Continuous recording of coronary sinus oxygen saturation during atrial pacing in patients with coronary artery disease or with syndrome X

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SUMMARY Coronary sinus oxygen saturation was measured continuously during incremental atrial pacing in 34 patients undergoing cardiac catheterisation. In eleven patients with normal coronary arteriograms, negative exercise tests, and no ST segment depression on the electrocardiogram, an increase in the rate of atrial pacing transiently decreased coronary sinus oxygen saturation but within 20 s oxygen saturation returned to the control value. In six patients with coronary artery disease ST segment depression developed during atrial pacing. The coronary sinus oxygen saturation fell and remained reduced until pacing was discontinued. The size of the fall of coronary sinus oxygen saturation increased with increasing heart rate. In seven patients with coronary artery disease the ST segments were unaltered during atrial pacing and coronary sinus oxygen saturation did not fall. Ten patients with syndrome X were studied. In six ST segment depression developed on atrial pacing. In five, three of whom developed ST segment depression, the changes in coronary sinus oxygen saturation during atrial pacing were similar to those observed in patients without any evidence of coronary artery disease. In three, all of whom developed ST segment depression, coronary sinus oxygen saturation gradually increased throughout the period of atrial pacing. In two patients coronary sinus oxygen saturation fell in a manner similar to that observed in patients with obstructive coronary artery disease who developed ST segment depression on pacing.

Thus regulation of coronary blood flow in normal persons in response to an increase of heart rate is rapid. Oxygen extraction across the coronary bed can increase by up to 30% and a persistent increase in oxygen extraction is an indicator of myocardial ischaemia. The term "syndrome X" does not describe a homogeneous group of patients but in the majority coronary sinus oxygen saturation does not fall despite symptoms and changes on the electrocardiogram, indicating that inadequate coronary blood flow is not the dominant mechanism.

The heart is critically dependent on aerobic metabolism.¹ Oxygen extraction at rest is >55% so that a substantial increase of oxygen supply can only be brought about by an increase of coronary blood flow. Coronary blood flow can increase five times whereas oxygen extraction can increase by only a half. Although the relation between changes in coronary blood flow and myocardial oxygen consumption has been extensively investigated in animals,² less is known about the timing of these changes in people.

Myocardial ischaemia develops when myocardial

consumption of adenosine triphosphate exceeds the rate of production possible from the oxygen available in coronary blood³ and is initially characterised by increased glycogenolysis and lactate production. This usually occurs when myocardial work is increased and blood flow is limited by obstructive atheromatous coronary artery disease. More rarely ischaemia can result from a primary reduction of coronary blood flow caused by coronary constriction.⁴ Myocardial ischaemia caused by atheromatous obstructive coronary artery disease is recognised clinically by angina pectoris, changes on the electrocardiogram, and the presence of reversible abnormalities of wall motion.

Some patients with angina pectoris have positive

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exercise tests and normal coronary angiograms.⁵⁻⁷ The term syndrome X is used to describe this group.⁸ The pathophysiological mechanisms underlying syndrome X are not understood.

This study was designed to investigate the relation between changes in coronary sinus oxygen saturation during atrial pacing in patients with normal hearts, coronary artery disease, or syndrome X.

Patients and methods

PATIENTS

The table shows the three groups of patients that we studied.

Group 1 consisted of eleven patients (seven men and four women, aged 39–59 years). They had recurrent atypical chest pain not responsive to nitroglycerin, normal electrocardiograms, and negative exercise tests. Echocardiograms were normal. They were undergoing cardiac catheterisation to exclude organic heart disease as a cause of their symptoms.

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After investigation these patients were believed to be entirely free of any form of heart disease and thus constituted a control group of patients with normal hearts.

Group 2 consisted of thirteen patients, all men, aged 39–67 years. They had typical angina pectoris on exertion and 10 had positive treadmill exercise tests (>1 mm planar or downsloping ST segment depression 0.8 ms after the J point). All had clinically significant stenosis (>70% reduction of diameter) of the left anterior descending coronary artery. Two had additional disease of the circumflex artery and the remaining eleven had three vessel coronary artery disease. No patient had had a myocardial infarction and there was no evidence of left ventricular hypertrophy on echocardiography.

Group 3 consisted of ten patients (five men and five women, aged 39–63 years) with exertional chest pain relieved by rest and nitroglycerin. On treadmill exercise all developed chest pain typical of angina. Nine had normal resting electrocardiograms. On

Table Data on patients in the study

Patient	Age (yr)	Sex	Treatment	Exercise test*	Coronary artery disease†
1	44	M		—	N
2	58	M	N	—	N
3	40	M	BN	—	N
4	44	F		—	N
5	39	F		—	N
6	47	M		—	N
7	43	M	B	—	N
8	59	F	BC	—	N
9	53	F		—	N
10	33	M		—	N
11	39	M		—	N
12	52	M	B	+	LC
13	53	M	BC	+	LCR
14	67	M	BC	+	LCR
15	57	M	B	+	LCR
16	57	M		—	L
17	55	M	BC	+	LCR
18	56	M		—	LC
19	45	M	B	—	L
20	63	M		+	LCR
21	46	M	BCN	+	LCR
22	59	M		+	LCR
23	47	M	BN	+	LCR
24	39	M		+	LCR
25	58	F		+	N
26	47	F		LBBB	N
27	53	M		+	N
28	39	F		+	N
29	51	M		+	N
30	48	M		+	N
31	47	F	BC	+	N
32	52	M		LBBB	N
33	55	M		+	N
34	63	F		+	N

B, β -blocker; N, nitrate; C, calcium antagonist.

*—, no ST segment changes; +, ST segment depression. LBBB, left bundle-branch block; †N, normal coronary arteries; disease in left anterior descending, L; left circumflex, C; or right, R, coronary arteries. HR, heart rate, CSO₂, coronary sinus oxygen saturation.

exercise eight of these developed ST segment depression in at least one precordial lead and one developed left bundle branch block. One patient had left bundle branch block at rest but developed typical chest pain on exercise. All had normal coronary arteries. Chest x rays and left ventriculograms were normal. Echocardiography showed normal cardiac dimensions, normal valves, and no hypertrophy. Seven patients had ergometrine provocation studies at cardiac catheterisation and these did not show evidence of focal coronary constriction.

PROTOCOL

All patients were undergoing routine diagnostic cardiac catheterisation at the time of the study. They were premedicated with lorazepam (1 mg) one hour before catheterisation.

An optical fibre oxygen saturation catheter (7.5 Opticath, Oximetrix, California, USA) was inserted into the left subclavian vein and placed approximately 4 cm into the coronary sinus under fluoroscopic control. The position was checked by

injection of a small quantity of radiographic contrast medium (Urografin 370). Coronary sinus oxygen saturation was measured optically by a spectrophotometric catheter oxygen saturation system (Oximetrix Inc, California, USA) and recorded continuously. A pacing electrode was inserted into the right atrium either from the left subclavian or right femoral vein. An incremental atrial pacing test⁹ was performed after recording the 12 lead surface electrocardiogram. Heart rate was increased from 20 beats per minute above the resting rate by 10 beats per minute at one minute intervals. Pacing was performed for the first 50 s of each minute period, and during the last 10 s a 12 lead electrocardiogram was recorded in sinus rhythm. The pacing test was continued until a maximum heart rate of 180 beats per minute had been reached, until the development of severe chest pain, or until ST segment depression >2 mm or atrioventricular block occurred. Right ventricular pacing was performed in four patients from group 1 and in seven from group 2 according to the same protocol.

Atrial pacing test*

Heart rate (beats/min)		Systolic BP (mm Hg)		CSO ₂ (%)		ST segment changes
Basal	Maximum	Basal	At maximum heart rate	Basal	At maximum heart rate	
Group 1						
90	180	140		38	40	—
60	140	140	155	30	29	—
75	120	120	118	24	24	—
55	120	140	150	41	42	—
90	180	135	148	34	34	—
61	150	128		44	40	—
85	170	140	152	33	36	—
64	140	100	110	22	25	—
81	180	140	158	33	32	—
79	160	130		19	20	—
74	170	130		34	34	—
Group 2						
61	160	135	150	42	38	—
70	100	125	120	31	30	—
86	110	140	140	34	35	—
61	110	135	160	32	24	+
63	150	120		28	28	—
75	170	115	120	28	26	—
71	140	100	100	40	40	—
73	150	125	150	43	42	—
72	140	130		29	18	+
68	140	125		33	24	+
70	160	130		41	10	+
81	160	130		31	14	+
89	180	135		30	14	+
Group 3						
72	170	110	135	40	46	+
64	170	135	140	31	16	LBBB
71	180	128	142	40	59	+
80	170	120	125	22	32	+
60	180	110	115	51	50	+
72	180	130	135	22	20	+
70	180	110	120	35	35	—
68	150	115	125	20	19	LBBB
69	120	132	130	30	15	—
62	140	135		26	26	+

Patients subsequently underwent coronary angiography and left ventriculography by either the Judkins' or Sones' technique. All results are expressed as mean (SEM).

Results

The table shows the details of individual patients.

Group 1

Figure 1 shows a recording of changes in coronary sinus oxygen saturation in a patient from this group undergoing atrial pacing. Mean resting heart rate was 74 (4) beats per minute (range 55 to 90) and resting coronary sinus oxygen saturation was 32 (2)% (range 19–44%). With each incremental increase in heart rate there was an initial drop in coronary sinus oxygen saturation but within 20 s it returned to the basal value (fig 1). When atrial pacing was stopped there was a rapid transient rise in coronary sinus oxygen saturation; this fell abruptly when pacing was restarted. At the end of each increase in atrial pacing coronary sinus oxygen saturation was similar to the basal level (fig 1). The maximum incremental increase in heart rate that could be achieved before the onset of atrioventricular block varied from 45 to 100 beats per minute. Resting systolic blood pressure did not change throughout the atrial pacing test (131 (4) basal and 142 (7) mmHg at maximum heart rate). Four patients underwent right ventricular pacing to a heart rate 80 beats per minute above the resting rate. Despite a fall in systolic blood pressure from a basal level of 131 (4) to 110 (6) mmHg ($p < 0.05$) at the maximum heart rate, coronary sinus oxygen saturation changes were similar to those seen during atrial pacing. Transient depression of the ST segments of the electrocardiogram was seen in two patients after the end of pacing.

Group 2

We saw variable responses in this group of thirteen

Fig 1 Coronary sinus oxygen saturation during an incremental atrial pacing test in a patient believed to have a normal heart. Note that the saturation remained almost constant. At higher pacing rates there was a small and transient decline of saturation after the onset of pacing.

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patients. Six patients who had positive exercise tests developed pain and significant ST segment depression on atrial pacing. Figure 2 shows the response from one such patient. At heart rates up to 20–30 beats per minute above the basal rate the changes in coronary sinus oxygen saturation were similar to those seen in the control subjects. When pacing was performed at heart rates of ≥ 40 beats per minute above the resting rate, however, a different response was seen. Coronary sinus oxygen saturation rapidly fell at the onset of atrial pacing and in contrast with the control subjects in group 1 it remained significantly below the resting value until the end of atrial pacing. Oxygen extraction increased with increasing heart rate (fig 2). In seven patients significant ST segment depression did not develop during atrial pacing. In two of these seven patients, atrioventricular block developed at heart rates of 100 and 110 beats per minute. The remaining five patients, three of whom had negative exercise tests, were paced to similar heart rates as the six in whom ST segment depression did develop, but the changes in coronary sinus oxygen saturation were similar to those observed in normal subjects (group 1). There was no change in systolic blood pressure during the atrial pacing test (125 (5) basal and 134 (8) at the end of atrial pacing, $n = 7$).

In the seven patients without ST segment depression during atrial pacing right ventricular pacing was performed to a heart rate of 180 beats per minute. In contrast with the control group there was a sustained fall in coronary sinus oxygen saturation which persisted until the end of pacing. The fall in coronary sinus oxygen saturation increased with increasing heart rates. Systolic blood pressure at the maximum pacing rate was significantly lower during ventricular pacing than during atrial pacing (90 (7) vs 136 (9) ($p < 0.05$, $n = 6$)).

Group 3

The ten patients in this group were atrially paced to

Fig 2 Coronary sinus oxygen saturation in a patient with atheromatous obstructive coronary artery disease. The saturation fell after the onset of pacing and the fall was greater at higher heart rates.

heart rates of between 120 and 180 beats per minute (mean 164 (21)). In five of these patients the changes in coronary sinus oxygen saturation were identical to those observed in the control subjects; three of these five patients developed >1 mm ST segment depression during atrial pacing. In three other patients, all of whom developed ST segment depression, a different response was observed in that the coronary sinus oxygen saturation at the end of atrial pacing was higher than the resting value (fig 3). This increase varied between 6% and 20%. Two patients showed a response which was similar to that seen in the group 2 patients who developed myocardial ischaemia during atrial pacing. One of these patients had left bundle branch block at rest and the other had a normal resting electrocardiogram and developed ST segment depression on exercise testing (fig 4). This patient was severely limited by angina pectoris and he consistently developed pain on minimal exercise and when paced at only 10 beats per minute above his resting rate. Inspection of fig 4 shows that coronary sinus oxygen saturation fell and remained low throughout each increment of atrial pacing. The maximum heart rate that could be attained before severe chest pain terminated the test was 120 beats per minute and ST segment changes were not observed. Evaluation of ST segment changes in the first of these two patients was not possible because of the presence of bundle branch block.

Discussion

Coronary sinus oxygen saturation was recorded during and after atrial pacing in patients with normal hearts, coronary artery disease, or syndrome X. A fiberoptic method was used to measure oxygen saturation. The method depends on the illumination of blood by light at three selected frequencies and the sensing of the reflected light at these frequencies. The output of the analyser gave a mean for data collected over a 5 s interval. The accuracy, reliability,

Fig 3 Coronary sinus oxygen saturation in a patient with syndrome X. The saturation never fell below the control value and the mean rose during the test. At higher heart rates the saturation fell substantially at the onset of pacing.

Fig 4 Coronary sinus oxygen saturation in a patient with syndrome X. The pattern observed in this patient is similar to that in patients with obstructive coronary artery disease.

and stability of the recording system have been reported previously.¹⁰ The method avoids the errors that might arise from intermittent sampling and allows rapid changes of saturation to be followed accurately. The necessity of following continuously oxygen saturation is evident from inspection of figs 1-4.

When any variable is measured in the coronary sinus it must be remembered that the blood originates from different regions of the heart and that mixing may be incomplete. This is of particular importance when changes are measured during atrial pacing in patients with coronary artery disease. Parts of the myocardium may be rendered ischaemic whereas others are not. The relative blood flow from the two regions changes during atrial pacing and if mixing is incomplete the size of the change in oxygen saturation in the coronary sinus may be less than that if only blood from the ischaemic region had been sensed. To minimise these problems we selected patients who had left anterior descending coronary artery disease and placed the sensing catheter 4 cm into the coronary sinus.

We used atrial pacing to increase cardiac work.⁹ The development of chest pain during atrial pacing has been reported as being non-specific for ischaemia.¹¹ None of our control patients experienced chest pain during atrial pacing whereas eight out of 13 patients with coronary artery disease did. During atrial pacing the ST segment was depressed in only six of the 13 and there was no ST segment depression in the control patients. Thus in our hands atrial pacing is a relatively insensitive means of detecting coronary artery disease as determined by ST segment depression or chest pain but is specific when a positive result is obtained. Similar findings have been reported by others and appear to be largely the result of an inability to pace at a rate sufficient to induce myocardial ischaemia before atrioventricular block occurs. Right ventricular pacing can be performed, but the interpretation of

the electrocardiogram immediately after the end of pacing is complicated by persisting abnormalities of repolarisation or ischaemia caused by the fall of blood pressure and perfusion pressure in the coronary circulation. In the present study right ventricular pacing of four control patients resulted in transient ST segment depression in two whereas all seven patients with coronary artery disease developed ST segment depression.

Coronary blood flow and arterial oxygen saturation were not measured in this study, but in animals^{12 13} and people^{14 15} atrial pacing has been shown to increase coronary flow in normal myocardium but decrease flow in myocardium whose coronary arteries are severely obstructed by atheroma. In our study in patients with what finally were considered to be normal hearts, an increment in pacing rate was accompanied by a transient fall of saturation lasting approximately 15 s. The saturation then returned to the control value and on cessation of pacing the reverse sequence was observed. An increased heart rate increases the myocardial work and initially oxygen extraction increases. After 15 s, vasodilatation of the coronary bed occurs so that the venous saturation returns to normal and the increased oxygen consumption is provided by an increase of flow. Such rapid adjustments to coronary flow have previously been demonstrated in animals, where an increase of coronary flow can be demonstrated after a single added beat.¹⁶ In dogs an increase of heart rate increases myocardial work and coronary blood flow so that coronary sinus oxygen is unchanged.¹³ These observations are entirely compatible with the rapid metabolic control of coronary flow.¹⁷ In individual normal patients the coronary sinus oxygen saturation in the steady state remained almost constant at a mean value of approximately 32%. The reason why this should be so is not clear but an oxygen saturation of 32% may represent the minimal value for optimum transport of oxygen into the cell.

The response to atrial pacing in patients with atheromatous obstructive coronary artery disease was similar to that in controls in the absence of ST segment depression or chest pain. In patients who developed chest pain or ST segment depression on the electrocardiogram, the coronary sinus oxygen saturation fell after an increment in pacing rate and then remained at a reduced value. The reduction of the saturation increased at higher rates of pacing. The earliest changes of saturation preceded the development of chest pain or changes on the electrocardiogram, as has been reported previously when chest pain was precipitated by vasoconstriction.⁴ The probable explanation for these observations is that oxygen extraction increases after an increment

in pacing but that an increase of coronary flow is not possible because flow is limited by stenoses in large coronary arteries in the presence of an almost maximally dilated distal vascular bed. If ischaemia is defined as occurring when myocardial adenosine triphosphate consumption exceeds the rate of adenosine triphosphate production that is possible from the oxygen available in coronary blood, then the presence of oxygen extraction greater than that which occurs in normal individuals demonstrates the presence of myocardial ischaemia. A maintained reduction of the coronary sinus oxygen saturation in the presence of increased myocardial work was associated with other indicators of ischaemia. This observation reinforces the idea that active control mechanisms maintain the coronary sinus oxygen saturation at a value of approximately 32%.

The term "syndrome X" has been used to describe very different groups of patients.^{5-8 18-33} For the purposes of this study syndrome X was defined as a clinical syndrome consisting of angina pectoris, normal coronary arteriograms, and a positive exercise test. The inclusion of a positive exercise test in the definition is crucial. We have included two patients with heart block because although the exercise electrocardiograms could not be interpreted the patients developed reproducible and typical angina pectoris on the treadmill. Many studies of patients with chest pain and normal coronary arteries have not required a positive exercise test. The exercise test has been reported as positive in only a proportion of patients, for example 12/19,⁶ 2/50,³³ 2/26,¹⁸ 1/6,²⁴ 1/7,²⁵ 19/19,²¹ and 2/13.³¹ If this requirement is omitted then more patients will be included who have genuinely non-cardiac reasons for chest pain, such as oesophageal disease^{31 32} or musculoskeletal abnormalities.³¹ The differing characteristics of patients admitted to studies of patients with normal coronary angiograms almost certainly account for the widely differing frequency of oesophageal disease and ventricular dysfunction.

Many mechanisms for syndrome X have been put forward including impaired coronary vasodilator reserve,^{6 7} disease of small vessels (disease of vessels beyond the resolution of coronary angiography),^{24 28} epicardial-endocardial redistribution of blood flow,²⁶ and myocardial cell abnormalities.^{6 25} Disease of small vessels has been shown only in patients with evidence of cardiomyopathy, hypertrophy, decreased ventricular compliance, and negative exercise tests.²⁴ That patients with syndrome X develop myocardial ischaemia is suggested by the demonstration of perfusion defects²² and ventricular wall motion abnormalities on exercise¹⁹ although others, in differently defined groups of patients, have been unable to show a change in left

ventricular function by continuous monitoring of pulmonary end diastolic pressure.²³ The presence of ischaemia has also been claimed because changes of the ST segment were detected during 24 h monitoring of the electrocardiogram.²¹ Equating ST segment changes with myocardial ischaemia is as yet unjustified, except in patients with known coronary artery disease and angina pectoris.³⁴ ST segment changes are common in patients with cardiomyopathy, hypertrophy, or on treatment with digoxin. The ST segment may alter on exercise or over 24 h in a substantial proportion of apparently normal persons.³⁵ ST segment changes are not therefore always synonymous with myocardial ischaemia, and even left ventricular dysfunction does not necessarily imply ischaemia since there are many other mechanisms for such abnormalities.

We measured the coronary sinus oxygen saturation in ten patients with syndrome X. All except two developed ST segment changes on the exercise test. One of these had left bundle branch block at rest. The other developed left bundle branch block on exercise. Both had typical and reproducible chest pain on exercise. No patient was diagnosed as having overt cardiomyopathy and none had hypertrophy of the myocardium. In two out of the ten patients with syndrome X the coronary sinus oxygen saturation changed with a pattern similar to that observed in patients with known atheromatous coronary artery disease. Since the coronary angiograms were normal these patients may either have had vasoconstriction on exercise³⁶ and atrial pacing or have disease of the small vessels. In the other eight patients coronary sinus oxygen never fell and in three it rose. Since six out of eight of these patients had changes on the electrocardiogram and chest pain similar to the group of patients with known coronary artery disease it is difficult to argue that these patients had myocardial ischaemia in the sense defined above. It is conceivable that the endocardium became ischaemic and the epicardium was abundantly perfused so that the mixed venous blood in the coronary sinus had a normal oxygen saturation. Such a phenomenon would be a form of "steal" except that the epicardial bed would have an excessive flow and a high venous oxygen saturation. If that were the explanation then ventricular dysfunction should be evident on exercise and in the majority of these patients no abnormality of ventricular function has been described.²³

Alternative mechanisms may account for syndrome X. The syndrome could be caused by an increased retention of potassium in the extracellular space between cells.³⁷ Potassium is lost from the normal heart as heart rate increases³⁸ and in response to other stimuli. If this potassium could

not freely exchange with the vasculature, potassium would accumulate and bring about the changes on the electrocardiogram that the physician might mistakenly interpret as ischaemia.³⁹ A rise of extracellular potassium concentration can largely account for the change in the configuration of the action potential^{40 41} and by causing the depolarisation of pain sensors it could account for the onset of chest pain. The reason for the accumulation of potassium in the tissue may be minor changes of anatomy as presumably are present in hypertrophied myocardium or in the cardiomyopathic heart where ST segment depression is known to occur on exercise in the absence of obstructive coronary disease.

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References

- 1 Berne RM, Rubio R. Coronary circulation. In: Berne RM, ed. *Handbook of physiology. Vol. 1, sect 2 The cardiovascular system*. Bethesda, Maryland: American Physiological Society, 1979:873-952.
- 2 Marcus ML. *The coronary circulation in health and disease*. New York: McGraw-Hill, 1983.
- 3 Poole-Wilson PA. Angina—pathophysiological mechanisms; clinical expression and treatment. *Postgrad Med J* 1983;59(suppl 3):11-21.
- 4 Chierchia S, Brunelli C, Simonetti I, Lazzari M, Maseri A. Sequence of events in angina at rest, primary reduction in coronary flow. *Circulation* 1980;61:759-68.
- 5 Arbogast R, Bourassa MG. Myocardial function during atrial pacing in patients with angina pectoris and normal coronary arteries. Comparison with patients having significant coronary artery disease. *Am J Cardiol* 1973;32:257-63.
- 6 Opher 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.
- 7 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.
- 8 Kemp HG, Elliot WC, Gorlin R. The anginal syndrome with normal coronary arteriography. *Trans Assoc Am Physicians* 1967;80:59-70.
- 9 Sowton GE, Balcon R, Cross D, Frick MH. Measurement of the angina threshold using atrial pacing: a new technique for the study of angina pectoris. *Cardiovasc Res* 1976;1:301-7.
- 10 Poole-Wilson PA, Canepa-Anson R. Continuous measurement of coronary sinus O₂ saturation as a method for detecting coronary artery disease. In: Schweiss

- JP, ed. *Continuous measurement of blood oxygen saturation in the high risk patient*. San Diego: Berch International, 1985:59–65.
- 11 Markham RV, Winniford MD, Firth BG, *et al*. Symptomatic, electrocardiographic, metabolic and haemodynamic alterations during pacing induced myocardial ischaemia. *Am J Cardiol* 1983;51:1589–94.
 - 12 Selwyn AP, Allan RM, L'Abbate A, *et al*. Relation between regional myocardial uptake of rubidium-82 and perfusion: absolute reduction of cation uptake in ischaemia. *Am J Cardiol* 1982;50:112–21.
 - 13 Macho P, Hintze TH, Vatner SF. Regulation of large coronary arteries by increase in myocardial metabolic demands in conscious dogs. *Circ Res* 1981;49:594–9.
 - 14 Selwyn AP, Forse G, Fox K, Jonathan A, Steiner R. Patterns of disturbed myocardial perfusion in patients with coronary artery disease. Regional myocardial perfusion in angina pectoris. *Circulation* 1981;64:83–90.
 - 15 Remme WJ, Van den Berg R, Mantel M, *et al*. Temporal relation of changes in regional coronary flow and myocardial lactate and nucleoside metabolism during pacing-induced angina. *Am J Cardiol* 1986;58:1188–94.
 - 16 Schwartz GG, McHale PA, Greenfield JC. Coronary vasodilation after a single ventricular extra-activation in the conscious dog. *Circ Res* 1982;50:38–46.
 - 17 Olsson RA, Bunker R. Metabolic control of coronary blood flow. *Prog Cardiovasc Dis* 1987;29:369–87.
 - 18 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.
 - 19 Schoffield PM, Brooks NH, Bennett DH. Left ventricular dysfunction in patients with angina pectoris and normal coronary angiograms. *Br Heart J* 1986;56:327–33.
 - 20 Legrand V, Hodgson JM, Bates ER, *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.
 - 21 Kaski JC, Crea F, Nihoyannopoulos P, Hackett D, Maseri A. Transient myocardial ischaemia during daily life in patients with syndrome X. *Am J Cardiol* 1986;58:1242–7.
 - 22 Meller J, Goldsmith SJ, Rudin A, *et al*. Spectrum of exercise thallium-201 myocardial perfusion imaging in patients with chest pain and normal coronary angiograms. *Am J Cardiol* 1979;43:717–23.
 - 23 Levy RD, Shapiro LM, Wright C, Mockus L, Fox KM. Syndrome X: the haemodynamic significance of ST segment depression. *Br Heart J* 1986;56:353–7.
 - 24 Mosseri M, Yarom R, Gotsman MS, Hasin Y. Histologic evidence for small-vessel coronary artery disease in patients with angina pectoris and patent large coronary arteries. *Circulation* 1986;74:964–72.
 - 25 Richardson P, Livesley B, Oram S, Olsen E, Armstrong P. Angina pectoris with normal coronary arteries. Transvenous myocardial biopsy in diagnosis. *Lancet* 1974;ii:677–80.
 - 26 Epstein SE, Cannon RO. Site of increased resistance to coronary flow in patients with angina pectoris and normal epicardial coronary arteries. *J Am Coll Cardiol* 1986;8:459–61.
 - 27 James TN. Pathology of small coronary arteries. *Am J Cardiol* 1967;20:679–91.
 - 28 Eliot RS, Bratt G. The paradox of myocardial ischaemia and necrosis in young women with normal coronary arteriograms. Relation to abnormal haemoglobin-oxygen dissociation. *Am J Cardiol* 1969;23:633–8.
 - 29 Mammohansingh P, Parker JO. Angina pectoris with normal coronary arteriograms: haemodynamic and metabolic response to atrial pacing. *Am Heart J* 1975;90(suppl 5):555–61.
 - 30 Dwyer E, Wiener L, Cox J. Angina pectoris in patients with normal coronary angiograms. Haemodynamic and clinical aspects. *Am J Cardiol* 1969;23:639–46.
 - 31 Dart AM, Davies A, Lowndes RH, Dalal J, Ruttley M, Henderson AH. Oesophageal spasm and angina: diagnostic value of ergometrine (ergonovine) provocation. *Eur Heart J* 1980;1:91–5.
 - 32 Dart AM, Davies A, Dalal J, Ruttley M, Henderson AH. "Angina" and normal coronary arteriograms: a follow-up study. *Eur Heart J* 1980;1:97–100.
 - 33 Cannon RO, Leon MB, Watson RM, Rosing DR, Epstein SE. Chest pain and "normal" coronary arteries—role of small coronary arteries. *Am J Cardiol* 1985;55:50B–60B.
 - 34 Deanfield JE, Shea M, Ribiero P, *et al*. Transient ST-segment depression as a marker of myocardial ischemia during daily life. *Am J Cardiol* 1984;54:1195–200.
 - 35 Quyyumi AA, Wright C, Fox K. Ambulatory electrocardiographic ST segment changes in healthy volunteers. *Br Heart J* 1983;50:460–4.
 - 36 Gage JE, Hess OM, Murakami T, Ritter M, Grimm J, Kravenbuehl HP. Vasoconstriction of stenotic coronary arteries during dynamic exercise in patients with classic angina pectoris: reversibility by nitroglycerin. *Circulation* 1986;73:865–76.
 - 37 Poole-Wilson PA. Potassium and the heart. In: Morgan DB, ed. *Clinics in endocrinology and metabolism*. London: WB Saunders, 1984: Vol 13, No. 2: 249–68.
 - 38 Webb SC, Poole-Wilson PA. Potassium exchange in the human heart during atrial pacing and myocardial ischaemia. *Br Heart J* 1986;55:554–9.
 - 39 Webb SC, Canepa-Anson R, Rickards AF, Poole-Wilson PA. High potassium concentration in a parenteral preparation of glyceryl trinitrate. Need for caution if given by intracoronary injection. *Br Heart J* 1983;50:395–6.
 - 40 Weiss J, Shine KI. Extracellular potassium accumulation during myocardial ischemia: implications for arrhythmogenesis. *J Mol Cell Cardiol* 1981;13:699–704.
 - 41 Boyett MR, Fedida D. A simple model of ion concentration changes in the heart during repetitive activity. *J Physiol (Lond)* 1983;342:52P–3P.