Original articles

Coronary flow reserve and oesophageal dysfunction in syndrome X

Anoop Chauhan, Paul A Mullins, Roy Gill, Ged Taylor, Michael C Petch, Peter M Schofield

Summary
The relative prevalence of abnormalities of coronary flow reserve and oesophageal function was ascertained in 32 syndrome X patients with typical angina chest pain, a positive exercise test, and normal coronary arteries. Coronary flow reserve in response to a hyperaemic dose of papaverine was measured using an intracoronary Doppler catheter positioned in the left anterior descending coronary artery. An abnormal coronary flow reserve was defined as being <3.0. Patients were investigated for oesophageal dysfunction by manometry and 24-hour pH monitoring. Thirteen patients had an impaired coronary flow reserve (group 1) and 19 patients had a normal flow reserve (group 2). Eight of the 13 group 1 patients (62%) and 13 of the 19 group 2 patients (68%, *p* = NS) had evidence of oesophageal dysfunction on either manometry or pH studies. Therefore, a total of 26 (81%) syndrome X patients had either an abnormality of coronary flow reserve or oesophageal dysfunction suggesting that chest pain in these patients may be due to myocardial ischaemia or oesophageal dysfunction, thus confirming the heterogeneous nature of this syndrome. The prevalence of oesophageal abnormalities was independent of any abnormalities of coronary flow reserve.

Keywords: coronary flow reserve, oesophageal dysfunction, syndrome X

was to ascertain the relative prevalence of abnormalities of oesophageal function (motility and reflux disorders) and coronary flow reserve in strictly characterised syndrome X patients (box 1).

Patients and methods

Thirty-two syndrome X patients were studied. All patients underwent oesophageal manometry tests, 24-hour pH monitoring, and coronary flow reserve studies. The patient variables are shown in table 1. All patients gave a history of chest pain typical of angina pectoris and had a positive exercise electrocardiogram. The Bruce protocol was used for the exercise test and the test was said to be positive if there was at least 1 mm of horizontal or downward sloping ST segment depression at 80 ms after the J point. The left ventricle and the coronary arteries were completely normal on angiography, as confirmed by two independent observers. Patients with hypertension, diabetes mellitus, and valvular heart disease were excluded from the study. Echocardiographic assessment was also performed in all patients. Cross-sectional and M-mode assessment of the left ventricular posterior wall and septal thickness was made. Patients with a diastolic septal or posterior wall thickness of more than 11 mm were excluded from the study to minimise any effect of left ventricular hypertrophy on coronary flow measurements.

The study was approved by the Huntingdon Health Authority Ethical Committee. Full informed consent was obtained from all patients prior to the study.

Regional Cardiac Unit, Papworth Hospital, Papworth Everard, Cambridge, UK
A Chauhan
PA Mullins
R Gill
G Taylor
MC Petch
PM Schofield

Correspondence to
Dr A Chauhan, Laurel Cardiology, 865 West 10th Avenue, Vancouver, British Columbia, V5Z 1L7, Canada

Accepted 25 August 1995

Approximately 10–30% of patients undergoing coronary angiography for the investigation of chest pain turn out to have normal coronary arteries.^{1–3} These patients are said to have ‘angina pectoris with a normal coronary angiogram’ and patients who also have a positive exercise test are said to have ‘syndrome X’. The spectrum of controversy regarding the pathophysiology of syndrome X is wide and seems to include all aspects of the disease.⁴ Many have an abnormal coronary flow reserve (microvascular angina) which provides support for an ischaemic basis for this syndrome. However, many patients also have oesophageal dysfunction. The aim of this prospective study

Features of syndrome X
<ul style="list-style-type: none">• patients have chest pain, a positive exercise test, and normal coronary angiogram• average age in late 40s with female preponderance• chest pain not reproducibly related to exertion• variable response to sublingual nitrates• resting ST or T wave changes in approximately 50%• good long-term prognosis• low incidence of myocardial infarction and death• considerable residual morbidity

Box 1

Table 1 Patient variables (*n* = 32)

Age (years)	58 (44–69)
Sex (Male:female)	14:18
Weight (kg)	71.6 ± 12.6
Smokers	9
Haemoglobin	13.0 ± 1.2
White cell count (10 ⁹ /l)	6.58 ± 1.98
Platelets (10 ⁹ /l)	265 ± 59
Haematocrit	0.40 ± 0.04
ESR (mm/h)	16 ± 11
Urea (mmol/l)	6.1 ± 1.2
Creatinine (μmol/l)	107 ± 17
Glucose (mmol/l)	5.9 ± 0.7
Cholesterol (mmol/l)	6.0 ± 0.96
HDL (mmol/l)	0.96 ± 0.31
LDL (mmol/l)	4.2 ± 0.8
Triglycerides (mmol/l)	1.76 ± 0.67
LVEDP (mmHg)	9.3 ± 4.3
<i>Exercise test data*</i>	
Heart rate (beats/min)	146 ± 13
Systolic pressure (mmHg)	176 ± 11
Time (s)	608 ± 129

Values are expressed as mean ± SD where appropriate. *exercise test data at 1 mm ST depression; ESR, erythrocyte sedimentation rate; HDL, high density lipoprotein; LDL, low density lipoprotein; LVEDP, left ventricular end-diastolic pressure.

CATHETERISATION PROTOCOL

All the patients were fasted overnight before cardiac catheterisation. All cardiac medications had been stopped for at least 48 hours. Patients were premedicated with diazepam 10 mg prior to catheterisation. Coronary angiography was performed by the Judkins technique through the right femoral artery in all patients. Coronary injections were performed manually with up to 8 ml of intracoronary radio-opaque contrast medium (Niopam). Cine film recordings were performed in multiple projections. The proximal left anterior descending coronary artery was centred for optimal viewing after the initial angiograms had been obtained. To eliminate vasoactive effects of the contrast medium at least 10 minutes were allowed to lapse before the coronary blood flow study.

Heparin sodium, 10 000 units, was then given intravenously. A 3.6 F 20 Mega Hertz Doppler-tipped catheter (Schneider, UK) was positioned in the proximal segment of the left anterior descending coronary artery and was connected to a Millar velocimeter (Model MDV-20, Millar Instruments, Houston, Texas). The Doppler catheter and the range-gate of the velocimeter were adjusted to obtain good quality phasic and mean coronary blood flow velocity signals. These signals were recorded on a Mingograf recorder (Siemens-Eléma, Sweden). This technique of coronary blood flow velocity measurements has been extensively validated and described in detail.^{5,6}

Baseline mean resting and phasic coronary blood flow velocity were then recorded. After an initial 2 mg intracoronary test dose of papaverine hydrochloride through the guide catheter, further injections of up to 14 mg of papaverine (2 mg/ml in 0.9% saline) were given in 2-mg increments until maximum flow was achieved. The hyperaemic response was

recorded in the form of maximum mean and phasic blood flow velocity.

CORONARY FLOW RESERVE

Coronary flow reserve was defined as the ratio of mean flow velocity achieved at peak hyperaemia to the mean resting flow velocity. A normal heart with normal coronary arteries is capable of increasing coronary flow by approximately four- to five-fold.⁷ Previous studies in animals have demonstrated that intracoronary papaverine is capable of inducing maximal hyperaemia resulting in a four- to six-fold increase in coronary blood flow after intracoronary administration.^{8,9} A similar increase in coronary blood flow has been reported in conscious humans.^{10,11} For the purpose of this study, impaired coronary flow reserve was defined as <3.0.

OESOPHAGEAL FUNCTION TESTS

All cardiac medications had been discontinued at least 24 hours prior to the study. After an overnight fast, lignocaine topical anaesthetic was sprayed in to the nasopharynx. A multi-sensor catheter (Gaeltec, Scotland, diameter 2.5 mm) was passed into the oesophagus. This probe has six mounted microtransducers spaced at 5-cm intervals from the tip. This was connected to a GR 800 analysing station and signals were displayed on a screen and stored in the computer for analysis. A respiratory transducer and an electrocardiogram were also connected to the patient. The lower oesophageal sphincter was located manometrically by the station pull-through technique. The probe was withdrawn from the stomach in 1-cm stages and the upper limit of the lower oesophageal sphincter was marked by its distance from the external nares. Sphincteric pressure was measured in a standard way. Peristaltic activity was assessed with five wet and dry swallows, each separated by a 30-second interval. Patients were asked to report any chest pain and to distinguish whether the pain was typical or atypical of their usual pain. After the baseline study, edrophonium hydrochloride (80 μg/kg) was administered intravenously followed immediately by five wet swallows. Manometric responses were recorded for later analysis. Criteria for abnormal oesophageal function are shown in box 2.

OESOPHAGEAL pH MONITORING

Twenty-four hour pH monitoring of the distal oesophagus was performed following manometry in all patients using a standard technique (Gaeltec Research, 1987). Before the pH electrode (PHELPD miniature pH electrode system) was passed, the equipment was calibrated. An ambulatory pH recorder unit (Gaeltec Research, type PH100) was connected to the pH replay unit (GR 800 system, Gaeltec Research, Scotland). A reference electrode was attached to the patient's left upper arm and also to the pH recorder unit. The equipment was calibrated using buffer solutions of pH 7.38 and pH 4.0. The pH electrode was passed via the external nares into the patient's stomach. The pH electrode was then withdrawn and

Criteria for abnormal oesophageal function
<ul style="list-style-type: none">• achalasia: aperistalsis of the oesophageal body with incomplete lower oesophageal sphincter relaxation and elevated lower oesophageal sphincter pressure ≥ 26 mmHg• nutcracker oesophagus: mean peristaltic amplitude, measured with the catheter lumen 3 or 8 cm above the lower oesophageal sphincter, of ≥ 180 mmHg averaged over five wet swallows• diffuse oesophageal spasm: repetitive, spontaneous, non-peristaltic contractions in at least 30% of contractions, with otherwise normal peristalsis• non-specific motility disorder: prolonged duration of oesophageal contraction (> 7 s) and/or isolated repetitive contractions after wet swallows

Box 2

positioned 5 cm above the lower oesophageal sphincter, the position of which had been determined during the manometry study. The recorder was set to the beginning of the memory and recording was commenced.

TREADMILL EXERCISE TESTING

During oesophageal pH monitoring, the patients underwent symptom-limited treadmill exercise testing using the standard Bruce protocol. The onset and termination of the exercise test was recorded and it was determined whether or not gastro-oesophageal reflux (pH less than 4) occurred during exercise testing. The development of at least 1 mm of horizontal or downsloping ST segment depression or at least 2 mm of upsloping ST depression at 80 ms after the J point from resting values were considered abnormal. It was noted whether or not the patients experienced chest pain during treadmill exercise testing and whether this pain was typical of their usual pain.

INTERPRETATION OF 24-h pH RECORDINGS

Gastro-oesophageal reflux was defined as a fall in distal oesophageal pH to less than 4 for more than 10 seconds. Abnormal reflux during the 24-hour recording period was present when oesophageal pH was < 4 for more than 5.5% of the study period.¹² A 'pH score' was also calculated as described by Johnson and DeMeester.¹³ A score greater than 21.3 was considered abnormal.^{13,14} The number of episodes of chest pain associated with gastro-

oesophageal reflux and the number not associated with reflux were determined for each patient during 24-hour pH monitoring.

STATISTICAL ANALYSIS

Values are given as mean $\pm$ SD where appropriate. Group differences were analysed using a one-way analysis of variance. Comparison of proportions was made using the Chi-square test and Fisher's Exact test, as appropriate.

Results

CORONARY FLOW RESERVE STUDY

The results of the coronary flow reserve study are shown in table 2. The coronary flow reserve was < 3.0 in 13 patients (41%). There were no significant changes in heart rate and mean arterial pressure before and after intracoronary papaverine injections.

OE SOPHAGEAL MANOMETRY

Twelve (38%) syndrome X patients had oesophageal manometric abnormalities (table 3). The commonest abnormality observed was repetitive contractions which occurred in seven (22%) patients. Excluding the abnormalities seen with edrophonium challenge, eight (25%) patients had an abnormal baseline study. Using the classification of oesophageal motility disorders described above, of the 12 syndrome X patients in this study with manometric abnormalities, three (9%) had diffuse oesophageal spasm, five (16%) had non-specific motility disorder, and four (13%) had a nutcracker oesophagus. One patient had a hypertensive lower oesophageal sphincter together with repetitive contractions. Table 4 shows the oesophageal manometric findings in

Table 3 Oesophageal manometry abnormalities in syndrome X patients*

Manometric abnormality	Number of patients
Nutcracker oesophagus	4
Repetitive contractions	7
Simultaneous contractions	3
Prolonged duration of contractions	5
Hypertensive lower oesophageal sphincter	1
Positive edrophonium challenge	6
no other abnormality	2
prolonged duration	1
simultaneous contractions	1
nutcracker oesophagus	2

*12 out of 32 patients with oesophageal dysmotility.

Table 2 Haemodynamics and coronary flow reserve

	Resting			Post hyperaemic papaverine dose				
	HR	MAP	CFV	HR	MAP	CFV	CFR	% LAD
Normal CFR (n = 19)	69 $\pm$ 14	94 $\pm$ 10	7.9 $\pm$ 3.4*	69 $\pm$ 14	95 $\pm$ 10	33 $\pm$ 15	4.3 $\pm$ 1.1*	6.3 $\pm$ 9
Impaired CFR (n = 13)	77 $\pm$ 11	100 $\pm$ 12	13.1 $\pm$ 7.0	78 $\pm$ 10	101 $\pm$ 12	29.3 $\pm$ 15	2.37 $\pm$ 0.5	6.8 $\pm$ 8

All values are given as mean $\pm$ SD; *p < 0.01. CFR = coronary flow reserve; HR = heart rate (beats/min); MAP = mean arterial pressure (mmHg); CFV = coronary blood flow velocity (cm/s); % LAD = per cent change in left anterior descending coronary artery diameter in response to papaverine.

syndrome X patients with a normal and an abnormal baseline study. There was no significant difference in the age and sex distribution in the two groups. Both the mean and maximum amplitudes of contractions on wet swallows were significantly higher in syndrome X patients with an abnormal baseline manometric study compared to patients with a normal baseline study ($p < 0.05$). The mean duration of contractions in the distal oesophagus of syndrome X patients with an abnormal baseline study was also significantly longer ($p < 0.01$).

Table 4 Oesophageal manometric observations in syndrome X patients with a normal and an abnormal baseline study

	Baseline manometry	
	abnormal (n = 8)	normal (n = 24)
Age (years)	56.4 ± 7.8	57.9 ± 7.2
Sex (male:female)	4:4	10:14
Mean lower oesophageal sphincter pressure (mmHg)	15.4 ± 3.9	16.5 ± 8.0
Mean amplitude of contractions on dry swallows (mmHg)	43.7 ± 27.5	40 ± 19.4
Maximum amplitude of contractions dry swallows (mmHg)	65.7 ± 42.9	57.4 ± 28.1
Mean amplitude of contractions on wet swallows (mmHg)	101.8 ± 55.4*	61.7 ± 31.6
Maximum amplitude of contractions wet swallows (mmHg)	130 ± 59.9*	84.8 ± 27.5
Mean duration of contractions (s)	8.1 ± 2.1**	4.0 ± 0.9

Values are given as mean ± SD. Significantly different from syndrome X patients with normal baseline oesophageal manometry, * $p < 0.05$, ** $p < 0.01$.

Table 5 24-hour pH score and exercise-induced gastro-oesophageal reflux in syndrome X patients

	Group 1 (n = 7)	Group 2 (n = 10)	Group 3 (n = 15)
24-hour pH score	61.9 ± 22.4*	14.9 ± 8.2	15.8 ± 8.7
<i>Exercise test</i>			
No chest pain/no reflux	0	0	4
Chest pain/no reflux	1	0	11
No chest pain/reflux	0	0	0
Chest pain/reflux	6	10	0

Group 1 = patients with abnormally high 24-hour oesophageal pH score
Group 2 = normal oesophageal pH score. Exertional gastro-oesophageal reflux coincident with chest pain
Group 3 = normal oesophageal pH score. No exertional gastro-oesophageal reflux
*Significantly different from groups 2 and 3, $p < 0.01$.

Table 6 Coronary flow reserve and oesophageal disorders in syndrome X

	Impaired CFR (n = 13)	Normal CFR (n = 19)
Motility abnormality	4	8
Abnormal pH score	2	5
GOR disease	7	10
Abnormal motility and GOR disease	3	5
Normal motility and pH study	5	6
Oesophageal abnormality	8 (62%)	13 (68%)

CFR = coronary flow reserve (normal ≥ 3.0); GOR = gastro-oesophageal reflux disease (patients with a high 24-hour pH score or exertional reflux).

OESOPHAGEAL pH STUDIES
Table 5 shows the results of the 24-hour pH score and the results of the treadmill test. Seven out of the 32 syndrome X patients (group 1) had an abnormally high 24-hour oesophageal pH score. Six of these demonstrated gastro-oesophageal reflux during treadmill exercise testing which was associated with their usual chest pain. One patient had chest pain not associated with reflux. A further 10 patients had a normal 24-hour oesophageal pH score but also experienced chest pain with coincident gastro-oesophageal reflux during exercise testing (group 2). Therefore, patients in group 2 demonstrated exercise-induced gastro-oesophageal reflux but did not reflux significantly at other times. The remaining 15 patients (group 3) had a normal 24-hour oesophageal pH score and did not have gastro-oesophageal reflux during exercise testing.
The 17 patients in groups 1 and 2 were considered to have gastro-oesophageal reflux disease. There was no significant difference in age or sex between patients in groups 1 and 2 (seven males and 10 females; mean age 56.9 ± 7.5) and patients in group 3 (seven males and eight females; mean age 58.2 ± 7.4). The mean lower oesophageal sphincter pressure of patients in group 3 (20.3 ± 9.9 mmHg) was significantly higher than that of patients in groups 1 and 2 (13.3 ± 2.5 ; $p < 0.01$). There was no difference in the mean lower oesophageal sphincter pressure between patients in group 1 (14 ± 2.4 mmHg) and group 2 (12.8 ± 2.6).
During the exercise test all the syndrome X patients developed an abnormal ST segment response (thus confirming their previously positive exercise test). Fifteen (88%) patients from groups 1 and 2 developed their usual anginal pain during the exercise test compared to only eight (53%) patients in group 3 but this difference did not reach statistical significance.

CORONARY FLOW RESERVE AND OESOPHAGEAL DYSFUNCTION
Table 6 shows the prevalence of oesophageal motility disorders and gastro-oesophageal reflux in syndrome X patients with an impaired coronary flow reserve and in patients with a normal flow reserve. Thirteen (41%) patients had an impaired coronary flow reserve as defined earlier. Eight (62%) of these had evidence for oesophageal dysmotility or gastro-oesophageal reflux disease as compared to 13 (68%) patients with normal coronary flow reserve ($p = \text{NS}$). There was no significant difference in the prevalence of oesophageal disorders in patients with impaired or normal coronary flow reserve.

Discussion
Our study demonstrated that approximately 41% of syndrome X patients had an impaired coronary flow reserve in response to papaverine-mediated vasodilatation, indicating microvascular dysfunction. Also, 66% had an abnormality of oesophageal function indicating that the oesophagus may be an important

source of pain in these patients. Twenty-six (81%) of the 32 patients in this study had either an abnormal coronary flow reserve or an oesophageal abnormality.

SYNDROME X AND OESOPHAGEAL DYSFUNCTION

Oesophageal disorders can closely mimic the chest pain produced by coronary artery disease due to the common innervation of the heart and oesophagus. Oesophageal abnormalities have been commonly reported in patients with chest pain and normal coronary arteries.¹⁴⁻¹⁶ However, many of these studies have included patients with atypical chest pain and patients who did not have completely normal coronary arteries. In this study, only patients with typical anginal chest pain, a positive exercise test, and completely normal coronary arteries were included. This is also the first study to compare coronary flow reserve, oesophageal motility, and oesophageal reflux in the same patients. Cannon *et al*¹⁷ reported oesophageal motility and coronary flow reserve studies in patients with chest pain and normal coronary arteries. However, this study included patients with atypical chest pains and a positive exercise test was not a requirement. Also, they did not perform 24-hour oesophageal pH monitoring.

Abnormal oesophageal motility was demonstrated in 38% of the syndrome X patients in our study. The commonest abnormalities observed were non-specific motility disorders and nutcracker oesophagus. The high incidence of oesophageal abnormalities in patients with chest pain and normal coronary arteries does not provide conclusive evidence to explain the cause of chest pain. However, it does provide circumstantial evidence to support a causal relationship in some syndrome X patients. Also, 13% of our syndrome X patients developed their usual chest pain associated with a new abnormality of oesophageal motility which was not present on the baseline study following the administration of intravenous edrophonium.

Although several studies have examined oesophageal motility in patients with 'non-cardiac chest pain',^{16,18,19} only a few studies have performed 24-hour oesophageal pH monitoring.^{14,15,20,21} Again, only the study by Schofield *et al*¹⁵ used strict criteria to include patients with typical anginal chest pain and completely normal coronary arteries, although even in their study a positive exercise test was not required.

In the present study, seven patients (22%) were found to have an abnormal pH score on 24-hour pH monitoring, six of whom demonstrated gastro-oesophageal reflux coincident with chest pain. A further 10 (31%) patients, who had a normal 24-hour pH score, demonstrated gastro-oesophageal reflux associated with their usual chest pain during exercise testing. In other words, 16 (50%) patients were demonstrated to have exertional gastro-oesophageal reflux which was associated with their typical anginal chest pain. These findings are similar to the abnormalities reported by Schofield *et al*²² and also confirm their sugges-

tion that treadmill exercise test is a useful 'stress test' for gastro-oesophageal reflux.

Of the 32 syndrome X patients in this study, 21 (66%) patients had evidence of either oesophageal motility disorder, or gastro-oesophageal reflux disease, or both. As this is the first study to use strictly characterised syndrome X patients which involved both oesophageal manometry studies and 24-hour pH monitoring, no other studies are available for comparison. In the study of Schofield *et al*¹⁵ 60% of patients with chest pain and normal coronary angiograms had evidence of oesophageal motility or reflux disorder. However, exercise test details are not given and many patients may not have had syndrome X.

SYNDROME X AND CORONARY FLOW RESERVE

An abnormal coronary flow reserve (<3.0) was present in 13 (41%) of the 32 patients. There was no significant difference in the prevalence of oesophageal disorders in patients with impaired or normal coronary flow reserve. Also, 26 (81%) of the 32 syndrome X patients in this study had either an abnormal coronary flow reserve or an oesophageal abnormality. These findings are similar to those reported by Cannon *et al*.¹⁷ In their study, a pathophysiological basis for chest pain could be ascribed to coronary microvascular, oesophageal motility dysfunction, or acid reflux in 85% of patients. Our study also confirms the heterogeneous nature of syndrome X.

The resting coronary flow velocity was significantly higher in the group of patients with an abnormal coronary flow reserve (table 2). The peak coronary flow velocity was lower in this group but the difference was not statistically significant. Studies using positron emission tomography have reported that resting coronary flow is increased in syndrome X patients, suggesting that the reduction in flow reserve is related to an increase in resting myocardial perfusion as opposed to the maximal perfusion available during stress.^{23,24} However, in a large controlled study of 53 syndrome X patients an impaired flow reserve to papaverine was reported while there was no significant difference in coronary flow velocity and calculated coronary blood flow between the two groups.¹¹

An impaired coronary flow reserve has been reported in syndrome X by several investigators using different methodologies.^{4,11} A reduced coronary reserve in conjunction with the presence of angina and electrocardiographic changes closes the loop of the classical ischaemic cascade and supports the presence of myocardial ischaemia in syndrome X. However, it is clear from most studies that a significant number of syndrome X patients do not have abnormalities of coronary flow reserve and may have other underlying pathophysiological mechanisms as a cause of their pain. Abnormal pain perception,²⁵ increased sympathetic tone,²⁶ insulin resistance,²⁷ an abnormal microvascular endothelial function,^{28,29} and significant reduction in coronary blood flow on hyperventilation and mental stress³⁰ have all been reported in syndrome X.

SYNDROME X AND 'LINKED ANGINA'

Clinicians have long suspected that oesophageal disease may aggravate myocardial ischaemia. Smith and Papp, coined the term 'linked angina' which implies that gastrointestinal factors can bring on attacks of genuine angina in patients with established coronary artery disease.³¹ It has also been shown previously that oesophageal acid stimulation can produce typical angina in syndrome X patients which is associated with a reflex decrease in coronary blood flow.³² The high prevalence of oesophageal abnormalities in syndrome X raises the possibility that myocardial ischaemia may occur as a result of 'linked angina'. This may be of particular importance in patients who have an impaired coronary flow reserve.

Conclusions

The findings of our study suggest that an impaired coronary flow reserve, abnormal oesophageal motility, or gastro-oesophageal reflux disease may provide a pathophysiological basis for chest pain in over 80% of the

Summary/learning points

- 10–30% of patients undergoing diagnostic cardiac catheterisation for the investigation of chest pain have normal coronary arteries
- over 40% of these patients may have an impaired coronary flow reserve
- over 60% of syndrome X patients may have abnormalities of oesophageal function
- an impaired flow reserve or oesophageal dysfunction may be present in over 80%
- anti-ischaemic therapy may help patients with microvascular dysfunction
- if patients remain symptomatic oesophageal dysfunction should be sought and treated
- possibility of 'linked-angina' should be remembered

Box 3

syndrome X patients investigated in this study, thus highlighting the heterogeneous nature of this syndrome.

Dr A Chauhan was supported by a British Heart Foundation Junior Research Fellowship.

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