New diseases

Syndrome X – angina and normal coronary angiography

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Summary

It is clear that angina pectoris with normal coronary arteries is a heterogeneous and ill-defined syndrome that encompasses different pathogenic entities. Differences in patient selection and in definition of 'syndrome X' has made comparison between different study groups rather difficult. Two decades of investigations have not revealed a specific cause of this syndrome. There is now a general belief that syndrome X probably encompasses several pathophysiological disease entities and the mechanisms involved in syndrome X remain to be fully elucidated.

Keywords: chest pain, coronary angiography, syndrome X

Syndrome X

Patients with chest pain and normal coronary angiograms who have typical angina and a positive exercise test

Syndrome X: clinical features

- average age in late 40s
- female preponderance
- typical angina pain may be present in < 50%
- not reproducibly related to exertion
- duration of chest pain is variable
- variable response to sublingual nitrates
- resting ST or T wave changes in about 50%
- one-third have a positive exercise test
- associated breathlessness in over 50%
- prevalence of risk factors similar to patients with coronary artery disease

Introduction

Many patients undergo coronary angiography each year for investigation of chest pain believed to be due to coronary artery disease. However 10% to 30% of such patients are found to have normal coronary arteries on angiography.^{1–6} The term syndrome X was first used by Kemp⁷ in his editorial comment accompanying an article by Arbogast and Bourassa,⁸ in which these authors compared the features of a group of patients with angina and angiographically normal coronary arteries (group X) with those of a group of patients with angina and coronary artery stenoses. Subsequently, the term has become a label for patients with normal coronary angiograms who present with typical exertional angina pectoris. The term syndrome X is now widely used, particularly in European centres, to define patients with symptoms of typical angina pectoris, positive exercise test (≥ 0.1 mV of ST segment depression) and normal coronary angiograms. The exclusion of extra-cardiac and known cardiac causes of chest pain with normal coronary arteries, such as left ventricular hypertrophy, systemic hypertension, valvular heart disease, and cardiomyopathy is usually required for the diagnosis of syndrome X. However, over the years, a lack of agreed hard diagnostic criteria has resulted in a confusing overall picture as studies of syndrome X have tended to use their own terms of reference, making comparisons between studies, even sometimes by the same laboratory, difficult.⁹

Clinical features and prognosis

Syndrome X is associated with a wide range of clinical characteristics which may reflect differences in aetiology and outcome. The average age is in the late 40s and there is usually a female preponderance. The chest pain is commonly left-sided, often related to exertion, with a gradual onset and radiation to the left arm or jaws. However, the pain is not reproducibly related to exertion in a large number of patients and its response to sublingual nitrates and duration are also typically variable.

It has been shown in many studies that patients with chest pain and normal coronary arteries have an excellent long-term life expectancy with a low incidence of myocardial infarction and death.^{2,4–6,10} However, the same studies also indicate that there is a considerable residual morbidity. Long-term follow-up studies of functional disability have shown that about 75% continue to see a physician, less than half are reassured that they do not have serious heart disease and about 75% continue to experience chest pain at follow-up.^{2,6,10,11} It has also been reported recently that patients with syndrome X who present with unstable angina have a significantly better functional prognosis than those presenting with symptoms of stable angina which may reflect differences in underlying pathophysiological mechanisms.¹¹

Possible causes of chest pain in patients with normal coronary angiograms

CARDIAC CAUSES

A number of aetiological mechanisms for ischaemia in the presence of normal coronary arteries has been proposed. However, most studies provide indirect evidence for these pathophysiological mechanisms.

Metabolic abnormalities

Myocardial lactate production, as a marker of myocardial ischaemia, has been demonstrated in 12–100% of syndrome X patients.¹² However, the decrease in myocardial lactate extraction depends in part on substrate availability and may be a normal response to pacing stress. The majority of published studies have shown actual lactate production during pacing or isoproterenol stress to be

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Syndrome X: pathogenic hypotheses

- metabolic abnormalities
- impairment of left ventricular function over time
- impaired coronary flow reserve
- abnormal pain perception
- increased tone of microvasculature
- endothelial dysfunction
- increased sympathetic tone
- potassium pump alteration
- oestrogen deficiency in post-menopausal women
- early coronary artery disease not detectable on angiography

uncommon in this patient population and often to be unassociated with the same haemodynamic responses as noted in patients with coronary artery disease.^{8,13-14}

Recently, insulin resistance has also been reported in patients with chest pain and normal coronary angiograms.^{15,16} It is possible that myocardial handling of glucose and lactate is also abnormal in some patients because of higher circulating levels of gluconeogenic substrates (lactate and alanine), as has been shown in non-insulin dependent diabetes mellitus.¹⁷ The demonstration of myocardial lactate output in patients with abnormal insulin and glucose responses to a carbohydrate load may therefore not necessarily be a metabolic marker of ischaemia.

Long-term ventricular function

Although virtually all studies have indicated a benign prognosis with regard to mortality in patients with chest pain and normal coronary angiograms, recent studies suggest that a subgroup may experience deterioration in left ventricular function over time. Opherke *et al*¹⁸ have reported that syndrome X patients with left bundle branch block on resting or exercise electrocardiograms (ECGs) commonly demonstrate a deterioration in rest and exercise left ventricular ejection fraction and exercise pulmonary artery pressure over an average follow-up of four years. Relevant to these findings, Cannon *et al*,¹⁹ have reported a follow-up of 61 patients with microvascular angina over a period of four and a half years; 15 (25%) demonstrated a significant deterioration in resting left ventricular function (decline in ejection fraction > 10% and/or new wall motion abnormality). In contrast with Opherke's study, decline in left ventricular function was not restricted to patients with left bundle branch block patterns on the initial or follow-up ECG. Further, a decline in function was actually more common in patients without ischaemic-appearing ECG responses to exercise stress (11 of 39 patients) than in patients with ischaemia-appearing ST segment depression during exercise (0 of 15 patients).

Coronary flow reserve

Coronary flow reserve is the difference between baseline autoregulated flow and flow with maximal coronary vasodilatation. A reduction in coronary flow reserve is a common finding in patients with atherosclerotic narrowing of the epicardial coronary arteries.²⁰ This abnormality has also been reported in patients with angina and normal coronary arteries by several investigators using several different methodologies, a fact that further strengthens the conclusion that an abnormal vasodilator reserve truly exists.¹¹

Recently, however, it has been suggested that the impaired coronary flow reserve in syndrome X may reflect the variability in response to different pharmacologic agents and may involve an abnormality of adenosine metabolism in the myocardium.²¹ Holdright *et al* studied the response of 25 patients with chest pain and angiographically normal coronary arteries to intracoronary papaverine.²¹ Sixteen patients had a positive exercise test. Normal coronary flow reserve in response to papaverine was found in all patients, irrespective of the exercise test response. In addition they studied eight patients with a positive exercise test who received intracoronary papaverine, intracoronary adenosine, and high-dose intravenous dipyridamole. Significantly lower values were obtained with dipyridamole than with papaverine, or adenosine.

We have recently reported the response of intracoronary papaverine in 53 syndrome X patients and 26 heart transplant patients (control group).²² The coronary flow reserve was significantly lower in the syndrome X group (2.72 ± 1.39) compared to the transplant group (5.22 ± 1.26 , $p < 0.01$; figure 1). This would seem to exclude the possibility that impaired flow responses in syndrome X could be simply related to abnormal adenosine responsiveness. The results suggest that abnormalities in flow reserve in syndrome X are related to either a structural abnormality in the microcirculation or a functional abnormality in smooth muscle relaxation that affects both adenosine- and papaverine mediated-vasodilation.

The concept of an impaired flow reserve in syndrome X is challenged further by Rosen *et al*, who measured myocardial blood flow and coronary vasodilator reserve in 29 patients with syndrome X and 20 matched controls using positron emission tomography with $H_2^{15}O$.²³ When patients with syndrome X were compared with control subjects, no difference was found in myocardial blood flow either at rest or after dipyridamole, thus questioning the ischaemic basis for syndrome X.

Syndrome X and coronary artery disease

It has been suggested that some cases with chest pain and apparently normal coronary arteries do in fact have significant atheromatous coronary disease.¹⁰

Figure 1 Coronary flow reserve measurements in response to intracoronary papaverine. * $p < 0.01$

Causes of chest pain and normal coronary angiograms

- coronary vasospasm
- microvascular angina
- early coronary artery disease
- oesophageal disorders
- psychosomatic symptoms
- linked angina
- biochemical abnormalities
- left ventricular function abnormalities
- cardiomyopathy
- mitral valve prolapse
- musculoskeletal chest pain
- hyperventilation or mental stress

Figure 2 The effect of hyperventilation and mental stress on resting coronary blood flow velocity (CBFV) in syndrome X. * $p < 0.01$

Figure 3 Mean increase in coronary blood flow (CBF) in response to intracoronary nitrate (Nitr), papaverine (Pap), and graded doses of acetylcholine (Ach 1 $\mu\text{g}/\text{min}$, 3 $\mu\text{g}/\text{min}$, 10 $\mu\text{g}/\text{min}$, 30 $\mu\text{g}/\text{min}$) in control subjects and patients with syndrome X. * $p < 0.01$. ** $p < 0.05$

Coronary anatomy is assessed by eye in virtually all published investigations. Whereas significant stenoses are unlikely to be missed, minor atheroma may only be detected using quantitative techniques.²⁴ This is generally considered a very minor source of error when multiple projections and good imaging techniques are used. The physician should, however, remain alert to the possibility of coronary artery disease as a new cause of chest pain in individuals previously diagnosed as having syndrome X as these patients may develop serious fixed coronary disease over a relatively short time.²⁵

OTHER CAUSES

The prevalence of oesophageal abnormalities has been reported in between 17% and 100% of patients with chest pain and normal coronary arteries, depending on the selection criteria.^{26–28} Oesophageal reflux is seen more commonly than motility disorders. This may be of relevance as it has also been reported recently that gastro-oesophageal reflux may reduce coronary blood flow in syndrome X patients.²⁹ Psychosomatic symptoms referred to the heart have also long been recognised under a variety of terms such as neurocirculatory asthenia, effort syndrome, soldier's heart, and hyperventilation syndrome.^{30,31} The mechanism by which hyperventilation and psychological stress produce chest pain has not been clear. In a recent study, however, both hyperventilation and mental stress produced chest pain in patients with syndrome X associated with a reduction in coronary blood flow, suggesting a direct effect on the microvascular tone (figure 2).³²

New pathogenetic hypotheses

INCREASED TONE OF MICROVASCULATURE

The only consistent finding in syndrome X seems to be an impaired coronary vasodilator reserve, which has been observed by different investigators using different techniques. In contrast, myocardial ischaemia was convincingly documented in only a minority of patients. Cannon *et al*³³ and Maseri *et al*³⁴ have proposed that the fundamental abnormality in syndrome X might be an increased tone of the pre-arteriolar coronary vessels interposed between the conductance arteries and the arterioles responsible for the metabolic regulation of coronary blood flow. A patchy distribution of increased pre-arteriolar tone can cause myocardial ischaemia through three mechanisms: a) a reduction of coronary flow reserve with consequent inadequate oxygen supply during stress; b) a reduction in perfusion pressure at the origin of the arteriolar vessels, resulting in their collapse; and c) a transmural blood flow 'steal' phenomenon during pharmacological or physiological vasodilation among pre-arteriolar segments with a different degree of impairment of coronary flow. Maseri *et al*³⁴ have also proposed that a compensatory release of adenosine as a result of reduced pre-arteriolar vasodilator capacity might cause chest pain, even in the absence of myocardial ischaemia.

ENDOTHELIAL DYSFUNCTION

There is also evidence that endothelium-dependent dilatation of the coronary arteries is defective in patients with anginal chest pain and normal coronary arteries. An attenuated response of coronary blood flow to acetylcholine has been reported in syndrome X by several investigators.^{35–37} In one of the larger studies, both endothelium-dependent and -independent coronary vasodilatation was found to be impaired in syndrome X patients.³⁸ The response to the endothelium-dependent vasodilator acetylcholine and the endothelium-independent vasodilator papaverine was studied in 32 syndrome X patients and 15 control subjects (patients with atypical chest pain, negative exercise test, and normal coronary arteries on angiography). The mean increase in coronary blood flow in response to a 12 mg dose of papaverine and acetylcholine (given at doses of 1, 3, 10 and 30 μg per minute) was significantly less in the syndrome X group as compared to the control group suggesting a dynamic abnormality of coronary microvascular function (figure 3). Defective endothelium-dependent dilatation in the coronary microcirculation may therefore contribute to the altered regulation of myocardial perfusion and the ischaemic manifestations in syndrome X.

OESTROGENS

As opposed to coronary artery disease, syndrome X appears to be more frequent in women than in men. 17β -Oestradiol has been shown to cause coronary artery vasodilatation, probably related to block of calcium channels.^{39,40} Its deficiency may, therefore, result in an increase of coronary artery tone. Recently, a high incidence of hysterectomies and signs of insufficient ovarian hormones have been

reported among patients with syndrome X,⁴¹ suggesting that oestrogen deficiency may be the cause of symptoms in some postmenopausal women with syndrome X. Oestrogen replacement therapy has also been reported to reduce the frequency of chest pain in female menopausal patients with syndrome X.⁴² This, however, does not explain the male syndrome X.

INCREASED SYMPATHETIC TONE

The presence of an increased sympathetic drive in patients with syndrome X, as evidenced by an increased mean heart rate during 24-h ambulatory ECG recordings, a rapid rate of rise of the rate-pressure product during exercise, high plasma catecholamine levels, and increased ventricular contractility, has been suggested by several studies.⁴³ Furthermore, a recent report suggests that patients with syndrome X who show an increased sympathetic drive during exercise may develop hypertension during follow-up.⁴⁴ Maximal QT interval corrected for heart rate is significantly prolonged in patients with syndrome X,⁴⁵ adding further support to the hypothesis that there is excessive activation of the sympathetic nervous system in syndrome X. Rosano *et al*,⁴⁶ have studied 26 patients with syndrome X and 20 healthy sex- and age-matched control subjects by means of analysis of heart rate variability during 24-h Holter monitoring. Their study suggests that patients with syndrome X have a sympathovagal balance shifted toward sympathetic predominance. This increased sympathetic drive is associated with an increased mean heart rate. This dysfunction appeared to persist throughout the 24 h suggesting heterogeneity in autonomic function in syndrome X. However, neither clonidine nor prazosin improve myocardial ischaemia in patients with syndrome X.⁴⁷

POTASSIUM PUMP ALTERATION

Potassium accumulation in the extracellular space accounts for most of the changes of the action potential during myocardial ischaemia. It has been suggested that a reduced efficacy of the pump may lead to potassium accumulation during increase myocardial work.⁴⁸ A heterogeneous accumulation of potassium in the extracellular space may explain the presence of ECG changes during exercise and the cardiac observed in syndrome X patients.

PAIN PERCEPTION

The recognition that many patients with chest pain and angiographically normal coronary arteries do not have convincing evidence of myocardial ischaemia, in addition to the atypical features of pain, has led several groups to consider abnormal pain perception as a fundamental abnormality in this patient population. Turiel *et al*⁴⁹ reported that 12 women with 'typical angina', normal coronary angiograms, and ischaemic-appearing ECG response to exercise had a lower pain threshold and tolerance for forearm ischaemia and electrical skin stimulation than did 10 women with coronary artery disease. Chauhan *et al*⁵⁰ have recently reported abnormal cardiac pain perception in syndrome X. Intracardiac catheter manipulation provoked the typical anginal pain in over 90% of patients with syndrome X in the absence of any reduction in coronary blood flow, manipulations which were unappreciated by patients with coronary artery disease, mitral stenosis or heart transplants. Similar findings have been reported by other investigators in patients with chest pain and normal coronary angiograms.^{51,52} Relevant to this, Cannon *et al* have recently reported that imipramine improved the symptoms of patients with chest pain and normal coronary angiograms as compared to clonidine or placebo.⁵³ Imipramine reduced the frequency of chest pain by approximately 50% and the benefit of imipramine was independent of the results of extensive cardiac, oesophageal, and psychiatric testing. It is proposed that imipramine produces its effects through a visceral analgesic effect.

Angiotensin-converting enzyme (ACE) INHIBITORS AND SYNDROME X

Kaski *et al* have reported recently that ACE inhibition lessens exercise-induced ischaemia in patients with syndrome X who have a reduced coronary blood flow reserve.⁵⁴ Ten patients with syndrome X and a reduced coronary flow reserve underwent a randomised, single-blind, crossover, placebo-controlled study of the effects of enalapril on angina and exercise-induced ST segment depression. All patients had a positive exercise test while taking placebo, whereas six patients had a positive test result during enalapril therapy. Total exercise duration and time to 1 mm ST segment depression were prolonged by enalapril over those obtained with placebo. The magnitude of ST segment depression was also less with enalapril. It is postulated that this beneficial effect may be due to direct modulation of the coronary tone at the microcirculation level which results in an increased myocardial oxygen supply.

Summary/learning points

- 10% of patients undergoing coronary angiography for the investigation of chest pain have normal coronary arteries
- good long-term prognosis
- low incidence of myocardial infarction and death
- considerable residual morbidity
- normal activity and exercise should be encouraged
- anti-ischaemic therapy should be tried for symptomatic therapy
- if reassurance fails to help, a noncardiac cause should be sought
- oesophageal reflux should be sought and treated
- therapies useful in chronic neuropathic pain syndromes may be helpful
- patients who are overly anxious or who have panic disorders may benefit from counselling and therapy
- physicians should remain alert to the possibility of development of coronary artery disease

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