Syndrome X: the haemodynamic significance of ST segment depression

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SUMMARY The relation between chest pain, ST segment depression, and changes in left ventricular function was assessed in six patients with angina, a positive exercise test, and normal coronary arteries as assessed by arteriography (syndrome X). In the six patients with syndrome X and in six controls there was no significant rise in pulmonary artery diastolic pressure during treadmill exercise, although there was ST segment depression (range 1-4.5 mm) in the patients with syndrome X. In 19 patients with coronary artery disease, however, the pulmonary artery diastolic pressure increased by a median 5 mm Hg (range 0-13.6 mm Hg) on treadmill exercise. In only one patient with coronary artery disease, who showed 1 mm ST segment depression, was there no rise in pulmonary artery diastolic pressure. During ambulatory monitoring in patients with syndrome X there were 12 episodes of ST segment depression (> 1 mm) (4 painful, 8 painless) in which there was no change in pulmonary artery diastolic pressure. In the patients with coronary artery disease there were 29 episodes of angina during ambulatory monitoring and during all of them pulmonary artery diastolic pressure rose by a median 7.5 mm Hg (range 1.8-19.7 mm Hg).

Unlike the haemodynamic changes that usually occur during myocardial ischaemia in coronary artery disease, chest pain and ST segment changes in patients with syndrome X are not associated with impaired left ventricular function as assessed by ambulatory pulmonary artery pressure monitoring.

Syndrome X is defined as anginal chest pain with ST segment depression on exercise and normal coronary arteriography without vascular spasm. The pathophysiological basis of syndrome X has often been studied but remains poorly understood.¹⁻³ We have used ambulatory pulmonary artery diastolic pressure monitoring, which reflects left ventricular end diastolic pressure,^{4,5} to investigate the haemodynamic changes accompanying ST segment depression during treadmill exercise and unrestricted ambulatory activity in patients with syndrome X and we have compared these results with those in patients with coronary artery disease.

Patients and methods

PATIENTS

We studied three groups of patients (a) six with syndrome X (5 male, 1 female, mean (SD) age 48 (12) years) all of whom had had negative responses to ergometrine maleate provocation and no evidence of ST segment elevation on 24 hour ambulatory electrocardiographic monitoring; (b) six controls (4 male, 2 female, mean age 39 (7) years) with chest pain of non-cardiac origin, normal exercise test, and normal coronary arteriography; (c) 19 men (mean age 57 (11) years) with coronary artery disease (anginal chest pain with positive exercise test and $> 50\%$ narrowing in one or more coronary arteries).

All antianginal medication other than glyceryl trinitrate was discontinued 48 hours before the study. The protocol was approved by the hospital ethics committee and patients gave their informed and written consent.

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PULMONARY ARTERY PRESSURE MONITORING

A polyurethane six French NIH type catheter with a miniature strain gauge transducer mounted on the tip was immersed in saline for an hour before use and was calibrated. The transducer was driven and demodulated by an electrically isolated Gaeltec pre-amplifier. The catheter was introduced percutaneously via a subclavian vein to a proximal pulmonary artery under fluoroscopy in the cardiac catheter laboratory when the patient was undergoing cardiac catheterisation. The pulmonary artery pressure was recorded on an Oxford Medilog I miniature tape recorder that had been modified by the insertion of an AM4 pressure module.⁴

ST SEGMENT MONITORING

ST segment monitoring was performed with a frequency modulated recorder and leads CM2 and CM5 were recorded. The electrocardiogram was replayed on an Oxford MA20 scanner. Changes in the ST segment were measured 80 ms after the J point to an accuracy of 0.1 mm by means of a magnifying lens equipped with a graticule. A change of 1 mm ST segment depression lasting more than 30 seconds was regarded as significant. The heart rate and ST segment changes were analysed on a beat to beat basis for 5 min before each episode and again up to 5 min after the ST segment had returned to basal levels.

The pulmonary artery pressure recording was linked to the frequency modulated electrocardiogram by an event button that when it was pressed marked both the frequency modulated electrocardiogram and the pulmonary artery trace. Ambulatory pulmonary artery pressure monitoring and ST segment monitoring were performed for 24–48 hours in each patient.

EXERCISE TESTING

Exercise testing was performed according to a modified Bruce protocol.⁶ Transducer tipped pulmonary artery pressure and the frequency modulated electrocardiogram were recorded continuously. A 12 lead electrocardiogram was recorded at one minute intervals. The exercise test was terminated by anginal pain, dyspnoea, multiple ventricular extrasystoles, hypotension, ST segment depression

> 3 mm, or exhaustion.

ANGINA DIARY

Patients were instructed to keep diaries during the period of ambulatory pulmonary artery pressure and ST segment monitoring. They were asked to note the time of onset and severity of chest discomfort and their activity at the time of pain. In addition, they were asked to press the event marker so that both the ST segment and pulmonary artery traces were marked.

At the end of 24–48 hours of recording, the pulmonary artery catheter was removed and the pulmonary artery trace was replayed through a PB2 and PM3 unit. This was displayed on an oscillograph (SE Laboratories 6008). The entire period of recording of the pulmonary artery diastolic pressure was displayed on ultraviolet paper and measured by means of a calibrated scale from a zero reference point. The pulmonary artery diastolic pressure was measured during both painful and painless episodes of ST segment depression on a beat to beat basis 5 min before the onset of the earliest change in pulmonary artery pressure and for 5 min after the pulmonary artery pressure had returned to baseline values. The pulmonary artery diastolic pressure was measured at the end of expiration in each respiratory cycle.

STATISTICAL ANALYSIS

A significant change in the basal ST segment, heart rate, or pulmonary artery diastolic pressure was taken to be a change of at least 3 SD from a mean level measured over 5 min before any change in the pulmonary artery pressure or ST segment. Wilcoxon rank sum testing was used for analysis.

Results

EXERCISE TESTING

In patients with syndrome X and normal controls there was no important increase in pulmonary artery diastolic pressure during treadmill exercise despite the development of ST segment depression in those with syndrome X (table 1). Five of the six control patients reached stage 4 with a heart rate >150 beats/min. In one control patient pulmonary artery

Table 1 Changes in the ST segment and pulmonary artery diastolic pressure during treadmill exercise in patients with syndrome X, coronary artery disease, and in controls

	Syndrome X	Coronary artery disease	Controls
ST segment change (mm)	1.7 (1–4.5)*	1.9 (1–5.2)*	0 (0)
Increase in pulmonary artery diastolic pressure:			
mm Hg	0 (0–4.4)	5 (0–13.8)	0 (0–3)
%	0 (0–72)†	69 (0–262)†‡	0 (0–55)‡

Medians and ranges are shown.

*NS; †, ‡, $p < 0.01$.

diastolic pressure rose by 2 mm Hg and in another by 3 mm Hg on exercise in the absence of electrocardiographic changes. There was no change in pulmonary artery diastolic pressure in the remaining control subjects.

Pulmonary artery diastolic pressure did not rise in four of the six patients with syndrome X (fig 1); in the remaining two patients it rose by 3 and 4.4 mm Hg. All patients reached at least stage 3 of the modified Bruce protocol (median 11.9 min, range 7.4–17) and had an increase in heart rate (median 155, range 135–190 beats/min). All the patients with syndrome X had ST segment depression (median 1.7 mm, range 1–4.5).

Changes on treadmill exercise in patients with coronary artery disease are included for comparison (table 1, fig 2). The results have been reported previously.⁷ In most patients with coronary artery disease there was a significant rise in pulmonary artery diastolic pressure associated with ST segment depression and angina.

AMBULATORY MONITORING

Twelve episodes of ST segment depression > 1 mm (4 painful and 8 painless) were recorded in patients

with syndrome X (table 2). All episodes occurred between 6 am and 9 pm. Pulmonary artery diastolic pressure did not rise during these episodes, even when an episode of ST segment depression of 2.2 mm lasted 52 minutes.

In patients with coronary artery disease there were 29 anginal episodes with ST segment depression all of which were associated with a rise in pulmonary artery diastolic pressure (median 87.5%, range 20–237).

Discussion

The pathophysiology of the syndrome of chest pain with a positive exercise test and normal coronary arteriography is poorly understood. We have shown that in patients with syndrome X there were no changes in pulmonary artery diastolic pressure during ambulatory monitoring and treadmill exercise despite chest pain and ST depression. In patients with arteriosclerotic coronary artery disease changes in pulmonary artery diastolic pressure reflected impaired left ventricular function that was seen during myocardial ischaemia.⁷

Ambulatory pulmonary artery pressure moni-

Fig 1 Changes in the ST segment and pulmonary artery diastolic pressure (PADP) during treadmill exercise in a patient with syndrome X. There was no rise in pulmonary artery diastolic pressure despite important ST segment depression. Maximum heart rate was 160 beats/min.

Fig 2 Changes in the ST segment and pulmonary artery diastolic pressure (PADP) during treadmill exercise in a patient with coronary artery disease. There was a rise in pulmonary artery diastolic pressure with significant ST segment depression. Maximum heart rate was 130 beats/min.

Table 2 Changes in the ST segment and pulmonary artery diastolic pressure during ambulatory monitoring in syndrome X and coronary artery disease

	Syndrome X	Coronary artery disease
Number of episodes	12	29
ST segment change (mm)	1.35 (1-3)	1.5 (1-4)
Increase in pulmonary artery diastolic pressure:		
mm Hg	0 (0-1)	7.5 (1.8-19.7)
%	0 (0-15)*	87.5 (20-237)*

Medians and ranges are shown.

* $p < 0.001$.

toring with a transducer tipped catheter has been shown to be a reliable method of assessing pulmonary artery diastolic pressure in ambulant patients.⁴ Beat to beat analysis of the ST segment and pulmonary artery diastolic pressure during periods of interest can be performed and the drawbacks of fluid filled systems have been overcome.

There have been many studies of syndrome X, often with conflicting results. One of the difficulties has been that there are no uniform diagnostic criteria.^{1,8} Patients without a positive exercise test have been included in some studies.^{9,10} All patients in our

study had a positive exercise test. In addition, coronary arteriography was performed in multiple views to reduce the possibility of inadequate opacification and misinterpretation of the coronary arteriograms.

Several explanations have been suggested for the mechanism of syndrome X. An early concept was that it was a disease of the small vessels¹¹; however, biopsy specimens showed no evidence of this,^{2,10} though vessels between 40 and 200 μ m cannot be seen adequately by light or electron microscopy or by angiography.² It has been suggested that coronary dilatory capacity is considerably reduced in syndrome X,^{2,12,13} as it is in atherosclerotic coronary artery disease, and that vasoconstrictor stimuli such as the cold pressor test or ergometrine maleate provocation may unmask the flow abnormality.^{3,14} This may be caused by abnormal arteriolar regulation of calcium handling¹⁵ and certainly calcium antagonists prolong exercise duration and the time to the onset of ST segment depression in some though not all patients with syndrome X.¹⁶

Some patients with syndrome X have abnormal myocardial lactate production, and mitochondrial abnormalities have been seen by electron microscopy.² Regional perfusional abnormalities were identified in some patients by xenon-133 imaging, and this accords with the concept of a compromised

flow disorder.¹⁷ Gated blood pool studies have also shown abnormal left ventricular function in response to isometric stress.^{2,3}

We found that if there is an alteration in coronary blood flow in syndrome X it is insufficient to cause a rise in left ventricular filling pressure, as it does in patients with proven coronary artery disease. Furthermore, because the prognosis for patients with syndrome X is good^{1,18} it is likely that the abnormality is of little haemodynamic importance.

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