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Effects of beta blockade on work—ΔST segment curves during exercise, and relation to subsequent results of coronary artery bypass surgery

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SUMMARY In 44 patients with coronary disease the relation between work and ST segment depression (ΔST) was investigated during graded exercise standardised in terms of each subject's maximum work capacity (W max). In 10 patients who were subsequently treated medically (group M) the relation remained unaltered during subsequent studies at three and 12 months.

In all patients the effect of beta blockade (3 mg pindolol iv) on the work–ΔST relation was examined and two groups were identified before surgery on the basis of their response to the beta blocker. In 28 patients who subsequently underwent coronary bypass surgery (group S_A) and the 10 patients of group M beta blockade significantly altered the relation so that there was less ST depression at a given workload. However, in six patients who also subsequently underwent bypass surgery (group S_B) there was paradoxically more pronounced ST depression after pindolol. There was no alteration in maximum work capacity after pindolol in any of the groups.

In the 28 group S_A patients there was one death after surgery; the work–ΔST relation in the other 27 patients of this group was even less depressed than with pindolol at a given workload and maximum work capacity had increased by 32 ± 6 per cent; most patients were asymptomatic. In group S_B patients the response to surgery was uniformly poor and all patients continued to have angina. No change occurred in the work–ΔST relation after surgery, there were two late deaths, and all six patients had evidence of postoperative infarction.

The direction of shift by beta blockade of work–ΔST curve may have prognostic significance for subsequent coronary artery surgery.

There have been relatively few studies in which medical and surgical treatment for ischaemic heart disease have been compared in the same patients using objective methods.[1] While factors such as left ventricular dysfunction or distal coronary artery disease have been identified as important determinants of outcome after coronary artery bypass grafting, the identification by other criteria of subgroups with a good or poor prognosis remains an important priority.

In the present study, changes in maximum work capacity and the relation between work and ST segment depression (ΔST) were examined in 44 patients with ischaemic heart disease, before and after acute beta blockade. The effects of beta blockade were compared in 34 patients with those of coronary artery surgery and after long-term medical treatment in the remainder. A group was identified before surgery in whom there was a paradoxical response to acute beta blockade and in whom most of the subsequent postoperative morbidity and mortality occurred.

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Method

Forty-four patients with severe chronic stable angina under consideration for coronary artery bypass grafting were admitted to the study which was performed with the approval of the Alfred Hospital Ethics Committee.

Cardiac catheterisation with left ventricular angiography and coronary arteriography was performed within one to two days of the initial exercise test (see below). Selection for subsequent treatment was then made. Selection for medical treatment (10 subjects) (group M) was either because of mild symptoms (four patients) or distal

coronary artery disease (six patients). Surgery was advised in 34 patients (group S). This was usually because of severe angina in the presence of proximal coronary artery disease and good left ventricular function assessed from angiographic findings. The findings are given in Table 1.

After surgery or the institution of medical treatment patients were managed by their own doctors, and exercise tests were repeated in all patients after three and 12 months and in most after two years. Clinical, electrocardiographic, haemodynamic, and angiographic findings were classified according to the definitions of the American Heart Association.[2] Angina was classified as being either absent, mild if it occurred only on strenous exertion, moderate if it occurred during the patient's normal daily activities, and severe if it occurred at rest or on very mild exertion.

EXERCISE TESTS

Graded exercise testing was performed using the procedure previously described by Bailey *et al.*[3] The patients had previously become familiar with the exercise procedure and had ceased all medication except glyceryl trinitrate at least one week before each test. The meal immediately preceding the test was omitted. Exercise was performed on an Elema-Schonander bicycle ergometer with electrocardiographic monitoring using an Avionics Exerstress 3000 recorder. ST segment depression (ΔST) was measured by the shift in ST segment from the baseline established in the PR interval, 70 milliseconds from the end of QRS complex. Heart rate and ST were averaged over 15 beats for three consecutive 15 beat periods at the end of each workload. Blood pressure was recorded by sphygmomanometry using a microphone situated over the brachial artery.

After a two-minute warm up period with no load on the bicycle ergometer, a 'sprint' test was performed with work progressively increased by 100 kpm each minute until symptoms prevented a further increase in workload. The workload at which this occurred was designated as maximum work capacity (W max). If a given workload was not completed the time was rounded off to the nearest 30 seconds and maximum work capacity expressed to the nearest 50 kpm/min. Before treatment the reason for stopping exercise in all patients was typical angina pectoris. In some patients this was associated with breathlessness, calf pain, or leg fatigue, but these symptoms were not dominant.

Displacement of the ST segment was measured at each level of exercise and the result plotted against workload. The results for a typical patient are shown in Fig. 1. For presentation of group work–ΔST relation (for example Fig. 2, 3) work in kpm/min has been normalised in terms of the W max for each test to allow for the variation in maximum workload achieved by different subjects.[3] Since no change occurred in W max after acute beta blockade normalisation in this way has no effect on the work–ΔST curves after pindolol though the increase in W max in some patients after surgery tends to exaggerate slightly the change in ST segment after surgery when work is normalised.

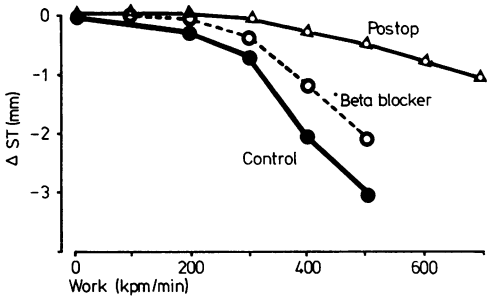

Fig. 1 *Relation between work (kpm/min) and ST segment depression in a typical group S_A patient before surgery (control), after 3 mg iv pindolol (beta blocker), and three months after coronary artery bypass grafting (postop).*

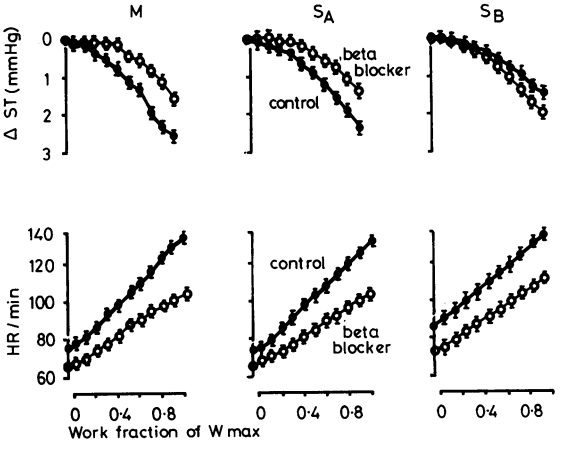

Fig. 2 *The relation between work normalised as a fraction of each patient's maximum work capacity and ST segment displacement* (top half), *and with heart rate* (lower half) *before and after 3 mg iv pindolol. HR, heart rate; M, medically treated group (n=10); S_A, surgically treated group with a favourable ST response to beta blocker (n=28); S_B, surgically treated group with an unfavourable response to beta blocker (n=6); W max, maximum work capacity.*

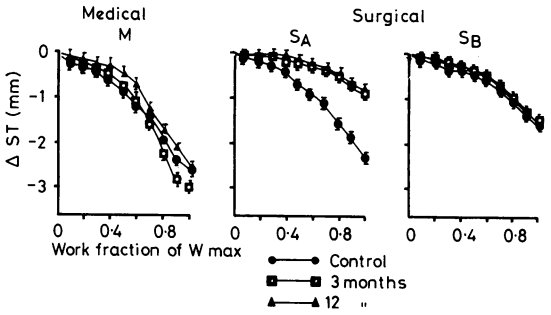

Fig. 3 *Relation between normalised work and ST segment displacement in each of the three groups before treatment (control), and three months and 12 months later. M, medically treated group (n=10); S_A, surgically treated group with a favourable ST response to beta blocker (n=28); S_B, surgically treated group with an unfavourable response to beta blocker (n=6); W max, maximum work capacity.*

Ten minutes after the completion of the test pindolol 3 mg was administered intravenously over three minutes. The 'sprint' exercise test was then repeated after 45 minutes. Venous blood, 10 ml, was collected at the end of the second test for subsequent assay of plasma pindolol by the method of Pacha.[4]

CARDIAC CATHETERISATION AND ANGIOGRAPHY

Percutaneous femoral techniques were used. Injections for the left ventricular angiograms were in the right anterior oblique position and multiple projections were used for the coronary angiograms. Left ventricular dysfunction was classified as local if the abnormality was confined to one or two adjacent segments (defined by the American Heart Association[2]) or generalised if three or more segments were involved. Ejection fraction was greater than 35 per cent in all patients.

CORONARY ARTERY BYPASS GRAFTING

Coronary artery bypass grafting was performed by four different surgeons using aortocoronary saphenous vein grafts. Techniques varied slightly among surgeons, but in general all vessels found to have significant disease were grafted if possible. In three patients endarterectomy was performed on the right coronary artery before a graft was inserted. In one patient a small apical aneurysm was plicated at surgery. After operation electrocardiograms, serum aspartate transaminase (AST), lactic dehydrogenase (LDH), and creatinine kinase (CK) measurements were performed daily for at least five days. Technetium scans and CK MB isoenzyme measurements were also performed in some patients if the diagnosis of perioperative infarction was suspected.

MEDICAL TREATMENT

Group M (medically treated) were managed by their own physicians who prescribed beta-blocking drugs to most patients (Table 3).

STATISTICAL METHODS

Work–ΔST relations were analysed using standard methods of regression analysis as described by Snedecor and Cochran.[5] Other data were analysed by analysis of variance or paired t tests. Results are expressed as mean ± standard error of the difference caused by variation within subjects derived from the analysis of variance.[5]

Results

WORK–ΔST CURVES

The relation between work, normalised as a fraction of each patient's maximum work capacity, and ΔST was found to be curvilinear in all patients before treatment (Fig. 2). After administration of pindolol the relation altered in 38 patients so that less ST segment depression occurred for a given workload ($p < 0.01$). Ten of these patients were treated medically (group M). Operation was performed in 34 patients (group S). In 28 of these patients the shift from control after beta blockade was similar to that in group M (group S_A). However, in six patients there was a shift in the opposite direction after beta blockade in the work–ΔST relation so that there was more ST depression at a given workload above 0·5 maximum work capacity (group S_B) ($p < 0.01$). Each of these patients subsequently underwent surgery. The clinical characteristics of the three groups of patients are summarised in Table 1.

At three and 12 months (Fig. 3) the work–ΔST curves obtained without beta blockade in group M remained virtually unaltered from the control response. However, at three months the surgically treated patients who had responded favourably to acute beta blockade now had significantly less ST segment depression for a given workload (groups S_A) ($p < 0.01$). By contrast, for the surgical patients with the previous paradoxical response to pindolol the work–ΔST segment relation remained the same as before surgery. There was no further change in this relation in any of the groups after 12 months. Thus one year after entry into the study, only the patients in group S_A showed improvement in the work–ΔST relation. Not all patients reported for their exercise tests after two years though clinical

information was obtained from all surgically treated patients. In 18 group S_A patients and three group S_B patients no significant change occurred in the work–ΔST relation between one and two years after operation.

MAXIMUM WORK CAPACITY

Maximum work capacity before treatment was 900 ±82, 677 ±33, and 658 ±55 kpm/min for groups M, S_A, and S_B, respectively (Fig. 4). The higher value for group M reflected the greater heterogeneity of the extent of disease of patients in this group. No change occurred in any group after acute beta blockade. After three and 12 months of medical treatment mean maximum work capacity in group M patients was 867 ±110 kpm/min, not significantly different from control. However, three months after surgery maximum work capacity in group S_A patients had increased on average by 19·3 ±6 per cent to 808 ±34 kpm/min ($p < 0·001$) and this figure was still maintained 12 months after operation and was then 860 ±36 kpm/min. However, in three of the five patients in group S_B who were still alive three months after operation, maximum work capacity had not increased from the preoperative value.

Table 1 *Clinical characteristics at entry*

	Medical	*Surgical*	
Group	*M*	*S_A*	*S_B*
Number of patients	10	28	6
Age (y)	43·3 ±5 (range 32 to 62)	53·4 ±1·3 (range 38 to 62)	47·7 ±3·6 (range 39 to 62)
Past history			
Myocardial infarction	4	18	4
Unstable angina	2	3	1
Cardiac failure	2	4	0
Resting electrocardiogram			
Infarct	3	15	4
Haemodynamics			
LVSP (mmHg)	136 ±5	130 ±3·2	142·8 ±7·8
LVEDP (mmHg)	14 ±1·1	13·0 ±1	13·8 ±1·9
Cardiac index (l/min per m²)	3·1 ±0·15	3·0 ±0·15	2·9 ±0·29
LV angiogram			
Normal	5	13	3
Local dysfunction	3	12	2
Generalised dysfunction	2	3	1
Coronary angiograms			
One vessel diseased	2	2	0
Two vessels diseased	5	8	1
Three vessels diseased	3	18	5

LVSP, left ventricular pressure; LVEDP, left ventricular diastolic pressure.

HEART RATE CHANGES AND PLASMA PINDOLOL

There was a linear relation between heart rate and workload in all patients (Fig. 2). Maximum heart rates attained by the three groups were similar at 136 ±4·3, 133·6 ±1·7, and 133·8 ±2·4 beats/min for groups M, S_A, and S_B, respectively. After pindolol the rise in heart rate for increasing work was attenuated similarly in each group so that overall the slope of the work-heart rate relation was reduced by 31·7 per cent ($p < 0·001$). At three months maximum heart rates attained were similar to control in group M, but significantly higher in the post-surgery patients at 142·5 ±2·7 beats/min, the increase being in proportion to their increase in maximum workload.

Mean plasma pindolol concentrations 45 minutes after administration were 39·6 ±8·7, 43·2 ±6·7, and 42·6 ±5·7 ng/ml for groups M, S_A, and S_B, respectively.

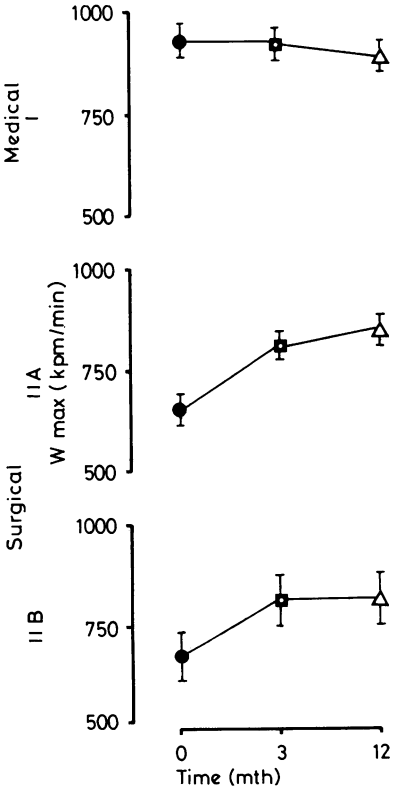

Fig. 4 *Maximum work capacity in groups M, S_A, and S_B before treatment at three months and 12 months. W max, maximum work capacity.*

MORBIDITY AND MORTALITY

Medical patients

Before coronary angiography each patient had either moderate or severe angina. In group M patients severity of angina was similar at each time period when they were taken off medical treatment. Two years after coronary angiography all 10 group M patients were alive, with symptoms unchanged from those at entry to the study.

SURGICAL PATIENTS

All patients had moderate or severe angina before surgery. The average number of grafts performed in each was 2·48 in group S_A and 2·67 in group S_B. The incidence of myocardial infarction after operation is shown in Table 2. All six patients in group S_B developed electrocardiographic evidence of myocardial infarction within the first two years after operation and in five of these the evidence was definite with typical electrocardiographic abnormalities as well as a diagnostic rise in myocardial enzymes.

Clinical response to surgery varied considerably between the two groups. In group S_A, one patient died suddenly three months after operation. In group S_B, one patient died in the perioperative period after a large myocardial infarct and another died suddenly 18 months after operation. Of the surviving patients, 25 in group S_A (93%) were completely without anginal symptoms three months after operation and 23 (82%) at two years. All four patients in group S_B were experiencing typical angina pectoris of moderate or severe degree two years after operation. The symptoms in these patients are reflected in the drugs prescribed by their physicians (Table 3). Beta blockers had been stopped one year after operation in 23 patients in group S_A and in only one patient in group S_B ($p < 0{\cdot}005$).

Discussion

The morbidity and mortality of the whole group of surgically treated patients are similar to those recently reported.[1] The effects of beta blockade and of surgery on maximum work capacity and ST changes during exercise are also in agreement with previous findings,[6–9] though, to our knowledge, the effects of beta blockers and surgery have been examined in the same patients in only one study.[6] However, using the change in work–ΔST curve after beta blockade a subgroup was identified in this study in whom there was subsequently a much higher incidence of patients with persistent angina, myocardial infarction, and death after surgery.

The present study has shown that the relation between standardised work and ST segment depression is curvilinear in patients with angina resulting from coronary artery disease, in agreement with previous findings.[3] The results of repeated tests over a period of one year in patients of group M in whom the degree of angina did not change shows that the relation is reproducible, as is the value of maximum work capacity, Thus, the fact that in the surgically treated patients of group S_A there was less ST depression for a given standardised workload as well as a significant rise in absolute value of maximum work capacity and maximum heart rates during exercise suggests diminution in the degree of myocardial ischaemia and improvement in myocardial function despite presumed increase in oxygen demand. The value of maximum work capacity in group S_A after surgery of 860 kpm is approaching the normal range for a middle-aged Australian population.[10] Improvement in exercise performance after coronary surgery has been noted in patients in whom no grafts are patent, possibly related to myocardial infarction at the time of surgery.[11] It is unlikely that this is the cause of

Table 2 *Postoperative myocardial infarction*

	S_A	S_B
Number of patients	28	6
In hospital		
No evidence	24	2
Enzymes only	2	1
New Q waves only	0	1
New Q waves and enzymes	1*	2
New Q waves, enzymes, and scan	1	1
	4	5
Late		
New Q waves and enzymes	0	2
Total possible postoperative infarction	4	6

*Normal scan.

Table 3 *Drug treatment*

	M	S_A	S_B
Digoxin			
Entry	3	9	1
3 months	2	6	2
12 months	2	2	2
Beta blockers			
Entry	8	24	4
3 months	8	2	3
12 months	8	1	3
No drugs			
Entry	1	4	2
3 months	0	17	2
12 months	0	22	2

the improved exercise performance in many patients in group S_A, as the graft patency rate around the time of the present study in this centre was 93 per cent in 63 consecutive patients who had 172 grafts (unpublished data). By contrast, group S_B patients showed no improvement in work–ΔST relation, despite having the least initial ST depression of the three groups, nor any improvement in maximum work capacity or maximum heart rate during exercise. Presumably, any improvement resulting from myocardial revascularisation was cancelled out by the clearly complicated postoperative course followed by these patients.

It is of interest that by standard clinical and haemodynamic criteria this latter group was considered suitable for bypass grafting and was indistinguishable from group S_A. The only retrospective difference between the two surgical groups was the response to acute beta blockade during the initial exercise test.

The attenuation, without complete restoration to normality in groups M and S_A observed in the standardised work–ΔST segment relation after pindolol, was similar to that observed previously after other beta blockers.[3 12] Beta blockade did not alter maximum work capacity, but lowered the heart rate at a given workload. The dose of pindolol produces maximum beta blockade of the heart rate response to exercise in normal subjects under conditions similar to those of the present tests.[13] The plasma pindolol concentrations of 25 to 35 mg/ml of the present study are on the upper plateau of the concentration-exercise heart rate response curve. Hence the reduction in ST depression at a given workload in groups M and S_A suggests diminution of myocardial ischaemia resulting from a reduction in myocardial oxygen demand, secondary to the attenuated heart rate response. However, in group S_B the degree of myocardial ischaemia is apparently aggravated at high workloads despite the fact that the heart rate response was attenuated to a similar degree to that in group S_A. The reason for the aggravation of ischaemia is not apparent from the present study, nor can it be determined whether similar results would occur after other beta-blocking drugs with somewhat different properties. It is likely, however, that the results would apply to other drugs in view of the results of studies showing approximately equal effectiveness in angina of non-cardioselective and cardioselective agents and drugs with intrinsic sympathomimetic activity.[14] A likely reason for deterioration after acute beta blockade is an increase in myocardial oxygen demand caused by an increase of ventricular dimensions associated with cardiac slowing.[15]

In group M and group S_A patients the increase in oxygen demand resulting from this factor is apparently more than balanced by the reduced demand caused by lowering of heart rate and arterial pressure. It seems likely that in group S_B patients acute beta blockade unmasks serious left ventricular dysfunction that has been masked by sympathetically mediated support of myocardial function. Such unmasking of ventricular dysfunction with propranolol has been previously observed in the open chest dog model of myocardial ischaemia.[16]

Some patients with angina caused by coronary artery spasm show a deterioration after beta blockade.[17] None of the patients in group S_B were noted to have coronary artery spasm during their coronary arteriogram, nor to have ST elevation, and it seems unlikely that this accounted for the response to acute beta blockade in these patients.

The present study suggested that using objective testing with work–ΔST curves a subgroup can be identified characterised by a paradoxical increase in ischaemia after acute beta blockade. Since inadequate clinical therapeutic response to beta blockers is an accepted indication for coronary artery surgery, distinction should be drawn between patients with an inadequate response to beta blocker, and those with a paradoxical result during the diagnostic test. The retrospective correlation between poor surgical results and the initial response to beta blockade warrants further investigations, as does the prognosis of such patients when treated medically.

References

[1] McIntosh HD, Garcia JA. The first decade of aorto-coronary bypass grafting 1967–1977. *Circulation* 1978; **57:** 405–31.

[2] Austen WG, Edwards JE, Frye RL, *et al.* A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975; **51:** No. 4., News from AHA, 5–40.

[3] Bailey IK, Anderson SD, Rozea PJ, Bernstein L, Nyberg G, Korner PI. Effect of beta-adrenergic blockade with alprenolol on ST-segment depression and circulatory dynamics during exercise in patients with effort angina. *Am Heart J* 1976; **92:** 416–26.

[4] Pacha WC. A method for the fluorometric determination of 4-(2-hydroxy-3-isopropyl-aminopropoxy)-indole, a β-blocking agent, in plasma and urine. *Experientia* 1969; **25:** 802–3.

[5] Snedecor GW, Cochran WG. *Statistical methods.* Ames, Iowa: Iowa State University Press, 1967: 94, 135, 299.

[6] Mason DT, Amsterdam EA, Miller RR, *et al.* Consideration of the therapeutic roles of pharmacologic agents, collateral circulation and saphenous vein bypass

in coronary artery disease. *Am J Cardiol* 1971; **28:** 608–13.
[7]Lapin EG, Murray JA, Bruce RA, Winterscheid L. Changes in maximal exercise performance in the evaluation of sphenous vein bypass surgery. *Circulation* 1973; **67:** 1164–73.
[8]Mathur VS, Guinn GA. Prospective randomized study of coronary bypass surgery in stable angina. *Circulation* 1975; **51** and **52:** suppl I: 133–9.
[9]Mnayer M, Chahine R, Raizner A. Mechanisms of angina relief in patients after coronary artery bypass surgery. *Br Heart J* 1977; **39:** 605–9.
[10]Calvert AF, Bernstein L, Bailey IK. Physiological responses to maximal exercise in a normal Australian population—comparative values in patients with anatomically defined coronary artery disease. *Aust NZ J Med* 1977; **7:** 497–506.
[11]Block TA, Murray JA, English MT. Improvement in exercise performance after unsuccessful myocardial revascularization. *Am J Cardiol* 1977; **40:** 673–80.
[12]Jackson WB. The use of propranolol in ECG diagnosis. *NZ Med J* 1971; **73:** 65–8.
[13]Jennings GL, Bobik A, Fagan ET, Korner PI. Pindolol pharmacokinetics in relation to time course of inhibition of exercise tachycardia. *Br J Clin Pharmacol* 1979; **7:** 245–56.
[14]Thadani U, Davidson C, Singleton W, Taylor SH. Comparison of the immediate effects of five β-adrenoceptor-blocking drugs with different ancillary properties in angina pectoris. *N Engl J Med* 1979; **300:** 750–5.
[15]Levine HJ, Wagman RJ. Energetics of the human heart. *Am J Cardiol* 1962; **9:** 372–83.
[16]Rosenfeldt FL, Gill CC, Wechsler AS, Sabiston DC Jr. Ventricular function following experimental coronary artery bypass grafting: the relationship to functional improvement to haemodynamics in the graft. *Cardiovasc Res* 1974; **8:** 26–36.
[17]King MJ, Zir LM, Kaltman AJ, Fox AC. Variant angina associated with angiographically demonstrated coronary artery spasm and REM sleep. *Am J Med Sci* 1973; **265:** 419–22.

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