Different mechanisms for the relief of angina after coronary bypass surgery

Physiological versus anatomical assessment

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SUMMARY To determine the physiological effect of coronary artery bypass surgery and the mechanisms for pain relief, 15 patients with exertional angina were studied before and after operation. Before the operation conventional tests included exercise tests (all positive) and coronary angiography (all patients had $\geq 70\%$ stenosis of major vessels). In addition, ambulatory electrocardiographic monitoring during 48 hours detected 92 episodes (≥ 1 mm) of ST depression. Regional myocardial perfusion was assessed with positron tomography using rubidium-82 ($t_{1/2}$ 78 s) and this showed reversible inhomogeneity with absolute regional reduction of cation uptake after exercise in all 15 patients. After coronary surgery 10 of the 15 patients had (a) no angina, (b) patent grafts (three or more), (c) no evidence of ischaemia during ambulatory monitoring out of hospital, and (d) homogeneous perfusion with reversal of the disturbances in regional myocardial perfusion after exercise. After operation one of the 15 patients had no angina and showed silent infarction in the segment that was previously ischaemic but supplied by a patent graft. All but one of the remaining patients had no angina, patent grafts, but disturbances of regional myocardial perfusion with silent ischaemia on exercise. Two of these patients continued to have asymptomatic and ischaemic episodes of ST depression during ambulatory monitoring out of hospital. This physiological study of regional myocardial perfusion in patients in hospital and in those with ischaemia out of hospital showed that three different mechanisms may account for the relief of pain—improved perfusion, infarction, and silent ischaemia. Silent ischaemia in particular raises puzzling pathophysiological and therapeutic questions that may affect prognosis and the interpretation of clinical trials.

Coronary artery bypass surgery relieves angina in most patients.^{1,2} Its long term effects on morbidity and mortality are, however, variable and are still being argued.^{2,3} In addition, the mechanism of symptomatic improvement and the physiological results still remain controversial and are difficult to assess in each patient.^{4,5} Relief of angina and exercise capacity correlate poorly with normalisation of exercise tests and graft patency.^{6,7} Although the graft patency is regarded as the gold standard of successful revascularisation,⁸ it does not provide physiological information on the relief of transient ischaemia.

The purpose of this study was to determine physiologically the effects of coronary bypass graft surgery on ischaemia and angina in individual patients. In addition to conventional clinical characterisation and exercise testing, positron tomography was used to measure regional myocardial perfusion and ischaemia in hospital before and after surgery. Furthermore, the effects of coronary surgery on transient myocardial ischaemia were assessed by ambulatory ST segment monitoring of patients outside hospital. These physiological observations were compared with the anatomical data as defined by graft patency.

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Patients and methods

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patients (13 men and two women) were selected from 165 patients who had the following characteristics: (a) refractory angina resistant to medical treatment; (b) a positive standardised electrocardiographic exercise test (described below); and (c) angiographically confirmed coronary disease (described below). Their ages ranged from 36 to 72 (mean 55) years. Patients were receiving conventional medical treatment including long acting nitrates (n=11), beta blocking agents (n=12), and calcium antagonists (n=4). These medications were continued during all the investigations except ambulatory monitoring. Patients with heart failure were excluded. Seven patients had previous myocardial infarction. Nine patients were smokers (≥ 15 cigarettes per day for at least 20 years), six were hypertensive (blood pressure $\geq 165/90$ mm Hg), and six had serum cholesterol concentrations >6.5 mmol/l. None of the patients had signs of hyperlipidaemia.

Investigations included a detailed medical history, clinical examination, blood pressure measurements, electrocardiography, and chest radiography. Patients were selected for study if logistically they could undergo all the following tests during the two weeks before coronary bypass surgery and after the operation: (a) exercise testing according to the Bruce protocol (described below); (b) coronary angiography; (c) forty eight hour ambulatory monitoring of the ST segment; and (d) positron tomography using rubidium-82 (^{82}Rb) at rest and after supine exercise.⁹ The same tests were repeated two months after coronary artery bypass graft surgery (range 1–4 months) using the same protocol for each test. Cardiac catheterisation after operation also included selective graft injections and supravulvar aortography.

EXERCISE TESTING

Electrocardiographic exercise testing was performed before and after coronary artery bypass grafting using a symptom limited treadmill protocol described by Bruce *et al.*¹⁰ The electrocardiogram was continuously monitored in leads V4, V5, and V6 and a 12 lead electrocardiogram recorded at rest and at the end of each stage of exercise. Changes in the electrocardiograms were considered to be significant according to conventional criteria.¹¹ None of the patients was taking digoxin and none had electrocardiographic conduction defects. Systolic blood pressure was measured at rest and at the end of each stage using an arm cuff and sphygmomanometer. Physical work capacity was calculated and expressed in metabolic equivalents (oxygen consumption in ml/min kg^{-1}), and the heart rate was calculated at: (a) the onset of chest pain, (b) the onset of ST depression, and (c) maximum workload.

AMBULATORY MONITORING

Medications for angina were withdrawn gradually so that only glyceryl trinitrate was taken 48 hours before and during the period of ambulatory monitoring, except in three patients with severe angina. Recordings were obtained using a calibrated Oxford Medilog II tape recorder with a frequency modulated signal (1 mV=10 mm). A modified inferior lead and precordial lead were used, and one of them corresponded to the position of maximum ST depression found during the exercise test. Leads with pathological Q waves or significant resting ST segment depression were avoided, and control recordings were made in each patient in the supine, prone, standing, and sitting positions to ensure that the ST segment was not affected by body position. Patients were instructed to press an event button on the recording box if they experienced chest pain. Tapes were analysed visually at $60 \times$ real time with an Oxford Medilog II analyser. An episode of transient ST depression was defined as horizontal or downsloping ST segment depression of ≥ 1 mm for at least 80 ms and lasting one minute or more. Once an episode fulfilling these criteria was identified the time of onset and termination were recorded. The maximal ST change was noted. Visual analysis was checked against a strip chart recorder of heart rate and ST segment position (Oxford analyser, model Medilog II).

CARDIAC CATHETERISATION

Preoperative coronary angiography was performed by the Judkins's technique. Angiograms were interpreted independently by two experienced observers, and in case of disagreement a consensus was reached with a third. Lesions were classified visually as $<50\%$ (diameter stenosis), between 50 and 70%, and $>70\%$. The postoperative evaluation included selective injection of the proximal graft and supravulvar aortography. Grafts were considered to be occluded if the stump was visualised or was not seen from aortic root injection. Ejection fraction was calculated using a single plane adaptation of the area length method described by Dodge *et al.*¹²

POSITRON TOMOGRAPHY

Preparation of the $^{82}\text{Sr}/^{82}\text{Rb}$ generator has been described elsewhere.¹³ Each patient was positioned within a hexagonal ring of sodium iodide crystal detectors (ECAT, produced by Ortec) that were calibrated to detect positron radiation. A mid left ventricular position was selected. The external position was fixed in relation to the detector by a laser. Transmission scans were collected for later attenuation correction of emission data and reconstruction by computer into images with a 100×100 matrix. The generator and tubing were prepared using an aseptic

Table 1 Clinical data, angina status before and after coronary surgery, angiographic results, and graft patency

Case No	Age (yr) and sex	Previous infarct	LV angiogram	No of vessels diseased*	Angina (NYHA class)		No of patent grafts
					Before surgery	After surgery	
1	61M	—	I akinesia	3	II	I	4/4
2	47M	—	AS and A akinesia	3	III	I	0/4
3	57M	I	I akinesia	3	III	I	3/3
4	46M	A	AS akinesia	3	III	I	3/4
5	53M	—	A hypokinesia	3	II	I	3/4
6	61M	—	Normal	3	III	I	3/4
7	36F	—	Normal	2	II	I	3/3
8	56M	I	I akinesia	3	IV	I	3/4
9	61M	I	I akinesia	2	III	I	0/4
10	56M	—	Normal	3	IV	I	3/4
11	71M	I	I akinesia	3	IV	I	4/4
12	51M	I, AS	I akinesia	2	III	I	3/3
13	62F	—	Normal	3	III	III	2/3
14	55M	I	A and I akinesia	3	III	I	3/4
15	61M	—	Normal	3	III	I	3/4

I, inferior; AS, anteroapical; A, apical.

* >70% stenosis.

technique, and the infusate was filtered (Millex, 0.22 μ m, Millex SA). An 18 gauge needle was placed in the antecubital vein. Rubidium-82 (15 mCi (540 MBq) during steady state) was eluted in 10 ml/min of 0.9% sodium chloride solution and infused intravenously.⁹

At equilibrium the arterial concentration may be measured from a tomogram recorded during infusion and the myocardial concentration measured 30–150 ms after cessation of the intravenous infusion. The regional myocardial uptake ($\text{ml/g min}^{-1} \times \text{extraction}$) of ⁸²Rb may be calculated in each segment of myocardium¹⁰; a perfusion defect in a tomogram, after supine exercise, was defined as a $\leq 20\%$ decrease in rubidium uptake in any segment of myocardium or a $\leq 20\%$ difference between the segments showing the highest and the lowest measure of uptake and which

was reversible with a return to control values.⁹

Measurements of regional myocardial uptake of ⁸²Rb were recorded before, during, and after a standardised symptom limited supine bicycle exercise test. External work (joules), heart rate, systolic blood pressure, and a 12 lead electrocardiogram were measured before, during, and after each stage. Maximum workload achieved by the 15 patients ranged from 8400 to 31 800 J. This procedure was repeated using the same protocol in each patient after operation. Written informed consent was obtained before each study.

After coronary artery bypass graft surgery, care was taken to obtain the same tomographic level as before the operation. The postoperative transmission scans and myocardial scans at rest were compared with the preoperative scans.

Table 2 Results of ambulatory electrocardiographic monitoring before and after coronary bypass surgery showing the incidence of ST segment depression

Case No	Before coronary surgery			After coronary surgery		
	No of episodes	Total duration (min)	Heart rate (beats/min)*	No of episodes	Total duration (min)	Heart rate (beats/min)*
1	3	16	130	0	—	—
2	14	169	65–80	0	—	—
3	6	33	80–105	0	—	—
4	0	0	0	0	—	—
5	2	24	100	0	—	—
6	8	85	70–95	0	—	—
7	19	396	90–120	0	—	—
8	2	8	90–110	0	—	—
9	—	—	—	—	—	—
10	0	0	0	0	—	—
11	2	14	75–85	0	—	—
12	8	90	115–145	4	18	120–135
13	9	190	80–125	2	8	100–125
14	1	10	100	0	—	—
15	18	245	95–140	0	—	—
Mean	6.6(6.5)	91(118)	91–111	3	13	110–130

*Heart rate at onset of ST depression.

CORONARY SURGERY

The surgical technique consisted of a median sternotomy and institution of cardiopulmonary bypass with bubble oxygenator, hypothermia (27–30°C), and haemodilution (haematocrit 20–25%). Pump flow was maintained at 2.0 l/m². Cold potassium cardioplegia was used for myocardial preservation. Reversed parallel segments of saphenous veins were anastomosed to coronary arteries. Proximal anastomoses were placed on the aortic wall under partial aortic clamping and during rewarming of the patient. Each patient received either three or four grafts. A total of 56 grafts was performed, a mean of 3.7 grafts per patient. After operation patients were treated with aspirin and dipyridamole in addition to routine medication for hypertension (cases 9 and 11). The patient in case 13 required nitrates, beta blocking agents, and a calcium antagonist for angina. Complete revascularisation was defined as revascularisation of all vessels with >50% proximal coronary stenosis. Using these criteria complete revascularisation was achieved in all patients.

STATISTICAL ANALYSIS

Mean and standard deviation were calculated in the usual way. Paired *t* tests were used to test the difference between the means.

Results

CLINICAL DATA

Before coronary artery bypass grafting all 15 patients had exertional angina and positive exercise tests. After operation 14 patients were angina free (Table 1).

Fig. 1 Case 8: ambulatory electrocardiograms showing two episodes of ST segment depression, one painful (+) and one painless (-), before coronary surgery. After surgery no episode of ST depression was recorded even at higher heart rates.

EXERCISE TESTING

Before coronary artery bypass grafting all patients had positive exercise tests. Maximum workload achieved for the group as a whole increased from 7.3(2.2) mets before operation to 10.4(2.4) mets after the operation ($p < 0.003$) and maximum heart rate from 115(21) to 142(19) beats/min respectively ($p < 0.05$). Before operation workload at the onset of ST depression and chest pain was 5.4(1.5) mets and 7.3(2.2) mets respectively. Heart rate at the onset of ST depression and chest pain was 106(21) and 113(23) beats/min respectively. After operation 12 patients showed no ST segment depression or chest pain even at a higher workload and heart rate. Nevertheless, three patients (cases 12, 13, and 14) had persistent positive exercise tests at a slightly higher workload but with a similar heart rate at the onset of ST depression. The positive exercise tests in two patients (cases 12 and 14) were not accompanied by angina as before the operation,

Fig. 2 Case 12: ambulatory electrocardiograms (a) showing eight episodes of ST segment depression before coronary surgery; all eight episodes were accompanied by typical chest pain. (b) After operation four episodes of ST depression were recorded, but they were all painless (silent ischaemia). Note similar heart rates at the onset of ST segment depression in the episodes before (a) and after (b) operation.

whereas the patient in case 13 complained of angina during the test.

AMBULATORY MONITORING

Table 2 summarises the results before and after coronary artery bypass surgery. Before operation 92 episodes of significant ST depression were recorded: 40 of 1 mm, 37 of 2 mm, and 15 of ≥ 3 mm. Seventy eight per cent of episodes were painless. Furthermore, there were 15 episodes of chest pain without ST-T changes. After operation 13 patients had no episode of ST segment depression (Fig. 1). There were six episodes of ST depression in two patients with a similar heart rate at the onset of ST depression compared with before operation (Table 2). Postoperatively all the episodes in the patient in case 12 were painless (Table 2, Fig. 2a).

CARDIAC CATHETERISATION

Before coronary artery bypass grafting 12 patients had three vessel coronary stenosis ($\geq 70\%$) and three patients had a $\geq 70\%$ stenosis in two vessels and a 50% stenosis in the third (Table 1). In addition, two patients had left main stem strictures of $>50\%$ (cases 8 and 11). Before operation mean (SD) ejection fraction for the 15 patients was 55(6)%, which is not significantly different from the postoperative value of 55(10)%. Left ventricular end diastolic pressure was not changed after coronary surgery (15(4) mm Hg

before compared with 15(5) mm Hg after). The graft patency rate was 83%, and a mean of 3.1 grafts per patient were patent. After coronary bypass surgery graftgrams were not performed in two patients (cases 2 and 9), in one because of transient ischaemia.

POSITRON TOMOGRAPHY

Before coronary surgery

All 15 patients showed evidence of reversible regional ischaemia with exercise in serial tomograms with a return to control values after exercise (Table 3). The patients in cases 1–10 ($p < 0.005$) and those in cases 11–14 ($p < 0.02$) all showed a significant regional decrease in cation uptake after exercise (Table 3, Fig. 3). The exercise test during tomography produced angina and ischaemic ST segment changes in all patients before operation. In addition, seven patients had tomographic evidence at rest of myocardial infarction on serial tomograms (that is, $\geq 20\%$ regional reduction of ^{82}Rb at rest and unaffected by exercise or the operation). These defects correlated with electrocardiographic and angiographic evidence of myocardial infarction. Nevertheless, three patients with electrocardiographic and angiographic evidence of inferior myocardial infarction had normal resting tomograms as this did not include a tomographic slice of the inferior wall of the ventricle.

Table 3 Mean (SD) values before and after exercise for regional myocardial uptake of ^{82}Rb before and after coronary surgery

Case No	Before coronary surgery				Tomographic detection of ischaemia	After coronary surgery				Tomographic detection of ischaemia
	Before exercise		After exercise			Before exercise		After exercise		
	A†	B‡	A†	B‡		A†	B‡	A†	B‡	
1	0.49(0.02)	0.48	0.47(0.05)	0.39	A	0.53(0.02)	0.51	0.52(0.03)	0.55	—
2	0.39(0.02)	0.38	0.38(0.06)	0.26	A	0.40(0.07)	0.42	0.47(0.07)	0.51	—
3	0.64(0.07)	0.59	0.67(0.13)	0.45	S	0.57(0.09)	0.44	0.61(0.06)	0.47	—
4	0.72(0.09)	0.63	0.68(0.11)	0.51	S	0.49(0.04)	0.52	0.64(0.09)	0.66	—
5	0.50(0.06)	0.53	0.60(0.07)	0.45	S	0.51(0.04)	0.53	0.57(0.05)	0.53	—
6	0.53(0.02)	0.47	0.59(0.04)	0.41	FW	0.44(0.02)	0.41	0.58(0.04)	0.55	—
7	0.55(0.05)	0.60	0.56(0.05)	0.50	S	0.51(0.06)	0.51	0.50(0.06)	0.55	—
8	0.57(0.07)	0.62	0.54(0.11)	0.30	S	0.50(0.05)	0.56	0.53(0.06)	0.58	—
9	0.45(0.07)	0.39	0.61(0.13)	0.41	S	0.46(0.08)	0.39	0.56(0.14)	0.51	—
10	0.57(0.07)	0.55	0.52(0.09)	0.42	FW/S	0.61(0.03)	0.64	0.60(0.07)	0.57	—
Total (cases 1–10)	0.54(0.09)	0.52(0.09)	0.56(0.09)	0.41(0.08)*		0.50(0.06)	0.50(0.08)	0.56(0.05)	0.55(0.05)	
11	0.66(0.55)	0.75	0.64(0.05)	0.50	FW	0.60(0.08)	0.58	0.61(0.06)	0.46	FW
12	0.54(0.04)	0.60	0.54(0.06)	0.44	FW	0.50(0.03)	0.52	0.51(0.10)	0.40	FW
13	0.44(0.04)	0.45	0.35(0.04)	0.31	FW	0.54(0.02)	0.56	0.65(0.23)	0.43	FW
14	0.51(0.05)	0.51	0.57(0.03)	0.44	S	0.45(0.02)	0.46	0.48(0.04)	0.36	S
Total (cases 11–14)	0.54(0.09)	0.58(0.13)	0.53(0.12)	0.42(0.08)**		0.52(0.06)	0.53(0.05)	0.56(0.08)	0.41(0.04)***	
15	0.52(0.06)	0.50	0.46(0.07)	0.35	S	0.54(0.03)	0.40	0.75(0.05)	0.41	

†Values for ^{82}Rb uptake ($\text{ml/min g}^{-1} \times \text{extraction}$) in normal myocardial segments.

‡Values for ^{82}Rb uptake in ischaemic myocardial segment.

FW, free wall of the left ventricle; S, septum; A, apex.

* $p < 0.005$; ** $p < 0.02$; *** $p < 0.001$.

Fig. 3 Case 12: positron tomograms. (a) Before coronary surgery the control tomogram (before exercise) shows regional myocardial uptake of ^{82}Rb in the posterior wall, free wall, apex, and septum. After supine exercise there is a region of decreased ^{82}Rb uptake in the free wall (arrows) accompanied by typical chest pain. (b) After coronary surgery the absolute decrease in ^{82}Rb uptake after exercise still persisted in a portion of the free wall but without chest pain (silent ischaemia). Note the new fixed septal defect of ^{82}Rb uptake (arrows) representing infarction. This patient had three patent bypass grafts after the operation.

After coronary surgery

The results in Table 3 show that the disturbances of regional myocardial uptake of ^{82}Rb induced by exercise in the patients in cases 1–10 were corrected by coronary bypass surgery (Fig. 3). One patient (case 15) had a new fixed and absolute decrease in regional myocardial uptake of ^{82}Rb after coronary surgery (Table 3). There was evidence that pain relief after coronary surgery was secondary to a perioperative infarction in the previously ischaemic segment even though grafts were patent. Three patients (cases 11, 12, and 14) lost their angina, showed patent grafts including grafts to the preoperative ischaemic segments, but still had abnormal regional perfusion and ischaemia after exercise in the same myocardial segment after the operation. In addition to silent ischaemia the patient in case 12 had a new septal infarct (Fig. 2b). A further patient (case 13) had persistent angina, a blocked graft to the ischaemic myocardial segment, and abnormal regional perfusion with exercise after operation. These four patients had significant ($p < 0.001$) regional abnormalities of perfusion with exercise after operation (Table 3).

Discussion

Coronary artery bypass surgery is a widely accepted treatment for the relief of angina. The physiological aims intend to abolish transient ischaemia and angina pectoris. Nevertheless, there are difficulties in assessing the results of this operation.¹ Angina is probably a subjective underestimation of transient ischaemia, and, furthermore, it is a difficult complaint to assess objectively. Graft patency is an anatomical measure only and may be far removed from function. The specificity and sensitivity of pain and the electrocardiogram in exercise tests do have some limitations, and in addition qualitative radionuclide studies have generally shown increased perfusion.^{6,7,14–16} Finally, patients experience relief of angina for different periods of time, and even with no symptoms and patent grafts the mortality is variable. This study examined a small number of patients to assess whether new physiological data on coronary blood flow and transient ischaemia can provide any extra information on or more insight into the effects of coronary artery surgery.^{9,17,18} This study has principally shown that relief of angina and even angio-

Fig. 4 Case 1: positron tomograms (a) before and (b) after coronary surgery. (a) Before exercise the tomogram shows regional myocardial uptake of ^{82}Rb in posterior wall, free wall, apex, and septum. After supine exercise there is a region of decreased ^{82}Rb uptake in the apex (arrows). (b) Note the correction of the transient apical defect (ischaemia) after coronary surgery (arrows).

graphic evidence of patent grafts does not mean that the operation has relieved transient ischaemia.

The different physiological results show that in most patients the relief of angina was accompanied by the disappearance of abnormal regional perfusion and transient ischaemia. This was shown by the correction of regional decreases in myocardial perfusion that occurred with exercise. Postoperatively, the patent grafts in these patients were able to conduct increases in perfusion with exercise and meet the demands of this stress. In the same patients ambulatory monitoring showed a disappearance of symptomatic and the more frequent asymptomatic episodes of ST depression. This notable result is of interest as it shows relief of underlying ischaemia out of hospital, away from medical provocation and during the patient's daily activities. Clearly, the operation can relieve electrocardiographic evidence of ischaemia that occurs not only under stress but also when heart rate is not increased—for example, when patients are at rest or asleep. Apart from raising interesting questions about the causative mechanisms of ischaemia in these different circumstances this approach may be useful and provide a more comprehensive physiological assessment of the relief of transient ischaemia out of hospital.

It is well known that myocardial infarction may account for the relief of angina after coronary surgery, and this study provides an example.^{4,19} Surprisingly, however, the graft to the infarcted segment was patent. The patient in case 12 had a new septal infarct after operation plus reversible silent ischaemia of the left ventricular free wall even though all three grafts were patent. There is experimental and clinical evidence that sympathetic denervation or a placebo effect may play a role.^{20–23} Nevertheless, these examples show that the relief of pain may be associated with complicated pathophysiological processes affecting the left ventricular myocardium.

Perhaps the most surprising finding in this study was that a proportion of the patients lost their angina, had patent grafts, but on further examination still showed reversible abnormalities of regional myocardial perfusion and silent ischaemia with exercise. Two of these patients continued to have episodes of ischaemia producing ST segment changes out of hospital that were also quite asymptomatic. Previous studies have shown that improved perfusion after operation suggests patent grafts and failure to improve perfusion suggests blocked grafts or infarction.^{8,15} This study shows a more complicated picture. If the relief of angina and patent grafts are used alone to assess the operation patients may still have disturbed regional myocardial perfusion and transient ischaemia. This persistent disturbance may be due to distal coronary stenoses,²⁴ failure of a graft to conduct

sufficient flow particularly under stress, or, finally, abnormal extravascular or intravascular resistance distal to the graft.

This study consisted of a small number of patients examined in detail and cannot assess the frequency of these different results or their long term importance. The intention was simply to show that there is much physiological information on regional myocardial perfusion and ischaemia in and out of hospital than can help in understanding the effects of coronary surgery in individual patients. It remains to be tested whether electrocardiographic evidence of ischaemia outside hospital is an important indicator for the patient. Nevertheless, ambulatory monitoring was able to show relief of ischaemia while patients were at home and undertaking their daily activities.

This study has shown that coronary surgery can relieve symptoms by three different mechanisms—namely, relief of transient ischaemia, perioperative infarction, and a change from painful to painless ischaemia which becomes silent in and out of hospital (Figs 2a and 2b). These results may all occur with patent grafts, and this highlights the limitations of using anatomical assessments alone. These different results with patent grafts raise puzzling pathophysiological questions that should be answered as they may affect the outcome of coronary surgery. Silent ischaemia is not identified by a history of angina or graft patency and may affect the prognosis in patients and the interpretation of clinical trials.

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