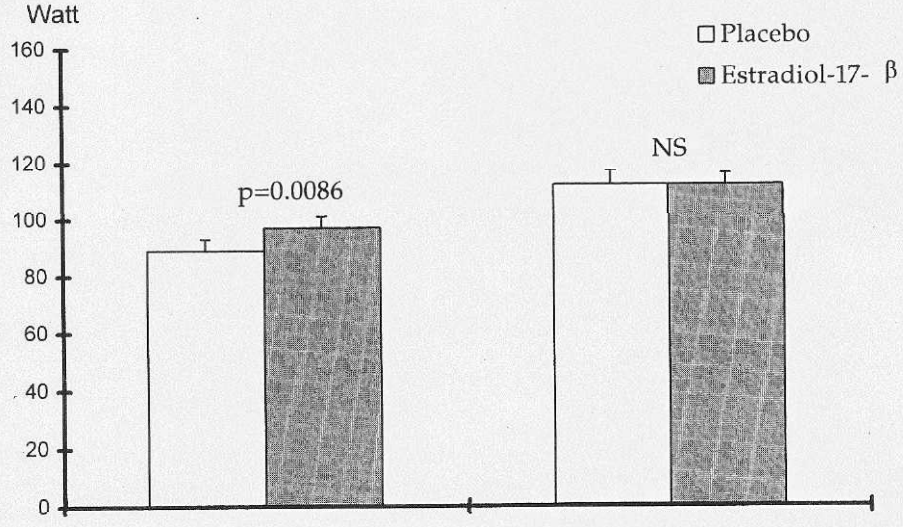



**Figure VI:I** Workload during placebo and estradiol treatment in patients with syndrome X (left bars) and controls (right bars).

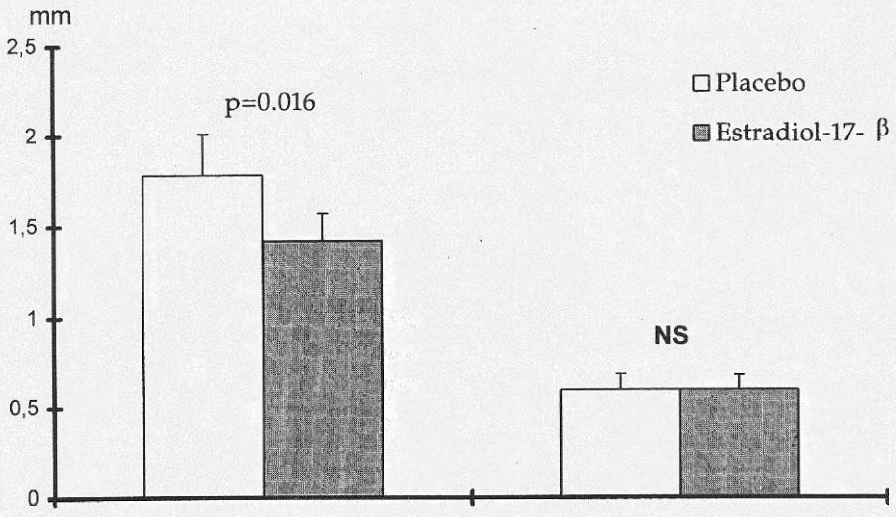



**Figure VI:II** ST-segments depression at comparable workload during placebo and estrogen treatment in syndrome X patients (left bars) and controls (right bars).

*Paper VII*

Spinal cord stimulation in patients with syndrome X was followed by an increased time to 1mm ST-segment depression, increased time to angina, and an increased maximal workload achieved (Table VII:I).

ST-segment depression on maximal workload was not significantly reduced, but since a higher workload was achieved on spinal cord stimulation, the ST-segment depression on comparable workload was analysed and was demonstrated to be reduced. Time to recovery from angina was not significantly reduced and the same was found for recovery time for ST-segment depression.

The rate pressure product on comparable workload was found to be increased from 24795 ± 5022 to 28038 ± 6124 mmHG x bpm. This increase in the rate pressure product at comparable workload during treatment may imply an increase in coronary blood flow.

**Table VII:I** Results on exercise test during control situation and during spinal cord stimulation.

| | Control | SCS | p |
|---|---|---|---|
| Rate pressure product (mmHgxbmp) | 24795±5022 | 28038±6124 | <0.01 |
| Maximal work load (watt) | 96±21 | 108±22 | <0.001 |
| ST-segment depression (mm) | 1.5±0.9 | 1.3±0.8 | |
| ST-segment depression comparable | 1.5±0.9 | 1.0±0.6 | <0.01 |
| TTA (min) | 2.66±1.9 | 5.39±2.16 | <0.01 |
| TT-ST (min) | 2.44±1.61 | 3.50±1.93 | <0.01 |
| ART (min) | 4.36±2.98 | 2.79±4.26 | |

# DISCUSSION

## Hospitalisation

Need for hospitalisation describes the morbidity since it could be an expression of severe symptoms. The present study (Paper I) was nevertheless *not* designed to investigate if there really was an improvement in symptoms during two years of follow up which had previously been reported (Bemiller *et al* 1973, Isner *et al* 1981). Except for improvement of symptoms, a reduction of hospitalisation could be a reassurance for both patients and physicians that no serious coronary artery disease is present (Ockene *et al* 1980), and consequently observation after an attack of chest pain is regarded as unnecessary.

The decrease of hospitalisation in Paper I is totally owing to reduction of hospitalisation due to cardiac reasons. The increase in use of medical resources due to non-cardiac reasons after the diagnostic angiogram can be explained by the fact that a diagnosis other than angina pectoris was given when patients were hospitalised due to chest pain (e.g. oesophagus or musculoskeletal disorders). It is however important to stress that it is possible that "other diseases" were less common during two years prior the diagnostic angiogram compared to two years after, since the patients were older during the latter period, and it is reasonable to suggest that utilisation of medical resources increases with age. With this in mind the result of a reduction in total need for hospitalisation is even more beneficial.

## Quality of life

Self-estimation of quality of life represents the patients view of the disease's impact on his social life.

All instruments, *NHP I, NHP II, PGWB* and *PAS*, used in the present study (Paper II) are well documented and validated (Hunt *et al* 1980, 1981, Dupuy 1984, Wiklund *et al* 1988). The advantage of using a specific questionnaire (PAS) is its ability to detect effects of an intervention in selected patient populations (Wiklund *et al* 1990) NHP and PGWB constitute general questionnaires. They are often used in epidemiological studies, and since reference scores are available (stratified for sex and age) it is possible to compare data from different population studies. NHP is most useful among patients with chronic diseases and severe symptoms. PGWB is a more generalised instrument which can be used to detect the impact of any symptoms on the quality of life and could even be used in a healthy populations.

Our data showed unexpectedly that patients with normal or near normal coronary angiograms demonstrated inferior quality of life compared with patients with coronary stenoses. They also seem to have at least as severe pain as patients with coronary stenoses. Since it is well known that young patients and females perceive their health as poorer all data were adjusted for sex and age (since patients with normal or near normal coronary angiograms were

younger and included more females), but the differences remained significant in most parameters. Earlier studies have indicated that there is a high psychiatric morbidity among patients with chest pain without significant stenoses (Bass *et al* 1984). A self-administered questionnaire designed to address quality of life is probably not a sensitive enough tool to detect psychiatric morbidity, but it is interesting to notice that we found small but significant differences in the subscale anxiety between the groups.

Finally, it is important to emphasise that the questionnaires were administered to the patients prior to the angiogram and the responses should not be biased by the angiographic result, and not by the physicians attitude towards a patient without significant stenosis

### Mild stenoses versus completely normal angiogram

As previously mentioned, earlier reports have been successful in demonstrating a more beneficial prognosis in patients with chest pain and normal angiograms compared to patients with mild stenoses. It has furthermore been suggested that there are different mechanisms behind the chest pain in the two groups. However, in Paper I the background data and outcome in terms of hospitalisation was very similar in the two groups, with more hospitalisations due to myocardial infarction among patients with mild stenoses as the only significant difference. Paper II also demonstrated very homogenous results between the two groups regarding quality of life.

### Exercise test

ST-segment changes is a rather blunt method for identification of ischemia, especially in females. In the CASS registry (matched for age and prevalence and severity of coronary artery disease, CAD), the specificity for predicting CAD was 64% in women compared to 73% in men (Weiner *et al.* 1979). Simultaneously there were no difference in sensitivity; 78 vs 76%. Regarding patients with normal coronary angio-grams, the specificity and sensitivity to predict a reduced coronary vasodilator reserve with exercise test (analysing ST-segment depression) was 45 and 86% respectively (Camici *et al.* 1992).

Still, it is the most common examination that distinguishes between ischemia and non ischemia. Almost every patient referred for coronary angiogram has performed the test and we therefore also used it in the definition of syndrome X.

In Paper I there were no differences between patients with normal or near normal angiograms whether the exercise tests were positive or not, and the same was found in Paper II. This is in contradiction to Paper III and IV where the exercise tests were able to show a distinction between patients with positive or negative exercise tests.

It is very important to emphasise that in the two latter papers both the patient group (syndrome X) and the control group were carefully selected. Patients were recruited not only with a positive exercise test but also with typical exertion angina pectoris showing a good response to sublingual nitro and also if an ischemic heart condition was clinically suspected to be the origin behind chest pain. The control groups in

these papers were, on the other hand, subjects with negative exercise tests and atypical chest pain and its origin was not believed to be an ischemic heart condition. The two groups in these papers subsequently constituted two extremes of a continuous spectrum among patients with normal or near normal coronary angiogram where both false positive and false negative exercise tests are probably quite common.

There are however suggestions that patients with positive and negative exercise tests constitute two different aspects of microvascular angina. In a study by Frøbert and co-workers regarding heart rate variability in patients with chest pain and micro-vascular angina it was found that only patients with a normal exercise tests showed an abnormal heart rate variability indicating a defect in the sympathetic balance as a possible pathogenic factor in this subgroup of patients (Frøbert *et al* 1995), whereas patients with a positive exercise test exhibited no signs of autonomic dysfunction.

**Rapid atrial pacing**

Atrial pacing has long since been used for induction of "experimental angina" (Sowton *et al.* 1967). The increase in myocardial demand during increment of heart rate produces vasodilatation of the microcirculation by autoregulatory control (Berne *et al.* 1979). The increase of shear activates mechanoreceptors on the endothelium, stimulating pro-duction and release of nitric oxide (NO) leading to appropriate vasodilatation to meet the demand (Pohl *et al* 1986). Thus, the flow increase during rapid atrial pacing is partially dependent on endothelial function.

One should keep in mind that there are drawbacks with atrial pacing as a method for induction of myocardial ischemia. First; ischemia is not induced solely by an increase of heart rate in most patients. Second; the method is not physiological in increasing heart rate since atrial pacing is accompanied by an increased PQ-time, whereas in exercise induced tachycardia the PQ-time is decreased.

Furthermore there are aspects other than vascular factors that influence the flow and vascular reserve during pacing. The contractility is probably not identical during pacing and physiological tachycardia, and if for example, an increased left ventricular end diastolic pressure is present, this can increase the extravascular component of the flow resistance. The reduction in flow increase in patients with syndrome X after atrial pacing in Paper III is nevertheless interesting but one should keep in mind that this is mainly due to an increased basal flow in these patients compared to the controls, and the absolute maximal flow was similar in the two groups - a speculation is that the reduction in flow response in syndrome X patients is due to a defect vaso-dilatation capacity for example based on endothelial dysfunction.

**Adenosine provocation**

In our opinion Adenosine may be the ideal substance for inducing maximal coronary flow. It could be given as a bolus and have a very short half-life (5-10 sec). Adenosine reacts with at least four different receptors (A1, A2a, A2b and A3), and is not dependent on a

normal endothelial function for vasodilatation (Fredholm *et al* 1994). In previous reports dipyridamole has been the most widely used drug for induction of maximal vasodilatation. It acts by inhibiting cellular uptake of adenosine, resulting in an increased concentration of adenosine which induces vasodilatation. When adenosine has been compared to dipyridamole, the former has been the most efficient (Holdright *et al.* 1993, Finnochiaro *et al.* 1994). The vasodilator response after dipyridamole has been shown to be variable (Rossen *et al.* 1989), whereas recruitment of coronary reserve by adenosine infusion appears to be consistent and near maximal (Wilson *et al.* 1990). The effect of left ventricular dysfunction in Paper IV is more difficult to explain. Obviously there is a difference between a bolus dose of adenosine and continuous administration (Lagerqvist *et al.* 1992). A bolus dose induces maximal dilatation and the chest pain is often not related to ischemia, whereas a steady-state infusion has the ability to induce ischemia, most probably by a coronary steal mechanism (Edlund *et al.* 1991).

**Adenosine vs. atrial pacing**

In Paper III we demonstrated that patients with syndrome X have a reduced coronary vasodilator capacity after rapid atrial pacing whereas it is normal after adenosine provocation. The difference in mechanism of action between the two methods can account for the discrepancy. Since the epicardial arteries had neither fixed stenosis, nor inducible spasm and offered little resistance to flow, the abnormality appears to originate from the microcirculation. The finding of reduced flow reserve on pacing but not after adenosine, indicates that patients with syndrome X have a selective impairment of flow increase to some stimuli whereas flow increase is normal to others. This study was not designed to investigate endothelium function (in which case acetylcholine administration would have been preferable), but a speculation is that patients with syndrome X have an impaired production, impaired release or excessive degradation of endothelium derived relaxing factor.

**Coronary sinus flow measurements**

We employed the sinus coronary thermodilution technique for flow measurement, since it was the only method available when the study was initiated. This method has some clear limitations. Phasic coronary flow or rapid changes in flow cannot be assessed correctly when this technique is applied. Furthermore, perfusion to the right ventricle cannot be assessed due to the anatomy of the venous drainage, and flow in specific transmural layers cannot be estimated (Marcus *et al.* 1987). The position of the catheter is very crucial and it should be checked repeatedly during the procedure. If the catheter is too close to the ostium of the coronary sinus, there are possibilities that efflux from the atrium could affect the measurements. Furthermore, blood can be "diluted" by tributary draining areas of the heart, other than the left ventricle. Bagger showed that blood flow can change from 23 to 68 ml/min per centimetre catheter movement, and in addition forced inspiration can increase the sinus flow two-fold (Bagger 1984).

### Concept of coronary flow reserve

Coronary reserve is expressed as the ratio between maximal flow which could be induced, and basal flow. Using the ratio rather than absolute flow makes it more efficient to compare different methods of measurement and different groups of patients. With this technique, however, it is impossible to determine if a reduction in flow reserve is due to reduced maximal flow or increased basal flow. Furthermore statement of flow reserve necessitates that the flow induced really is maximal (L´Ábbate *et al.* 1992). If we consider the flow obtained as maximal, however, it still does not take into account a second dimension of coronary reserve, the perfusion pressure (Klocke 1987). Flow measurements and then flow reserve calculations may be different depending on the corresponding coronary pressure. It should be emphasised that at each pressure level, the auto-regulatory curve moved up and down depending on beat-to-beat changes in myocardial metabolic demand, and the slope of the relation between coronary flow and coronary pressure is also affected by the heart rate (reduction in diastolic perfusion time).

The abundance of evidence of a reduced flow reserve is listed in Table 1, page 15, but a crucial question is if flow reserve impediment is always equivalent with myocardial ischemia. Theoretically this does not need to be the case if there is a decrease in cardiac performance to match a lower energy supply, such as in hibernating myocardium (Fedele *et al.* 1988). There is no evidence however that a reduced basal flow or a reduction in cardiac work and performance is present in syndrome X.

An almost opposite situation could also explain a condition with reduced vascular reserve in absence of ischemia. In the presence of an increased cellular "efficiency" with a large extraction of $O^2$ and substrates, this could be achieved but there are no experimental data supporting this theory. Investigations have, on the other hand, shown that patients with syndrome X have a normal $pO^2$ level during pacing (Crake *et al.* 1988), and a low intracellular energy charge (Waldenström *et al.* 1992). The most important opposing factor comes from the fact that in most works, including Paper III in this thesis, the reduced vascular reserve is accompanied by metabolic changes such as low lactate extraction or lactate production indicative of ischemia.

### Myocardial metabolism

The normal oxygenated and perfused myocardium extracts lactate. A low extraction rate (<10%) indicates ischemia. Severe ischemia leads to anaerobic glycolysis in the tissue resulting in a release of lactate into the venous effluent (e.g coronary sinus), while at the same time the systemic arterial lactate concentration remains stable, a higher content will be found in the vein - lactate production - which is the only certain indication of ischemia. Absence of lactate production does not rule out ischemia, since lactate produced by ischemic tissues may be diluted in the coronary sinus effluent by drainage from non-ischemic areas (Gertz *et al.* 1980), or ischemia may be present in an

area not drained to the distal part of the coronary sinus or great cardiac vein were blood was collected (Hood 1968). Nevertheless myocardial lactate production has been demonstrated in syndrome X.

This is in accordance with the findings in Paper III, where we could demonstrate lactate production in 4 of 13 patients with syndrome X.

**Forearm endothelial function**

Endothelial dysfunction has been demonstrated to be involved in several form of vascular disease, for example in hypercholesterolemia it has been shown to be a universal vascular phenomenon (Creager *et al* 1990). Egashira and coworkers have very convincingly demonstrated that patients with syndrome X have an endothelial dysfunction, contributing to the reduced vasodilator capacity (Egashira *et al* 1993). This study was however designed to investigate the coronary circulation only and did not address the question of a generalised disorder in the endothelial lining. The classical work by Sax and Cannon (Sax *et al* 1987) has earlier been shown to demonstrate that patients with microvascular angina have a blunted flow response and increased vascular resistance in the forearm after arterial occlusion. This reactive hyperaemia in the resistance vessel is however not mainly dependent on a normal endothelial function and the mechanism underlying this abnormal flow response was not obvious.

In our studies we could not demonstrate an abnormal endothelial dependent flow response in the resistance vessels after acetylcholine provocation, a method that has been extensively used and is very well validated. The use of acetylcholine provocation originates from the pioneer works of Furchgott and with this method an endothelial dysfunction has been revealed in patients with coronary heart disease, hypertension and hypercholesterolemia (Ludmer *et al* 1986, Panza *et al* 1990, Creager *et al* 1990). Flow-mediated diameter increase in the conduit vessel (brachial artery) that can be detected by ultrasound, has been extensively used during last years and is today an established method. For example, patients at risk for atherosclerosis and passive smokers have been demonstrated to display a reduced endothelial function (Celermajer *et al* 1992, 1996)

Our findings in Paper V very strongly disfavour the theory of a generalised endothelial disorder in syndrome X. It is important to address the fact that only three of altogether 21 patients with syndrome X who we investigated were smokers and none had hypertension or hypercholesterolemia - factors that could all have influenced the result.

**Effect of estradiol**

The classical action of steroid hormone is the gene activation pathway. Estrogen receptors have been demonstrated in different cell types and recently even in vascular tissue (Venkov *et al* 1995), but there is no evidence of their presence in coronary arteries (Collins *et al* 1996). There are other modes of action for estrogen's effect on vascular reactivity, including endothelium dependent flow increase and blockade of the cell membrane voltage-dependent calcium channels (Jiang *et al* 1992).

Our findings of a beneficial effect for exercise capacity in Paper VI can probably be explained by a reduction of ischemia due to a vasodilatation induced by estrogen. Since there were no significant difference compared to placebo in heart rate and blood pressure (rate pressure product) on peak exercise, peripheral mechanisms cannot explain the benefit and we speculate that a direct coronary vasodilator effect is more likely. Estrogen also showed to improve endothelium dependent forearm flow in Paper V, but there were no significant difference compared to placebo in this study, which does not support the fact that estrogen deficiency is a general feature in syndrome X. The discrepancy between the findings in Papers V and VI (performed mainly on the same subjects) indicates that the beneficial effect seen on exercise capacity and ischemia is not mediated via an endothelium dependent mode of action, unless the disease is localized to the coronary arteries only. Another explanation is that estrogen generally acts different on different vascular beds, and this field is open for debate and future research. It is also important to address the fact that the beneficial effect of estrogen has been demonstrated in short term studies only. There are suggestions that estrogens beneficial effect on endothelium-dependent flow will be reduced during long-term treatment. There are also concerns about the use of a combination of progesterone and estrogen since there are data supporting that progesterone substantially reduces the beneficial effects of estrogen.

**Effect of spinal cord stimulation.**

To our knowledge Paper VII is the first report of a beneficial effect with spinal cord stimulation in syndrome X. Several studies have demonstrated that the anti-anginal effect of spinal cord stimulation (SCS) is related to an anti-ischemic effect (Mannheimer *et al* 1988, Sanderson *et al* 1992). It has been demonstrated that during experimentally induced angina SCS can reverse lactate production into lactate extraction and reduce myocardial oxygen consumption in patients with coronary artery stenoses (Mannheimer *et al* 1993).

In the present study an increase in rate pressure product (RPP) was observed during treatment with SCS. This may imply an increase in coronary blood flow since RPP has been demonstrated to correlate well with myocardial oxygen consumption (Baller *et al* 1980, 1981). Studies are ongoing to clarify if the mechanism of action of SCS differs between patients with syndrome X and patients with coronary artery stenoses.

A limitation with the present study is that it is impossible to do a blind control/treatment study either for the investigator or the patient. This may produce an placebo effect, and for example the increase in working capacity that was found is in the same magnitude that has been reported for placebo. Our clinical experience with SCS in patients with syndrome X is though very positive and all patients voiced satisfied with this treatment.

# GENERAL CONCLUSIONS

**1.** Of 29362 patients performing coronary angiography due to chest pain, 63 (6%) were found to lack significant stenoses. Of these 113 demonstrated completely normal angiograms and 50 had mild (<50%) stenoses. Half of the patients without significant stenoses showed a positive exercise test.

**2.** Patients with normal or near normal coronary angiograms were younger and included more women (50% vs. 20%) than patients with coronary artery stenoses. They suffered less often from diabetes and had less often a previous cerebrovascular disease or myocardial infarction. During two years prior to the angiogram 66% of the patients with normal or near normal coronary artery stenoses had been hospitalised, compared to 35% during two years after the diagnostic procedure. This reduction in need for use of medical resources indicates that a negative coronary angiogram is of great value for the patient and the physician.

**3.** Patients with normal or near normal coronary angiograms show an inferior quality of life (measured with self-administered questionnaires) compared to patients with coronary artery stenoses. This included in *Nottingham Health Profile* subscales concerning pain, energy, mobility, sleep and emotions, and in *Psychological General Well-Being Index* subscales related to vitality, anxiety and well-being. This is an important observation for the future care of these patients.

**4.** Selected patients with syndrome X showed a normal maximal coronary flow reserve compared with controls when provoked with adenosine intracoronary. The flow increase after atrial pacing (which is partially endothelium-dependent) was lower among patients with syndrome X (1.5 vs. 2.2). Spasm was not induced in any subject by provocation with ergonovine.

**5.** Myocardial lactate extraction during rapid atrial pacing was insignificantly lower among patients with syndrome X compared with controls, but lactate production (the only definite proof for ischemia) was achieved in four patients with syndrome X and in none of the controls.

**6.** Adenosine infusion with simultaneous echocardiographic examination seems to be a valuable diagnostic tool in patients with chest pain and normal coronary angiogram. Among 20 patients with syndrome X, 14 subjects showed signs of regional left ventricular dysfunction during provocation, compared to only 4 of 17 subjects with atypical chest pain and a negative exercise test. The reaction with left ventricular dysfunction could imply that ischemia is induced by adenosine infusion in this group of patients.

**7.** Endothelium-dependent (acetylcholine infusion) and endothelium-independent (nitroprusside infusion) forearm resistance vessel response did not differ between patients with syndrome X and healthy controls.
Endothelium dependent conduit vessel responses was also unaffected in patients with syndrome X.
Endothelial dysfunction does not seem to be a universal phenomenon in syndrome X.

**8.** Transdermal estradiol improved the endothelium-dependent flow in the brachial artery to the same extent in patients with syndrome X and in controls. On the other hand transdermal estrogen showed a beneficial response to syndrome X patients on exercise capacity, angina pectoris and ST-segment changes during bicycle exercise tests compared with placebo.
Estrogen does seem to have a beneficial effect on myocardial ischemia in postmenopausal women with syndrome X and may in the future be a useful therapeutic agent in selected patients.

**9.** Spinal Cord Stimulation seem to be of benefit to patients with syndrome X. Exercise tolerance improved (from 96 to 108 watts) and the magnitude of ST-segment depression decreased on comparable workload. Furthermore time to angina and time to appearance of significant ST-segment depression increased. These effects are probably associated with a reduction of myocardial ischemia.

# ACKNOWLEDGEMENTS

Assoc. Professor Håkan Emanuelsson, my tutor, Head of Division of Cardiology

Professor Åke Hjalmarsson, Department of Heart and Lung Diseases

Maureen Anwyn Jehler, secretary, Division of Cardiology

Assoc. Professor Finn Waagstein, Division of Cardiology

Assoc. Professor Johan Herlitz, Division of Cardiology

Thomas Karlsson, statistician, Division of Cardiology

Professor Ed Varnauskas, Professor Emeritus, Division of Cardiology

Co-authors:
Lars Erik Augustinsson, M.D. PhD., Tore Eliasson, M.D. PhD., Maria Haglid, Msc, Peter Hårdhammar, M.D., Dalia Jablonskiene, M.D., Vuk Kujacic, M.D., Gunilla Lagerberg, R.N., Carl Lamm, M.D., Clas Mannheimer, M.D. PhD., Ian Milsom, M.D. PhD., Wanja Sandén, R.N., Helén Sjöland, M.D. PhD., Björn Wall, M.D., Professor Åke Wennmalm, Professor Ingela Wiklund.

Lisbeth Winberg, Laboratory technician

Margareta Sjölin, R.N.

Peter Währborg, M.D., PhD.

The Staff of the PTCA Unit

Personnel at the Division of Thoracic Radiology

Colleagues and Friends at the Division of Cardiology

*and last but not the least - my family*

# REFERENCES


Alfonso S, O´Brien GS. Enhancement of coronary vasodilator active adenosine triphosphate by dipyridamole. Circulation Res 1967;20:403.-8.

Amsterdam E, Hughes J, deMaria A, Zelis R, Mason D. Indirect assessment of myocardial oxygen consumption in the evaluation of mechanisms and therapy in angina pectoris. Am J Cardiol 1974;33:737-43.

Arbogast R, Bourassa MG: Myocardial function during atrial pacing in patients with angina pectoris and normal coronary arteriograms. Comparison with patients having significant coronary artery disease. Am J Cardiol 1973;32:257-63.

Bagger JP. Coronary sinus blood flow determination by the thermodilution technique: influence of catheter position and respiration. Cardiovasc Research 1984;19:27-31.

Baller D, Schenk H, Strauer B, Hellige G. Comparison of myocardial oxygen indices in man. Clin Cardiol 1980;3:116.

Baller D, Bretschneider H, Hellige G. A critical look at currently used indirect indices of myocardrial oxygen consumption. Basic Res Cardiol 1981;76:163-81.

Barret-Connor E, Bush T. Estrogen and coronay heart disease in women. JAMA 1991;265:1861-7.

Bass C, Wade C, Hand D, Jackson G. Patients with angina and normal or near normal coronary arteries: clinical and psychosocial state 12 months after angiography. BMJ 1983;287:1505-8.

Bass C, Wade C, Gardner WN, *et al.* Unexplained breathlessness and psychiatric morbidity in patients with normal and abnormal coronary arteries. Lancet 1983;ii:605-9.

Bass C, Wade C. Chest pain with normal coronary arteries: a comparative study of psychiatric and social morbidity. Psychol Med 1984; 14:51-61.

Becker LC. Conditions for vasodilator-induced coronary steal in experimental myocardial ischemia. Circulation 1978;57:1103-10.

Bemiller C, Pepine C, Rogers A. Long-term observations in patients with angina and normal coronary angiograms. Circulation 1973;47;36-43.

Bergen BC, Abramowitz R, Park CH *et al.*Abnormal thallium-201 scans in patients with chest pain and angiographically normal coronary arteries. Am J Cardiol 1983;52:365-71.

Berger H, Sands M, Davies R, *et al.* Exercise left ventricular performance in patients with chest pain, ischemic appearing exercise electrocardiograms and angiographically normal coronary arteries. Ann Intern Med 1981;94:186-91.

Bergstrand R, Vedin A, Wilhelmson C, Wilhelmsen L. Bias due to non-participation and heterogenous sub-groups in population surveys. J Chron Dis 1983;36:725-8.

Berne RM, Rubico R. Coronary circulation. In: Berne RM, Sperelakis N, Geiger SE editors: Handbook of Physiology. The cardiovascular system. Wiliams and Wilkins, Baltimore 1979, p873.

Berne RM. The role of adenosine in the regulation of coronary blood flow. Circulation Res 1980;47:807-13.

Bertrand M, LaBlanche J, Tilmant P, *et al.* Frequency of provoked coronary arterial spasm in 1089 consucutive patients undergoing coronary arteriography. Circulation 1982;65:1299-1306.

Biaggoni I, Olafsson B, Robertsson RM *et al.* Cardiovascular and respiratory effects of adenosine in conscious man. Circulation Res 1987;67:779-86.

Borer JS, Bacharach SL, Green MV *et al.* Real-time radionuclide cineangiography in the non-invasive evaluation of global and reginal left ventricular function at rest and during exercise in patients with coronary artery disease. N Engl J Med 1977;296:839-44.

Borg G. A category scale with ratio properties for intermodal and interindividual comparisons. *In:* Geissler H-G, Pezold P, ed. Psychophysical judgement and the progress of perception. Berlin:VEB Deutscher verlag der wissenschaften 1982:25-34.

Bortone AS, Hess OM, Eberli FR *et al.*Abnormal coronary vasomotion during exercise in patients with normal coronary arteries and reduced coronary flow reserve. Circulation 1989;79:516-27.

Boudoulas H, Cobb T, Leighton R, Wilt S. Myocardial lactate production in patients with angina-like chest pain and angiographically normal coronary arteries and left ventricle. Am J Cardiol 1974;34:501-5.

Bradley JW. Distribution -free statistical tests. London:Prentice-Hall 1968:68-86.

Bredt DS, Hwang HW, Glatt CE, *et al.* Cloned and expressed nitric oxide synthase structurally resembles cytochrome p-450 reductase. Nature 1991;351:714-8.

Bruschke A, Proudfit W, Sones M. Clinical course of patints with normal and slighty or moderately abnormal coronary arteriograms. a follow-up study on 500 patients. Circulation 1973;47:936-45

Bugiardini R, Pozzati A, Ottani F, Morgagni GL, Puddu P. Vasotonic angina:a spectrtum of ischemic syndromes involving functional abnormalities of the epicardial and microvascular coronary circulation. J Am Coll Cardiol 1993;22:417-25.

Bush TL, Barret-Connor E, Cowan LD *et al.* Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid research clinics program follow-up study. Circulation 1987;75:1102-9.

Bush TL, Fried LP, Barret-Connor E. Cholesterol, lipoproteins, and coronary heart disease in women. Clin Chem 1988;34:1360-70.

Busse R, Mülsch A, Fleming I, Hecker M. Mechanisms of nitric oxide release from the vascular endothelium. Circulation 1993;87:(suppl V) V18-25.

Bøtker H, Møller N, Ovesen P, Mengel A, Schmitz O, Ørskov H, Bagger JP. Insulin resistance in microvascular angina (syndrome X). Lancet 1993;342:136-40.

Camici PG, Lorenzoni R, Gistri R. Regional coronary vasodilator reserve in syndrome X. Circulation1990;828(suppl III):479.

Camici PG, Marraccini P, Lorenzoni R, *et al.* Coronary hemodynamics and myocardial metabolism in patients with syndrome X:response to pacing stress. J Am Coll Cardiol 1991;17:1461-70.

Camici PG, Gistri R, Lorenzoni R, *et al.* Coronary reserve and exercise ECG in patients with chest pain and normal coronary angiograms. Circulation 1992;86:179-86.

Cannon RO, Bonow RO, Bacharach SL, *et al.* Left ventricular dysfunction in patients with angina pectoris, normal epicardial coronary arteries and abnormal vasodilator reserve. Circulation 1985;71:218-26.

Cannon RO, Rosing DR, Maron BJ, *et al.* Myocardial ischemia in patients with hypertrophic cardiomyopathy: contribution of inadequate vasodilator reserve and elevated left ventricular filling pressures. Circulation 1985;71:234-43.

Cannon RO, Leon ML, Watson RM, Rosing DR, Epstein SE. Chest pain and "normal" coronary artery- role of small coroanry arteries. Am J Cardiol 1985;55:50B-60B.

Cannon RO, Watson RM, Rosing DR, Epstein SE. Efficacy of calcium channel blocker therapy for angina pectoris resulting from small-vessel coronary artery disease and abnormal vasodilator reserve Am J Cardiol 1985;56:242-6.

Cannon Ro, Cunnion RE, Parillo JE *et al.* Dynamic limitation of coronary vasodilator reserve in patients with dilated cardiomyopathy and chest pain. J Am Coll Cardiol 1987;10:1190-1200.

Cannon RO, Schenke WH, Leon MB, *et al.*. Limited coronary flow reserve after dipyridamole in patients with ergonovine-induced coronary vasoconstriction. Circulation 1987;75:163-74.

Cannon RO, Epstein SE. " Microvascular angina " as a cause of chest pain with angiographically normal coronary arteries. am J Cardiol 1988;61:1338-43.

Cannon RO, Quyyumi A, Schenke W, *et al.* Abnormal cardiac sensitivity in patients with chest pain and normal coronary arteries. J Am Coll Cardiol 1990;16:1359-66.

Cannon RO, Peden B, Berkebile C, *et al.* Airway hyperresponsiveness in patients with microvascular angina. Evidence for a diffuse disorder of smooth muscle responsiveness. Circulation 1990;82:2011-7.

Cannon R, Camici P, Epstein S. Pathophysiological dilemma of of syndrome X. Circulation 1992;85:883-92.

CASS Principal investigators and their associates. Coronary Artery Surgery Study (CASS); a randomized trial of coronary artery bypass surgery. Circulation 1983;68:939-50.

Celermajer DS, Sorensen KE, Gooch VM, *et al* . Non-invasive detection of endothelial dysfunction in children an adults at risk of atherosclerosis. Lancet 1992;340:1111-5.

Celermajer DS, Adams NR, Clarkson P, *et al.* Passive smoking and impaired endothelium-dependent arterial dilatation in healthy young adults. N Engl J Med 1996;334:150-4.

Chauan A, Petch M, Schofield P. Effect of oesophageal acid instillation on coronary blood flow. Lancet 1993;341:1309-10.

Chauan A, Foote J , Petch M, Schofield P. Hyperinsulinemia, coronary artery disease and syndrome X. J Am Coll Cardiol 1994;23:364-8.

Chauan A, Mullins P, Petch M, Schofield P. Is coronary flow reserve in response to papaverine really normal in syndrome X ?. Circulation 1994;89:1998-2004.

Chauan A, Mullins P, Thuraisingham SI, Taylor G, Petch M, Schofield P. Abnormal cardiac pain perception in syndrome X. J Am Coll Cardiol 1994;24:329-35.

Chilian WM, Marcus ML. Phasic blood flow velocity in intramural and epicardial coronary arteries. Circ Res 1982;50:775-81

Christlieb A, Krolewski A, Warram J, Soeldner J. Is insulin the link between hypertension and obesity? Hypertension 1985;7 (suppl.2):54-7.

Clarke JG, Kerwin R, Larkin S, *et al.* Coronary artery infusion of Neuropeptide Y in patients with angina pectoris. Lancet 1987;I:1057-59.

Cohen L, Elliot W, Klein M, Gorlin R. Coronary heart disease. Clinical, cinearteriographic and metabolic correlations. Am J Cardiol 1966;17:153

Collins P, Sheppard M, Beale CM, Dowsett N. The classical estrogen receptor is not found in human coronary arteries. J Am Coll Cardiol 1996;27:2(suppl A);272A.

Crake T, Canepa-Anson R, Shapiro L, Poole-Wilson P. Continous recording of coronary sinus oxygen saturation during rapid atrila pacing in patients with coronary disease or with Syndrome X. Br Heart J 1988;59:31-8.

Crea F, Pupita G, Galassi AR, El Tamimi H, Kaski JC, Davies G, Maeri A. Effect of teophylline on exercise-induced myocardial ischemia. Lancet 1989;I:683-6.

Crea F, Pupita G, Galassi AR *et al.*Role of adenosine in pathogenesis of anginal pain. Circulation 1990;81;164-72.

Creager MA, Cooke JP, Mendelsohn ME, *et al.* Impaired vasodilatation of forrearm resistance vessels in hypercholesterolemic humans. J Clin Invest 1990;86:228-34.

Curry RC, Pepine CJ, Sabom MB, *et al.* Effects of ergonovine in patients with and without coronary artery disease. Circulation 1977;56:803-9.

Dart AM, Alban H, Dalal JZ *et al.* "Angina" and normal coronary arteriograms: a follow up study. Eur Heart J 1980a;1:97-100.

Davies B. Psychiatric illness at general hospital clinics. Postgrad Med J 1964;40:15-8.

Dean JD, Jones CJH, Hutchinson SJ, Peters JR, Henderson AH. Hyperinsulinaemia and microvascular angina ("syndrome X"). Lancet 1991;337:456-7.

DeLandsherre C, Mannheimer C, Habets *et al.* Effect of spinal cord stimulation on regional myocardial perfusion assessed by positron emission tomography. Am J Cardiol 1992;69:1143-9.

DeMeester T, O´Sullivan G, Bermudez G, Midell A, Cimochowski G, O´Drobinak J. Esophageal function in patients with angina-type chest pain and normal coronary angiograms.Ann Surg 1982;196:488-98.

Downey JM. Myocardial contractile force as a function of coronary blood flow. Am J Physiol 1976;230:1-6.

Drury AL, Szent-Györgyi A. The physiological activity of adenosine compounds with special reference to their action upon the mammalian heart. J Physiol 1929;68:213-37.

Edlund A, Albertsson P, Caidahl K, Emanuelsson H, Wallentin I. Adenosine infusion to patients with ischaemic heart disesae may provoke left ventricular dysfunction detected by echocardiography. Clin Physiol 1991;11:477-88.

Egashira K, Inou T, Hirooka Y, Yamada A, Urabe Y, Takeshita A. Evidence of impaired endothelium-dependent coronary vasodilation in patients with angina pectoris and normal coronary angiograms. N Engl J Med 1993;328:1659-64.

Elias MF, Robbins MA, Blow FC, Rice AP, Edgecomb JL. A behavioral study of middle-aged chest pain patients:physical symptom reporting,anxiety and depression. Exp Aging Res 1982;8:45-51.

Ellstad MH, Savitz S, Bergdall D, *et al.* The false positive stress test. Am J Cardiol 1977;40:681-5.

Emdin M, Picano E, Lattanzi F, LÁbbate A. Improved exercise capacity with acute aminophylline administration in patients with syndrome X. J Am Coll Cardiol 1989;14:1450-3.

Endo T, Imaizumi T, Tagawa T, Shiramoto M, Ando S, Takeshita A. Role of nitric oxide in exercise-induced vasodilatation of the forearm. Circulation 1994;90:2886-90.

Epstein SE, Cannon RO, Talbot TL. Hemodynamic principles in the control of coronary blood flow. Am J Cardiol 1985;56:4E-10E.

Epstein SE, Cannon RO. Site of increased resitance to coronary flow in patients with angina pectoris and normal epicardial coronay arteries. J Am Coll Cardiol 1986;8:459-61.

Farhat M, Abi-Younes S, Ramwell P. Non-genomic effects of estrogen and the wessel wall. Biochemical Pharmacology 1995?

Favaro L, Caplin J, Fettiche J, Dymond D. Sex differences in exercise induced left ventricular dysfunction in patients with syndrome X. Br Heart J 1987;57:232-6.

Faxon DP, McCabe CH, Kreigel DE, *et al.* Therapeutic and economic value of a normal coronary angiogram Am J Med 1982;73:500-5.

Fedele F, Gewirtz H, Capone RJ, Sharaf B, Most AS. Metabolic response to prolonged reduction of myocardial blood flow distal to a svere coroary artery stenosis. Circulation 1988;78:729-35.

Feigenbaum H. Exercise echocardiography. J Am Soc Echo 1988;1:161-6.

Ferranini E, Bussigoli G, Giorco M. Insulin resistance in essential hypertension. N Engl J Med 1987;317:350-7.

Finocchiaro ML, Lupi A, Buffon A, *et al.* Coronary flow reponses to adenosine and dipyridamole are diffrent in Syndrome X and hypertensive patients: Pathogenetic implications. Circulation 1994;90(suppl II):113

Fredholm BB, Abbrachio MP, Burnstock G, *et al.* Nomenclature and classification of purinoreceptors. Pharmacol Rev 1994;46(2):143-56.

Frøbert O, Mølgaard H, Bøtker HE, Bagger JP. Autonomic balance in patients with angina and anormal coronary angiogram. Eur Heart J 1995;16:1356-60.

Furchgott RF, Zawadski JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;288:373-6.

Galassi A, Kaski JC, Pupita G, Vejar M, Crea F, Maseri A. Lack of evidence for alpha-adrenergic receptor-mediated mechanisms in the genesis of ischemia in syndrome X. Am J Cardiol 1989;64:264-9

Galassi AR, Kaski JC, Crea F *et al.* Heart rate response during exercise testing and ambulatory ECG monitoring in patients with syndrome X. Am Heart J 1991;122:458-63.

Galassi A, Crea F, Araujo L, *et al.* Comparison of regional myocardial blood flow in syndrome X and one-vessel coronary artery disease. Am J Cardiol 1993;72:134-9.

Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC. Measurement of coronary sinus blood flow by continous thermodilution in man. Circulation 1971;44:181-95.

Geltman EH, Henes CG, Sennef MJ, Sobel BE, Bergman SR. Increased myocardial perfusion at rest and diminshed perfusion reserve in patients with angina and angiographically normal coronary arteries. J Am Coll Cardiol 1990;16:586-95

Gerhard M, Ganz P. How do we explain the clinical benefits of estrogen? from bedside to bench. Circulation 1995;92:5-8.

Gertz EW, Wisneski JA, Neese R, Houser A, Korte R, Bristow JD. Myocardial lactate extraction: multi-determined metabolic function. Circulation 1980;61:256-61.

Gilligan DM, Badar DM, Panza JA, Quyyumi AA, Cannon RO. Estradiol potentiation of endothelium-dependent vasodilatation is dependent on nitric oxide production. J Am Coll Cardiol 1994;23:378A (Abstract).

Gilligan DM, Quyyumi AA, Cannon RO. Effects of physiological levels of estrogen on coronary vasomotor function in postmenopausal women, Circulation 1994;89:2545-51.

Gilligan DM, Badar DM, Panza JA, Quyyumi AA, Cannon RO: Acute vascular effects of estrogen in postmenopausal women. Circulation 1994;90:786-91.

Gilligan DM, Badar DM, Panza JA, Quyyumi AA, Cannon RO. Effects of estrogen replacement therapy on peripheral vasomotor function in postmenopausal women. Am J Cardiol 1995;75:264-8.

Giscard V, Miller VM, Vanhoutte PM. Effect of 17-b-estradiol on endothelial responses in the rabbit. J Pharmacol Exp Ther 1988;244:19-22.

Glendy RE, Levine SA, White PD. Coronary disease in youth:comparison of 100 patients under 40 with 300 patients past 80. JAMA 1930;109:1775-8.

Graham TP, Covell JW, Sonnenblick EH, Ross J, Braunwald E. Control of myocardial oxygen consumption: relative influence of contractile state and tension development. J Clin Invest 1968;475:375-85.

Greenberg M, Grose R, Neuburger N, Silverman R, Strain J, Cohen M. Impaired coronary vasodilator responsiveness as a cause of lactate production during pacing-induced ischemia with normal coronary arteries and a reduced coronary flow reserve. J Am Coll Cardiol 1987;9:743-51.

Hagman M, Bjurö T, Wennerblom B, *et al.* Coronary angiography, bicycle exercise test, glucose tolerance, serum lipids and body composition in angina pectoris. *In* Hagman M; Angina Pectoris in middle-aged men, Dissertation, University of Göteborg 1987.

Hampton AG, Beckwith JR, WoodJE. The relationship between heart disease and gallbladder disease. Ann Intern Med 1959;50:1135-48.

Herrington DM, Braden GA, Williams JK, Morgan T. Endothelial dependent coronary vasomotor responsiveness in postmenopausal women with and without estrogen replacement therapy. Am J Cardiol 1994;73:951-2.

Heupler FA, Proudfit WL, Razavi M, Shirley EK, Greenstreet R, Sheldon WC. Ergonovine maleate provocative test for coronary artery spasm. Am J Cardiol 1978;41:631-40.

Holdright DR, Lindsay DC, Clarke D, Fox K, Poole-Wilson PA, Collins P. Coronary flow reserve in patients with chest pain and normal coronary arteries. Br Heart J 1993;70:513-9.

Holmberg S, Serzyzko W, Varnauskas E. Coronary circulation during heavy exercise in control subjects and patients with coronary heart disease. Acta Med Scand 1971;190:465-80.

Hong MK, Romm PA, Reagan K, Green CE, Rackley CE. Effects of estrogen replacement therapy on serum lipid values and angiographically defined coronary artery disease in postmenopausal women. Am J Cardiol 1992;69:176-8.

Hood WB. Regional venous drainage of the human heart. Br Heart J 1968;30:105-9.

Hosobuchi Y. Electrical stimulation of the cervical spinal cord increases cerebral blood flow in humans. Appl Neurophysiol 1985;48:372-6.

Hunt SM, McKenna SP, McEwen J, Backett EM, Williams J, Papp E. A quantitative approach to percieved health status: a validation study. J Epidemiol Community Health 1981;35:297-300.

Hutchinson SJ, Poole-Wilson PA, Henderson AH. Angina with normal coronary arteries:a review. Quart J Med 1988;72:677-88.

Ihlen H, Simonsen S, Vatne K. Reproducibilty of ischemic lactate metabolism during atrial pacing in man. Cardiology 1983;70:177-83.

Ishihara T, Seki I, Yamada Y, *et al.* Coronary circulation, myocardial metabolism and cardiac cathecolamine flux in patients with syndrome X. J Cardiol 1990;20:267-74.

Isner J, Salem D, Banas J, Levine H. Long-term clinical course of patients with normal coronary arteriography: follow-up study of 121 patients with normal or near normal coronary arteriograms. Am Heart J 1981;102:645-53.

Jackson G, Atkinson L, Armstrong P, *et al.*Angina with normal coronary angiograms, value of of coronary sinus lactate estimation in diagnosis and treatment. Br Heart J 1978;40:976-8.

Jaffe MD. Effect of oestrogen on post-exercise electrocardiogram. Br Heart J 1977;38:1299-303.

Jiang C, Sarrel PM, Lindsay DC, Poole-Wilson PA, Collins JP. Endothelium- independent relaxation of rabbit coronary artery by 17-ß-oestradiol *in vitro.* Br J Pharamcol 1991;104:1033-7.

Jiang C, Poole-Wilson PA, Sarrel PM, Mochizuki S, Collins P, MacLeod KT. Effects of 17-ß-oestradiol on contraction Ca2+ current and intracellular free Ca2+ in guniea-pig isolated cardiac myocytes. Br J Pharmacol 1992;106:739-45.

Joannides R, Haefeli WE, Linder L, *et al.* Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo. Circulation 1995;91:1314-9.

Juelsgaard P, Ronnow Sand NP. Somatic and social prognosis of patients with angina pectoris and normal coronary arteriography: a follow-up study.
Int J Cardiol 1993;39:49-57.

Kaski JC, Tousoulis D, Galassi A, *et al* :Epicardial coronary tone and reactivity in patients with normal coronary arteriograms and reduced flow reserve (syndrome X). J Am Coll Cardiol 1991;18:50-4.

Kaski JC, McKenna W. Angina pectoris with normla coronary arteriograms-Overwiev. Coronary Artery Dis 1992;3:547-54.

Kaski JC, Tousoulis D, Rosano GMC, Clarke J, Davies GJ. Role of neuropeptide Y in pathogenesis of syndrome X. Eur Heart J 1992;13(suppl):102

Kaski JC. Syndrome X: A heterogenous syndrome. Historical background, clinical presentation, electrocradiographic features, and rational patient management. An overwiew. *In* Kaski JC ed. Angina pectoris with normal coronary arteries: Syndrome X. Norwell, Mass: Kluwer Academic Publishers.. 1994. p7.

Kaski JC, Rosano GMC, Collins P, Nihoyannopoulos P, Maseri A, Poole-Wilson P. Cardiac syndrome X: clinical caracteristics and left ventricular function. Long term follow-up study. J Am Coll Cardiol 1995;25:807-14.

Kemp HG, Elliot WC, Gorlin R: The anginal syndrome with normal coronary arteriography. Trans Assoc Am Physicians 1967;80:59-70.

Kemp HG: Left ventricular function in patients with the anginal syndrome and normal coronary arteriograms. Am J Cardiol 1973;32:375-6.

Kemp H, Vokonas P, Cohn P, Gorlin R. The anginal syndrome associated with normal coronary arteriograms. Report of a six-year experience. Am J Med 1973;54:735-42.

Kemp HG, Kronmal RA, Vliestra RE, Frye RL: Seven year survival of patients with normal and near normal coronary arteriograms; a CASS registry study. J Am Coll Cardiol 1986;7:479-83.

Kitamura K, Jorgensen C, Gobel F, Taylor H, Wang Y. Hemodynamic correlates of myocardial oxygen consumption during upright exercise. J Appl Physiol 1972;32:516-22.

Kjartansson J, Lundberg T. Effect of electrical nerve stimulation on healing of ischemic skin flaps. ScandJ Plast Reconstructive Hand Surg 1990;24:129-34.

Klocke F. Measurements of coronary flow reserve; defining pathophysiology versus making decision about patient care. Circulation 1987; 76: 1183-9.

Klocke FJ. Measurements of coronary blood flow and degree of stenosis: current clinical implications and continuing uncertainties. J Am Coll Cardiol 1983;1:31-41.

Knopp RH. The effects of postmenopausal estrogen therapy of the incidence of atherosclerotic vascular disease. Obstet Gynecol 1988;72:235-305.

Kujacic V, Albertsson P, Emanuelsson H, Eliasson T, Mannheimer C, Augustinsson L-E. Effects of spinal cord stimulation on left ventricular function in patients with severe angina pectoris. J Am Coll Cardiol 1992;19:241A (Abstract)

Kukoveitz WR, Holzmann S, Schmidt K. Cellular mechanisms of action of therapeutic nitric oxide donors. Eur Heart J 1991;12:(suppl E) 16-24

Kübler W, Opherk K. Angina pectoris with normal coronary arteries. Acta Med Scand (Suppl) 1984;694:55-7.

Kübler W, Hautman M. Syndrome X- an early form of Cardiomyopathy ? Coronary Artery Disease 1992;3:570-3.

LÁbbate A, Camici P, Reisenhofer B. Abnormal coronary flow reserve in syndrome X: a critical review of the concept of vasodilator reserve and its relation to ischemia. Coronary Artery Disease 1992;3:579-85.

Lagerqvist B, Sylvén C, Beermann B, Helmius G, Waldenström A. Intracoronary adenosine causes angina pectoris like pain- an inquiry into the nature of visceral pain. Cardiovasc Res 1990;24:609-13.

Lagerqvist B, Bylund H, Götell P, Mannting F, Sandhagen B, Waldenström A.. Coronary artery vasoregulation and left ventricular function in patients with angina pectoris-like pain and normal coronary angiograms. J Int Med 1991;230:55-65.

Lagerqvist B, Sylvén C, Waldenström A. Lower treshold for adenosine-induced chest-pain in patients with angina and normal coronary angiograms. Br Heart J 1992;68:282-5.

Lagerqvist B, Sylvén C, Theodorsen E, Kaijser L, Waldenström A.. Adenosine-induced chest pain- a comparison between intracoronary bolus injection and steady-state infusion. Cardiovasc Res 1992;26:810-4.

Landsberg L. Diet, obesity and hypertension: a hypothesis involving insulin, the sympathetic nervous system, and adaptive thermogenesis. Q J Med 1986;236:1081-90.

Lantinga LJ, Sprafkin RP, McCroskey JH, Baker MT, Warner RA, Hill NE. One-year psychosocial follow-up of chest-pain and angiographically normal coronary arteries. Am J Cardiol 1988;62:209-13

Larkin SW, Clarke JG, Keogh BE, *et al.* Intracoronary endothelin induces myocardial ischemia by small vessel constriction in the dog. Am J Cardiol 1989;64:956-8.

Legrand V, Hodgson J, Bates E, *et al.* Abnormal coronary flow reserve and abnormal radionuclide exercise test results in patients with normal coronary angiograms. J Am Coll Cardiol 1985;6:1245-53.

Lichtlen P, Bargheer K, Wenzlaf P. Long-term prognosis of patients with anginalike chest pain and normal coronary angiographic findings. J Am Coll Cardiol 1995;25:1013-8.

Lieberman E, Knab S, Creager M. Nitric oxide mediates the vasodilator responses to flow in humans. Circulation 1994;90:I-138 (Abstract).

Likoff W, Segal BL, Kasparian H. Paradox of normal selective coronary arteriogram in patients considered to have unmistakable coronary heart disease. N Engl J Med 1967;276:1063-1066.

Ludmer PL, Selwyn AP, Shook TL, *et al.* Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. N Engl J Med 1986;315:1046-51.

Lundberg T, Kjartansson J, Samuelsson U. Effect of electrical nerve stimulation on healing of ischaemic skin flaps. Lancet 1988;24:712-4.

Magness RR, Rosenfeld CR. Local and systemic estradiol 17-beta; effects on uterine and systemic vasodilation. Am J Physiol 1989;256:E536-42.

Mannheimer C, Carlsson C-A, Emanuelsson H, Vedin A, Waagstein F, Wilhelmsson C. The effects of transcutaneous electric nerve stimulation in patients with severe angina pectoris. Circulation 1985;71:308-16.

Mannheimer C, Augustinsson L-E, Carlsson C-A, Manhem K, Wilhelmsson C. Epidural spinal electrical stimulation in severe angina pectoris. Br Heart J 1988;59:56-61.

Mannheimer C, Eliasson T, Andersson B, *et al.* Effects of spinal cord stimulations in angina pectoris induced by pacing and possible mechanisms of action. BMJ 1993;307:477-80.

Marcus ML, Wilson RF, White CW. Methods of measurement of myocardial blood flow: a critical review. Circulation 1987;76:245-53.

Marmor A, Zeira M, Zohar S. Effects of bilateral hystero-salpingo-oophorectomy on exercise-induced ST-segment abnormalities in young women. Am J Cardiol 1993;71:1118-9.

Marzilli M, Klassen G, Marraccini P, *et al.* Coronary effects of adenosine in conscious man. Eur Heart J 1989;10:78-81.

Maseri A, Crea F, Kaski JC, Crake T. Mechanisms of angina pectoris in syndrome X. J Am Coll Cardiol 1991;17:499-506.

Maseri A, Crea F, Kaski JC, Davies G. Mechanisms and significance of cardiac ischemic pain. Prog Cardiovasc Dis 1992;35:1-18.

Mates RE, Gupta RL, Bell AC, Klocke FJ. Fluid dynamics of coronary artery stenosis. Circ Res 1978;42:152-62.

McRaven DR, Mark AL, Abboud FM, Mayer HE. Responses of coronary vessels to adrenergic stimuli. J Clin Invest 1971;50:773-

Melzack R, Wall PD. Pain mechanism: a new theory. Science 1965;150:971-9.

Modan M, Halkin H, Almog S. Hyperinsulinemia: a link between hypertension, obesity amd glucose intolerance? J Clin Invest 1985;75:809-17.

Mogil JS, Sternberg WF, Kest B, Marerk P, Liebeskind JC. Sex differences in the antagonism of swimstress-induced analgesia: effects of gonadectomy and estrogen replacement. Pain 1993;53(1):17-25.

Montorsi P, Fabbiocchi F, Loaldi A, *et al.* Coronary adrenergic hypereactiviy in patients with syndrome X and abnormal electrocardiogram at rest. Am J Cardiol 1991;68:1698-1703.

Moretti RL, Abraham S: Stimultion of microsomal prostaglandin synthesis by a blood plasma constituent which augments autoregulation and maintenance of vascular tone in isolated rabbit hearts. Circ Res 1978;42:317-23.

Motz W, Vogt M, Rabenau O, Scheler S, Lückhoff A, Strauer BE. Evidence of endothelial dysfunction in coronary resistance vessels in patients with angina pectoris and normal coronary angiograms. Am J Cardiol 1991;68:996-1003.

Neely JR, Morgan HE. Relationship between carbohydrate and lipid meabolism and the energy balance of heart muscle. Ann Rev Physiol. 1974;36:413-59.

Neill W, Kremkau E, Oxendine J, Phelbs N. Criteria for detecting myocardial hypoxia from lactate and pyruvate data during atrial pacing in humans. J Lab Clin Med 1974;83:428.

Nihoyannopoulos P, Kaski JC, Crake T, Maseri A. Absence of myocardial dysfunction during stress in patients with syndrome X. J Am Coll Cardiol 1991;18:1463-70.

Nitenberg A, Foult J-M, Antony I, Blanchet F, Rahali M. Coronary flow and resistance reserve in patients with chronic aortic regurgitation, angina pectoris and normal coronary arteries. J Am Coll Cardiol 1988;11:478-86

Ockene I, Shay M, Alpert J, Weiner B, Dalen J. Unexplained chest pain in patients with normal coronary arteriograms. A follow-up study of functional status. N Engl J Med 1980;303:1249-52

Okada RD, Leppo JA, Boucher CA, Pohost GM. Myocardial kinetics of thallium-201 after dipyridamole infusion in normal canine myocardium and in myocardium distal to stenosis. J Clin Invest 1982;69:199-209.

Okin PM, Kligfield P, Kilner MR *et al.* Heart rate adjustment of ST-segment depression for reduction of false positive electrocardiographic responses to exercise in asymptomatic men screened for coronary artery disease. Am J Cardiol 1988;62:1043-7.

Olsson R, Bünger R: Metabolic control of coronary blood flow. Prog Cardiovasc Dis 1987;29:369-87

Opherk D, Zebe H, Weihe E, *et al.* Reduced coronary dilatory capacity and ultrastructural changes of the myocardium in patients with angina pectoris but normal coronary arteriograms. Circulation 1981;63:817-25

Opherk D, Schwarz F, Mall G, Manthey J, Baller D, Kübler W. Coronary dilator capacity in idiopathic dilated cardiomyopathy. Analysis of 16 patients. Am J Cardiol 1983;51:1657-62.

Opherk D, Mall G, Zebe H, *et al.* Reduction of coronary reserve: a mechanism for angina pectoris in patients with arterial hypertension and normal coronary arteries. Circulation 1984;69:1-7.

Opherk D, Schuler G, Wetterauer K, Manthey J, Schwarz F, Kübler W. Four-year follow-up study in patients with angina pectoris and normal coronary arteriograms. Circulation 1989;80:1610-6.

Papanicolau M, Califf R, Hlatky M, *et al.* Prognostic implications of angiographically normal and insignificantly narrowed coronary arteries. Am J Cardiol 1986;58:1181-7.

Palmer RMJ, Ferrige AG, Moncada AS. Nitric oxide accounts for the biological activity of endothelium-derived relaxing factor. Nature 1987;327:524-6.

Palmer RMJ, Ashton DS, Moncada S. Vascular endothelial cells synthesize nitric oxide from L-arginin. Nature 1988;333:664-6.

Panza JA, Quyyumi AA, Brush JE, Epstein SE. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. N Engl J Med 1990;323:22-7.

Pasternac A, Noble J, Streulens Y, Elie R, Henschke C, Bourassa M. Pathophysiology of chest pain in patients with cardiomyopathies and normal coronary arteries. Circulation 1982;65:778-89.

Pasternak RC, Thibault GE, Savoia M, DeSanctis RW, Hutter AM: Chest pain with angiographically insignificant coronary arterial obstruction: Clinical presentation and long-term follow up. Am J Med 1980;68:813-17.

Pepine CJ, Mehta J, Webster WW, Nichols WW. *In vivo* validation of a thermodilution method to determine regional left ventricular blood flow in patients with coronary artery disease. Circulation 1978;58:795-802.

Phibbs B, Fleming T, Ewyg A, *et al.* Frequency of normal coronary arteriograms in three academic medical centers and one community hospital. Am J Cardiol 1988;62:472-4.

Picano E, Distante A, Masini M, *et al.* Dipyridamole-echocardiography test in effort angina pectoris. Am J Cardiol 1985;56:452-6.

Picano E, Lattanzi F, Masini M, Distante A, LÁbbate A. Usefulness of high-dose dipyridamole-echocardiography test for diagnosis of syndrome X. Am J Cardiol 1987;60:508-12.

Pohl U, Holtz J, Busse J, Bassenge E. Crucial role of the endothelium in the vasodilator response to increased flow *in vivo.* Hypertension 1986;8:27-44.

Poole-Wilson PA. Potassium and the heart. Clinics in Endocrinology & Metabolism 1984;13:249-68.

Poole-Wilson PA, Crake T. The enigma of syndrome X. Int J Microcirc 1989;8:423-32.

Potts SG, Bass CM. Psychosocial outcome and use of medical resources in patients with chest pain and normal or near-normal coronary arteries: a long-term follow-up study. Q J Med 1993;86:583-93.

Proudfit WL, Shirey EK, Sones FM. Selective cine coronary arteriography: Correlation with clinical findings in 1,000 patients. Circulation 1966;33:901-10.

Proudfit WL, Bruschke AVG, Sones FM. Clinical course of patients with normal or slightly or moderately abnormal coronary arteriograms: 10-year follow-up of 521 patients. Circulation 1980;62:712-7

Radice M, Giudici V, Marinelli G. Long-term follow-up in patients with positive exercise test and angiographically normal coronary arteries (syndrome X). Am J Cardiol 1995;75:620-21.

Reaven GM. Banting lecture 1988. Role of insulin-resitance in human disease. Diabetes 1988;37:1595-607.

Reis SE, Gloth ST, Blumenthal RS, *et al.* Ethinyl estradiol acutely attenuates abnormal coronary vasomotor responses to acetylcholine in postmenopausal women. Circulation 1994;89:52-60.

Remme WJ. Myocardial lactate metaboism-the gold standard when evaluating interventions in ischemia. Eur Heart J 1992;13 (suppl):362 (Abstract)

Richter JE, Castell DO. Esophageal disease as a cause of non-cardiac chest pain. Adv Intern Med 1988;33:311-36.

Romeo F, Gaspardone A, Ciavolella M, Gioffrè P, Reale A. Verapamil versus acebutolol for syndrome X. Am J Cardiol 1988;62:312-3.

Romeo F, Rosano GMC, Martuscelli E, Lombardo L, Valente A. Long-term follow up of patients initially diagnosed with syndrome X. Am J Cardiol 1993;71:669-73.

Rosano GMC, Lindsay D, Sarrel PM, Poole-Wilson PA. Beneficial effects of oestrogen replacement treatment in normalising skin blood flow in patients with syndrome X. Clin Sci 1990;8:9-10.

Rosano GMC, Lindsay D, Kaski JC, Sarrel P, Poole-Wilson P. Syndrome X in women: the importance of ovarian hormones J Am Coll Cardiol 1992;19:254A (Abstract)

Rosano GMC, Sarrel PM, Poole-Wilson PA, Collins P. Beneficial effects of estradiol on exercise-induced myocardial ischemia in women with coronary artery disease. Lancet 1993;342:133-6.

Rosano GMC, Kaski JC, Lindsay DC,Collins P, Sarrel PM, Poole-Wilson PA. Syndrome X in women is associated with estrogen deficiency. Eur Heart J 1995;16:610-4.

Rosselli M, Imthurn B, Keller PJ, Jackson EK, Dubey RK. Circulating nitric oxide (nitrate/nitrite) levels in postmenopausal women substituted with 17-ß-estradiol and norethisterone acetate: a two-year follow-up study. Hypertension 1995;25:848-53.

Rossen JD, Simonetti I, Marans ML, Winniford MD. Coronary dilation with standard dose dipyridamole and and dipyridamole combined with handgrip. Circulation 1989;79:556-72.

Sanderson JE. Epidural neurostimulators for pain relief in angina. Br Heart J 1990;63:141-3.

Sanderson JE, Brooksby P, Waterhouse D, Palmer RBG, Neubauer K. Epidural spinal electrical stimulation for severe angina: a study of its effects on symptoms, exercise tolerance and degree of ischaemia.Eur Heart J 1992;13:628-33.

Sarrel PM. Ovarian hormones and the circulation. Maturitas 1990;12:287-98.

Sarrel PM, Lindsay D, Rosano GMC, Poole-Wilson PA. Angina and normal coronary arteries in women: Gynecological findings. Am J Obstet Gynecol 1992;167:462-72.

Sax F, Cannon RO, Hanson C, Epstein S. Impaired forearm vasodilator reserve in patients with microvascular angina, Evidence of a generalized disorder of vascular function ? N Engl J Med 1987;317:1366-70.

Schrader J, Haddy FJ, Gerlach E. Release of adenosine, inosine and hypoxanthine from the isolated guinea pig heart during hypoxia, flow-autoregulation and reactive hyperemia. Pfluger Arch 1977;369:1-6.

Shapiro LM, Crake T, Poole-Wilson PA. Is altered cardiac sensation responsible for chest pain in patients with normal coronary arteries? clinical observation during cardiac catherization. BMJ 1988;296:170-1.

Schiller NB, Shah PM, Crawford M *et al.* Recommendations for qunatification of of the left ventricle by by two-dimensional echocardiography. J Am Soc Echo 1989;2:358-67.

Simonetti I, Rossen JD, Winniford MD, *et al.* Is coronary flow reserve actually reduced in Syndrome X ? Eur Heart J 1990;1:206 (Abstract).

Sketch MH, Mohiuddin SM, Lybch JD, Zencka AE, Runco V: Signicant sex differences in the correlation of electrocardiographic exercise testing and coronary arteriograms. Am J Cardiol 1975;36:169-73.

Sowton GE, Balcon R, Cross D, Frick MH. Measurement of the angina treshold using atrial pacing. A new technique for the study of angina pectoris. Cardiovasc Res 1967;1:301-7.

Stamler JS, Loh E, Roddy M-A, Currie KE, Creager MA. Nitric oxide regulates basal systemic and pulmonary vascular resistance in healthy humans. Circulation 1994;89:2035-40.

Stampfer MJ, Colditz GA, Willet WC. Postmenopausal estrogen therapy and cardiovascular disease. N Engl J Med 1991;325:756-62.

Sullivan JM, Vander Zwaag R, Lemp GF *et al.* Postmenopausal estrogen use and coronary atherosclerosis. Ann Intern Med 1988;108:358-63.

Sullivan JM, Vander Zwaag R, Hughes JP, *et al.* Estrogen replacement and coronary artery disease. Effect on survival in postmenopausal women. Arch Intern Med 1990;150:2557-62.

Swan J, Walton C, Godsland I, Crook D, Oliver M, Stevenson J. Insulin resistance syndrome as a feature of cardiological syndrome X in non-obese men. Br Heart J 1994;71:41-4.

Sylvén C, Beerman B, Jonzon B, Brandt R. Angina pectoris-like pain provoked by intravenous adenosine. Br Med J 1986;293:227-30.

Taddei S, Virdis A, Mattei P, *et al.* Aging an endothelial function in normotensive subjects and patients with essential hypertension. Circulation 1995;91:1981-7.

Thadani U, Lewis J, Mathew T, West R, Parker J. Reproducibility of clinical and hemodynamic parameters during pacing stress in patients with angina pectoris. Circulation 1979;60:1036-41.

Tousoulis D, Crake T, Lefroy D, Galassi A, Maseri A. Left ventricular hypercontractility and ST-segment depression in paients with Syndrome X. J Am Coll Cardiol 1993;22:1607-13.

Turiel M, Galassi A, Glazier J *et al.* Pain treshold and tolerance in women with syndrome X and women with stable angina. Am J Cardiol 1987;60:503-8.

Urschel HC, Razzuk MA, Hyland JW, *et al.* Thoracic outlet syndrome masquerading as coronary artery disease (pseudoangina). Ann Thoracic Surg 1973;16:239-48.

Vaitkevicius P, Wright KG, Fley JL. Effect of estrogen replacement therapy on the ST-segment response to postural and hyperventilation stimuli. Am J Cardiol 1989;64:1076-7

Venkov CD, Ramkin AB, Vaughan DE. Endothelial cells express estrogen receptor: Evidence for a full length mRNA. Circulation 1995;92:I-168(abstract).

Virtanen KS: Evidence of myocardial ischemia in patients with chest pain syndrome and normal coronary angiogram.. Acta Med Scand 1984;694 (suppl):58-68.

Vrints CJM, Bult H, Hitter E, Herman AG, Snoeck JP. Impaired endothelium-depenent cholinergic coronary vasodilation in patients with angina and normal coronary arteriograms. J Am Coll Cardiol 1991; 17:1461-70.

Waldenström A, Ronquist G, Lagerqvist B. Angina pectoris patients with normal coronay angiograms but abnormal thallium perfusion scan exhibit low myocardial and skeletal muscle energy charge. J Intern Med 1992;231:327-31.

Waxler E, Kimbiris D, Dreifus L. The fate of women with normal coronary arteriograms and chest pain resembling angina pectoris. Am J Cardiol 1971;28:25-32.

Webb SC, Poole-Wilson PA. Potassium exchange in the human heart during atrial pacing and myocardial ischemia. Br Heart J 1986;55:554-9.

Webb SC, Canepa-Anson R, Rickards AF, Poole-Wilson PA. Myocardial potassium loss after acute coronary occlusion in humans. J Am Coll Cardiol 1987;9:1230-4.

Weiner DA, Ryan TJ, McCabe CH, *et al.* Correlations among history of angina, ST-segment response and prevalence of coronary artery disease in the Coronary Artery Surgery Study (CASS). N Engl J Med 1979;301:230-5.

Weiner CP, Lizasoain I, Baylis SA, Knowles RG, Charles IG, Moncada S. Induction of calcium-dependent nitric oxide synthases by sex hormones. Proc Natl Acad Sci USA 1994;91:5212-6.

Wendelhag I, Gustafsson T, Suurküla M, Berglund G, Wikstrand J. Ultrasound measurement of wall thickness in the carotid artery: fundamental principles and description of a computerized system. Clin Physiol 1991;11:565-77.

Wenger N, Speroff L, Packard B. Cardiovascular health and disease in women. N Engl J Med 1993;329:247-56.

Wennmalm Å, Benthin G, Edlund A, Jungersten L, Kieler-Jensen N, Lundin S *et al.* Metabolism and excretion of nitric oxide in humans: an experimental and clinical study. Circ Res;1993:1121-7.

White L, Tursky B, Schwartz J. *In* Placebo.Guilford Press, London 1985.

Wiener L, Dwyer EM, Cox JW: Left ventricular hemodynamics in exercise-induced angian pectoris. Circulation 1968;38:240-9.

Wieshammer S, Delagardelle C, Sigel HA, *et al.* Haemodynamic response to exercise in patients with chest pain and normal coronary angiograms. Eur Heart J 1986;7:654-61.

Wiklund I, Dimenäs E, Wahl M. Factors of importance when evaluating quality of life in clinical trials. Controlled Clinical Trials 1990;11:169-179.

Williams JK, Adams MR, Klopfenstein HS. Estrogen modulates responses of atherosclerotic coronary arteries. Circulation 1990;81:1680-7.

Williams JK, Adams MR, Herrington DM, Clarkson TB. Short-term administration of oestrogen and vascular responses of atherosclerotic coronary arteries. J Am Coll Cardiol 1992;20:452-7.

Wilson A, Wiklund I, Lahti T, Wahl M. A summary index for the assessment of quality of life in angina pectoris. J Clin Epidemiol 1991;44:981-8.

Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxson DD. Effects of adenosine on human coronary circulation. Circulation 1990;82:1596-606.

Zoghbi WA. Use of adenosine echocardiography for diagnosis of coronary artery disease. Am Heart J 1991;122:285:92.

Zoghbi WA, Cheirif J, Kleiman NS *et al.* Diagnosis of ischemic heart disease with adenosine echocardiography. J Am Coll Cardiol 1991;18:1271-9.


GÖTEBORGS UNIVERSITET
GÖTEBORGS UNIVERSITETSBIBLIOTEK

Tryckt & Bunden
Vasastadens Bokbinderi AB
1996