INCREASING THE BENEFITS OF CORONARY ARTERY SURGERY: A COMPARISON OF THE EFFECTS OF AEROBIC AND POWER EXERCISE TRAINING ON ASPECTS OF CARDIOVASCULAR FUNCTION

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SUMMARY

Exercise rehabilitation is now widely used in cardiac disease as a means of attaining and even exceeding the pre-morbid functional state and level of physical activity.

This is a study of exercise rehabilitation after coronary artery surgery. The main aim was to compare the effects of aerobic exercise training with those of power or strength exercise training on aspects of cardiovascular function. There are few reports on power exercise training in previously untrained cardiac patients. In this study, exercise performance on a treadmill was the primary variable measured. Others were physical changes, arrhythmias, ST segments, haemostatic factors, lipids and lipoproteins, left ventricular function and myocardial perfusion. Effects of the programme that were not assessed include psychological factors, general wellbeing, employment status, dietary and smoking habits.

Eighty one men were studied. Their mean age was 56 years (range 35 to 70 years). They were assessed at baseline, three months and six months. After baseline measurements, they were randomised to three groups. The control group (n = 27) had no formal exercise training. The aerobic group (n = 27) had six months' graduated supervised aerobic exercise training. The power group (n = 27) had six months' graduated supervised power (strength) exercise training using circuit weight training.

The exercise sessions lasted 12 - 60 minutes and were held three times a week in a specially equipped gymnasium. They were supervised by a

physiotherapist, cardiac rehabilitation sister and a physician. No cardiovascular monitoring took place.

All measurements were done at each assessment except Thallium-201 scintigraphy and gated technetium scans which were done at baseline and six months. All results were initially analysed by analysis of variance and Scheffe test. The appropriate test of significance (Student's t-test, Mann-Whitney test or Wilcoxon test) was then employed when indicated.

In the aerobic group, there was a clear improvement in treadmill performance after three months (baseline 650.5s, three months 780.8s, $p = 0.004$); it was maintained at six months (846.9s, $p < 0.0001$). In the power group, significant improvement was delayed until six months (baseline 784.2s, three months 867.3s, six months 906.8s, $p = 0.007$). The control group showed no significant change (baseline 683.8s, three months 718.2s, six months 710.8s).

These improvements in exercise performance were not accompanied by significant changes in myocardial oxygen consumption as measured by submaximum and peak rate pressure product. Submaximum heart rate in the power group was lowered by training. There were no changes in the exercise electrocardiogram.

Body weight, body mass index and skin fold thickness showed variable responses. The power group showed the greatest fall in skin fold thickness, with no change in body weight and body mass index. This could have been due to muscle toning. The aerobic group gained weight, but their skin fold thickness also fell, and this may represent an increase in lean body mass. The

control group gained weight with no change in skin fold thickness.

Lipids, lipoproteins and apolipoproteins were unchanged. There was a significant fall in fibrinogen level in the aerobic group, and a small fall in factor VII in the power group. This is in keeping with the inverse relationship found between physical activity and fibrinogen levels.

Global left ventricular function at rest and after cold pressor stress was not changed by exercise training. In the aerobic group, there was an improvement in regional ejection fraction in the anterior zone in those with previous anterior myocardial infarction. In the power group, there was shorter systolic length at rest, shorter fast filling time at rest and after cold pressor, following the training period.

Myocardial perfusion was assessed by thallium-201 scintigraphy and circumferential profile analysis. The control group had smaller degrees of abnormality in the anterior view than the exercise groups at baseline. This increased at six months, while that in the aerobic group changed little and that in the power group decreased. In subgroup analysis, those with anterior myocardial infarction in the aerobic group showed smaller degrees of abnormality in washout profiles on the six month scans than the other two groups. This was in the anteroseptal regions, the 45° LAO and 65° LAO views and global washout, but the 95% confidence intervals of these changes do include zero.

On twenty four hour ambulatory Holter monitoring, the following changes were observed. Minimum and mean heart rates were significantly lower after both exercise training programmes. There were no changes in

maximum heart rate, ventricular ectopic activity, or ST segment analyses for total ischaemic burden.

On M-mode echocardiography, no clinically significant changes occurred in cardiac dimensions. Paradoxical septal motion was observed in a number of patients. In some, it resolved with time and exercise training. Left ventricular mass was reduced by exercise training, contrary to previous studies.

In conclusion, mean heart rate, exercise performance and haemostatic factors were influenced positively by exercise training after coronary artery surgery. Power (strength) training was safe and beneficial in these previously untrained cardiac patients. The other aspects of cardiovascular function were not affected to any clinically relevant extent by aerobic or power exercise training.

SECTION I

PLAN OF THESIS

The thesis is laid out in sections. The first part relates to introductory background information, rationale for the study, the protocol, statistics and calculation of the number of subjects required. The exercise programmes and interventions are discussed next.

In the second part (sections VII to XIV), the sections are self-contained with methods, results, discussion and review of the literature relating to that particular aspect of the study. Where relevant, links between the sections are discussed.

Finally in a general discussion the main findings are highlighted, limitations of the study are considered and suggestions for future studies are proposed. This is followed by the list of references and a list of abbreviations. The appendix is a copy of ARSAC permission for the use of radionuclides in the study.

SECTION II

INTRODUCTION

CORONARY ARTERY BYPASS SURGERY

The main benefit of coronary artery surgery is the relief of angina. This is particularly pertinent in those in whom medical therapy has failed. Symptomatic relief is reported in up to 90% of patients in the first post-operative year (Frick 1976; Mnayer et al 1977; Rogers et al 1990; Booth et al 1991). It is the direct result of bypass of obstructive coronary artery lesions, myocardial revascularisation and relief of ischaemia.

Coronary artery bypass grafting (CABG) had been performed in 1964 with follow-up of the patient reported in 1973 (Garrett et al). Favaloro described the operative technique involving the use of reversed autologous saphenous veins (1968). There has been an exponential rise in CABG since then. (Killip 1988; Rutherford & Braunwald 1988; ACC/AHA guidelines 1991). Techniques have improved and operative mortality has fallen to 1 - 1.5% in low risk patients. The symptomatic benefit it confers should mean that previously disabled patients can resume normal activities, including full-time employment, with socioeconomic gain. This expectation has not been borne out in practice (Oakley 1987; Channer et al 1988; Allen 1990).

In a selected subgroup of patients, coronary artery surgery (CAS) also prolongs life. In the Veterans' Administration Coronary Artery Bypass Surgery Cooperative Study (1984), 686 patients were randomised to medical or surgical

therapy. After sub-group analysis, patients with left main coronary artery stenoses, triple vessel disease and impaired left ventricular (LV) function fared better with surgery. After 11 years' follow-up no distinct surgical advantage was found overall in those without left main stem disease, with survival of 58% in both medical and surgical groups (Rutherford & Braunwald 1988).

In the European Coronary Surgery Study (ECSS), 768 patients were randomised. Surgically treated patients with triple vessel disease survived better initially. All had good left ventricular function. At five years, survival in the surgical group was 92.4% and in the medical group, 83.1%. At 12 years, the survival curves tended to converge, with 70.6% survival in the surgical group and 66.7% survival in the medical group (ECSS group 1982; Varnauskas & ECSS group 1988).

In the Coronary Artery Surgery Study (CASS), 780 patients were randomised. The patients were a low risk group with a good prognosis. At ten years, there was no survival advantage for surgery in the total group, with survival rate of 82% in surgical group and 79% in the medical group (Alderman et al 1990). Patients with proximal left anterior descending (LAD) lesions, or triple vessel disease and ejection fraction less than 0.50 had a better prognosis if treated surgically (Passamani et al 1985; Holloway & Schocken 1988; Myers et al 1989; Chaitman et al 1990).

These trials were started between 1972 and 1979. The differences in the results have been explained in various ways: different patient populations, decreasing operative mortality, improved operative techniques, improved medical management and new drugs. The general conclusions from the trials

are nevertheless the same. Surgery improves prognosis in symptomatic patients with left main stem disease, triple vessel disease, proximal LAD disease, and impaired LV function. There is some evidence that those with abnormal resting ECG, positive exercise test, and older patients also improve (Hampton 1984; Ryan 1987; Gersh et al 1989). Symptomatic and prognostic benefit decrease with time. In the CASS, the proportion of asymptomatic patients in the surgically treated group fell from 66% to 63% and 47% at one, five and 10 years' follow-up (Rogers et al 1990).

Since these trials there has been a change in the type of patient undergoing CAS. They are older, have more severe disease, poor LV function and concomitant conditions such as diabetes (McIntosh & Garcia 1978; Christakis et al 1989; Califf et al 1989; Jones et al 1991). In general, patients with triple vessel disease and good LV function have five-year survival rate of 90% and 10-year survival rate of 50 - 70% (Wheatley 1988).

CAS has not been shown to prevent subsequent myocardial infarction (Lipton et al 1986; Little et al 1990; Alderman et al 1990).

Graft failure occurs at the rate of 15-30% in the first year and at 1-3% per year thereafter, increasing sharply after 5-7 years to 3-12% per year. (Verstraete et al 1986; Buring & Hennekens 1990; Lipton et al 1990; Gavaghan et al 1991). Graft failure may be due to technical problems such as poor distal vessel run-off, thrombosis, intimal fibromuscular hyperplasia, or atheroma formation (Petch 1991). Early failure is mainly the result of surgical difficulties and poor calibre vessels (FitzGibbon et al 1978) whereas late occlusions are due to atheroma (Fuster & Chesebro 1986). Attention to risk

factor modification may help to reduce graft attrition (Fox et al 1987).

Re-operations may not yield ideal results and should be delayed if possible (de Feyter et al 1985). Hacker et al (1988) suggest that repeat CAS should not be witheld for technical reasons as the potential benefit is similar to the that of primary operation. The immediate operative risk of 200 repeat operations was 7 - 12%, but survivors did well subsequently (Verheul et al 1991). Patients for repeat CAS need to be carefully selected.

There has been a marked increase in the use of internal mammary artery (IMA) grafts, with associated excellent outcome in terms of graft function and prognosis (Tector et al 1981; Gibson & Loop 1986; Tector et al 1986; Lytle 1988; Loop 1987). Internal mammary artery grafts are more resistant to occlusion than are saphenous vein grafts (Cameron & Walker 1990).
Ten-year patency rates of 90% are reported (Gibson & Loop 1986). Their use has improved the outlook of CAS patients. Five-year survival rate in 179 patients with IMA grafts was 98.9% (Proudfit et al 1988). During 15 years' follow-up of 748 patients of whom 532 had one or two IMA grafts, survival was better in those with IMA grafts than in those with vein grafts alone. They had less recurrence of angina, fewer myocardial infarctions and re-operations (Cameron et al 1986).

Anti-platelet drugs are universally recommended after CAS to reduce the occurrence of occlusions, and have been subjected to several randomised studies (Chesebro et al 1982; Chesebro et al 1984; Brown et al 1985; Goldman et al 1988; Gershlick et al 1988; Sanz et al 1990; Gavaghan et al 1991). It is thought that activated platelets are mediators of both early thrombosis and later

atherogenesis. Most post-CAS patients in the United Kingdom are therefore on aspirin and/or dipyridamole.

It is not likely that CAS would directly affect the risk factors for CAD, such as hypertension, lipids, haemostatic factors and smoking. As part of the usual management of such patients, they are advised against smoking. Hyperlipidaemia is treated if present as patients with raised low density lipoprotein (LDL), and apolipoprotein B (apoB), and low high density lipoprotein (HDL) have a higher incidence of graft occlusion (Simons & Simons 1987; Solymoss et al 1988). Disease in native vessels tend to progress quicker if the graft is occluded than if it is patent (Kroncke et al 1988). The long term management of post-CAS patients should include risk factor modification, measures to enhance their quality of life and prevent graft attrition (Hoffmeister et al 1986; Kalan et al 1990).

The cardiovascular (CV) effects of CAS have been extensively studied. Exercise capacity, which may be dependent on graft patency, increases in conjunction with the relief of angina (Guiney et al 1973; Lapin et al 1973; Bartel et al 1973; Balcon et al 1974; Merrill et al 1975; Siegel et al 1975; McConahay et al 1977; Gohlke et al 1982; Talbot et al 1982; Allen 1990). The degree of ischaemia measured by ST segment depression during exercise, and on ambulatory ECG monitoring is reduced. It does not however predict outcome accurately (Quyyumi et al 1985; Crea et al 1987; Egstrup 1988; Gohlke-Barwolf et al 1990; Kennedy et al 1990; Kennedy 1990; Droste & Roskamm 1992; Patel et al 1993). The effect of CAS on arrhythmias is uncertain (Moller et al 1983; Rasmussen et al 1987; Yli-Mayry et al 1990;

Huikuri et al 1990; Rotman et al 1990; Smith et al 1992). Left ventricular function studied by echocardiography, radionuclide and contrast ventriculography, may improve post-operatively especially after exercise (Chatterjee et al 1972; Wolf et al 1978; Kent et al 1978; Zir et al 1979; Kronenberg et al 1983; Austin et al 1983; Taylor et al 1983; Brundage et al 1984; Tchervenkov et al 1985; Carroll et al 1985; Kawasuji et al 1988; Dilsizian et al 1988). Thallium scintigraphic scores are improved, as a direct result of myocardial revascularisation (Ritchie et al 1977; Verani et al 1978; Greenberg et al 1978; Kolibash et al 1979; Robinson et al 1979; Berger et al 1979; Hirzel et al 1980; Rubenson et al 1982; Gibson et al 1983; Fioretti et al 1988; Hamouratidis et al 1988). Thallium scintigraphy can be used in the prediction of graft occlusion (Sbarbaro et al 1979; Kolibash et al 1980; Wainwright et al 1980; Huikuri et al 1987).

EXERCISE REHABILITATION

The use of exercise rehabilitation for cardiac patients is gradually increasing, and should be recommended practice.

Pooled analyses of studies of exercise rehabilitation after myocardial infarction (MI) show a distinct benefit for exercise-trained patients, though the precise mechanism for this is uncertain. It is also associated with improved outcome in patients with angina and after CAS. In an overview of 22 trials of exercise rehabilitation post MI, O'Connor et al (1989) report a 20% reduction in overall mortality in exercise-based rehabilitation programmes due to a decreased risk of cardiovascular mortality and fatal infarction, operating over

at least three years. There was also a reduction in sudden death rate during the first year post MI (Oberman 1989). May et al (1981) reported a 19% reduction in mortality with exercise training after MI. This compares with a reduction of 23.5% by beta blockers, 17.8% by lipid-lowering drugs, 7.6% by anti-platelet drugs and a 4% increase with antidysrhythmic therapy. In another pooled data report Oldridge et al (1988) showed a 24% reduction in total and a 25% reduction in cardiovascular mortality with exercise training after MI.

The effect of exercise rehabilitation on prognosis has not yet been studied in post-CAS patients. This would require a very large multicentre trial, as some studies have shown 79% ten- year survival in CAS patients (CASS investigators), with even better results in those with IMA grafts as discussed earlier. Improvements on these figures would be difficult to show in a small study.

Improvement in quality of life has been shown in exercise rehabilitation after MI (Norris et al 1990; Oldridge et al 1991). There are those who are more doubtful about the psychological effects of exercise training (Langosch 1988).

In the studies in which CAS patients were included, they derived as much benefit from exercise training as did patients with angina or MI, in terms of improved exercise capacity. However, since CAS patients have been studied mainly as part of a group of cardiac patients, it makes it difficult to determine their particular benefits specifically.

There are studies of exercise training after CAS which show that quality of life and rates of return to work are markedly improved by exercise

rehabilitation (Murray & Beller 1982; Foster 1986; Hoad & Crawford 1990). In contrast others fail to show significant improvement in return to work rate after training (Danchin & Goepfert 1988). This factor is perhaps the one most influenced by extraneous and socioeconomic circumstances.

Exercise training in cardiac patients is usually based on aerobic exercises, such as running on the spot, step-ups,and trunk curls. These are also known as endurance, dynamic, isotonic or isokinetic exercises and involve the rhythmic movement of large muscle groups associated with increased ventilation, oxygen consumption and cardiac output. Aerobic training is of proven benefit in all groups of cardiac patients, with improved exercise capacity after a variable period of training.

Power or strength exercise training has not been studied in previously untrained post-CAS patients, and has only been reported in post-MI and other cardiac patients who have already undergone aerobic training. It is often discouraged in cardiac patients because of unfounded fears and lack of information on the physiological effects of such exercise. There is also confusion with static or isometric exercise such as sustained weight-lifting. That form of exercise causes a pressure rather than a volume load and therefore does not cause a sustained increase in cardiac output. The rise in blood pressure from static exercise is thought to be harmful in cardiac patients. It is important not to discourage cardiac patients from performing strength-training exercise. Many activities of daily living involve a power component eg. gardening, do-it-yourself, shopping and lifting. It is important to assess its effects in a controlled situation, in order to help clinicians to give appropriate

advice to their cardiac patients.

Weight-training in a circuit is not strictly isometric. During circuit-training, there are rhythmic movements of large muscle groups to move a moderate weight load repetitively, with short periods of rest between each element of the programme. Like aerobic exercise, it should also cause an increase in ventilation, oxygen consumption and cardiac output. In addition, there may be increased skeletal muscle strength and mass.

It makes sense to compare the two forms of exercise directly in previously untrained patients after CAS.

The most compelling end-point of all is death. There is yet to be conclusive evidence demonstrating that exercise rehabilitation reduces mortality. This is because of flaws in study designs, small study sizes, inhomogeneous groups of patients, and non-uniform exercise protocols. Results of meta-analyses do indicate a survival advantage for patients who take part in exercise rehabilitation after myocardial infarction over those who do not, as discussed earlier.

Mortality is the most persuasive primary end point in exercise training and other interventional studies. This is not a practicable one for most investigators because it would require prolonged follow-up of a large number of patients to show any differences. In any case there are other important variables involved in morbidity which are of more value to the patient than is mortality. These include well-being, exercise capacity and risk of future cardiovascular events.

Most CAS patients are familiar with the exercise test using treadmill or bicycle ergometer. It is therefore a useful method to assess the effects of exercise training in these patients. A valid primary end point in such a study is exercise performance. It is also a reflection of their physical well-being and ability to cope with daily activities.

EFFECTS OF EXERCISE TRAINING

Chronic exercise training in young rats causes myocardial hypertrophy, increased ratio of capillary to muscle fibres in myocardium, increased coronary artery size, development of collaterals in the coronary bed, improved cardiac performance, increased skeletal muscle mitochondria and respiratory enzymes and improved peripheral blood flow during exercise (Froelicher 1987a).

Cardiac output, stroke volume, left ventricular end diastolic volume and exercise capacity increase with endurance exercise training in normal subjects and in cardiac patients (Buttrick & Scheuer 1987; Hossack 1987; Oberman 1988). Resting heart rate and rate pressure product at submaximum exercise is reduced after exercise training (Laslett et al 1985; Todd & Ballantyne 1986). Power exercise in wrestlers and weight trainers, can cause increased left ventricular wall thickness (Froelicher 1987b; Hanson & Nagle 1987).

There is substantial evidence in favour of the idea that exercise can prevent coronary artery disease (CAD) (Morris et al 1973; Paffenbarger & Hale 1975; Morris et al 1980; Oberman 1985; Paffenbarger et al 1986; Slattery et al 1989; Morris et al 1990; Shaper & Wannamethee 1991). In those in whom CAD has already developed, exercise may be a means of retarding its progress,

by modification of risk factors (Goldberg 1989). It is certainly a means of improving their quality of life (Laslett et al 1987; Shepard 1989).

Studies on exercise training in cardiac patients often combine those with different categories of disease - angina, myocardial infarction and post-CAS. One of the most widely quoted is the PERFEXT study. In this, 146 patients were randomised to control (n = 74) and exercise (n = 72) groups. Coronary artery surgery patients formed a third of the group. They showed similar benefit as did the other patients after one year. In summary, these benefits were increased exercise time, thallium scores, and left ventricular function in the subgroup of patients with angina (Froelicher et al 1984).

Evidence to date supports the view that peripheral rather than central adaptations account for the improvement in exercise capacity that has been consistently demonstrated in exercise-trained patients (Coplan et al 1986). This seems to occur even after short periods of training such as four weeks (Ignone et al 1988; Nordrehaug et al 1989). These peripheral adaptations serve to improve the efficiency of skeletal muscle. Studies that use cardiopulmonary exercise testing show that there is also improved cardiovascular and respiratory status, and that the effect is not merely one of habituation and better confidence (Ades & Grunvald 1990; Blumenthal et al 1991). There is growing speculation that by inducing ischaemia, exercise training results in the formation of a coronary collateral circulation. This has been suggested on perfusion scans (Todd et al 1991), but demonstration by angiography is lacking.

Studies of exercise training after CAS show that exercise capacity is increased (Stevens & Hanson 1984; Froelicher et al 1985; Froelicher 1987b;

Hoad & Crawford 1990), some risk factors are reduced (Hedback et al 1990) and graft patency is increased (Nakai et al 1987) in the trained groups.

Whether or not exercise training can increase the benefits of CAS is an open question. Whether or not aerobic and power training cause different cardiovascular effects after CAS is unknown. Whether or not it is possible to influence known risk factors for CAD by exercise training after CAS is undetermined.

This study was undertaken to try to provide some answers to these questions.

It is a study of the effects of aerobic and power exercise training in 81 men who had undergone coronary artery surgery six to 48 weeks prior to their enrolment. They were randomised to three groups:

1. control (no formal exercise training),
2. supervised, graduated, aerobic exercise three times weekly for six months,
3. supervised, graduated, power (strength) exercise training three times a week for six months.

SECTION III

PROTOCOL

The following protocol was assessed and accepted by the Higher Degrees Committee at Glasgow University. There was initial criticism of the original number of patients of 60. The next section explains the modification in the protocol to increase the number of patients to 81.

PROPOSAL FOR THE DEGREE OF MD

"The effects of exercise training on cardiac function, lipids and coagulation in post-coronary artery bypass graft patients"

Introduction

Coronary artery bypass grafting (CABG) has been a significant advance in the management of patients with ischaemic heart disease. In their first year after CABG, 80-90% of patients report definite symptomatic improvement, if not cure. The prognosis is improved in patients with left main stem, triple vessel and proximal left anterior descending artery disease, especially in those with moderately impaired left ventricular function (EF 35-50%) and readily inducible ischaemia (on exercise testing).

However 10-30% of grafts occlude in the first year post-operatively, with or without a recurrence of angina. Exercise training provides added advantages to coronary artery surgery. Scientific evidence on the effects of exercise training post CABG is in short supply from the United Kingdom. Most reports on exercise training in heart disease are from America, Scandinavia and Japan.

Cardiac rehabilitation centres have been set up in only a few centres in the United Kingdom and there is scope for increasing their numbers. As coronary artery disease is the commonest cause of death in the West of Scotland, it would be good sense to invest in means of secondary prevention. This includes advice on diet and social behaviour, as well as exercise training sessions.

This study has therefore been designed to investigate the effects of endurance and power exercise on cardiac function, coagulation factors and lipids in men who have had coronary artery surgery.

Aims

1. To assess the cardiovascular effects of supervised exercise training in male patients post CABG. Effects on exercise tolerance, exercise induced ischaemia, myocardial perfusion, left ventricular systolic and diastolic function will be studied.

2. To determine the prevalence of silent myocardial ischaemia in post-CABG patients and to assess the effects of exercise training on silent myocardial ischaemia.

3. To determine possible factors contributing to graft occlusion in the short term.

4. To assess the effects of exercise training on lipid levels and haemostatic factors.

Patients and Methods

Sixty male patients aged 30-70 years, who have had CABG in the previous 18 months will be enrolled in the study.

They will be randomised to three groups: supervised graded endurance exercise training; supervised graded power exercise training; no exercise training. The programme will run for six months. Patients who are unable to perform the treadmill exercise test will be excluded.

At entry, at three months and at six months, patients will be evaluated as follows - clinical history and cardiovascular examination, resting ECG, chest X-ray, symptom-limited exercise ECG (modified Balke II protocol), echocardiography (Hewlett-Packard System), Thallium-201 myocardial perfusion scintigraphy scan (at entry and six months) gated Technetium 99 scan at rest and following cold pressor (entry and six months), assays of factor VII activity, fibrinogen, fibrinopeptide A, fasting lipids and apolipoproteins.

The training programme has been devised in collaboration with the Physiotherapy Department, Victoria Infirmary. Endurance exercises include running on the spot, step-ups, bridging, side flexion, back extension and trunk curls. Power exercises include pull down, push down, biceps curl, triceps curl, hamstrings and quadriceps curls and sit-ups. Training sessions will take place three times a week and last 30-40 minutes on each occasion. Attendance records will be kept. Each patient will be instructed on the exercises by a senior physiotherapist. The sessions will be supervised by a physiotherapist, cardiac rehabilitation sister and a doctor.

Any patient requiring treatment for angina will be given nifedipine

initially. Further treatment and investigation will be carried out as indicated.

Anticipated problems

Patient non-compliance, not only with exercise therapy, but also with other therapy will be overcome with counselling and encouragement. Drop-outs, for medical and social reasons will no doubt occur, as has been the case in most trials of this nature.

Results

Patients in the exercise programmes will be their own controls. In addition, comparisons will be made between the groups. Differences in the measured variables will be assessed. Initial analysis of variance followed by paired "t" test or rank test, where appropriate, will be performed.

SECTION IV

Calculation of number of subjects required

This was based on results from reported studies on exercise training in cardiac patients. Based on statistical power of 90%, with significance level of 0.05, a total of 75 subjects are required in a two-group comparison (Altman 1982). I have been unable to find any statistical formulae or nomograms pertaining to three groups.

There are statistical formulas that can be used to estimate the number required in each group based on standard tables (Kirkwood 1988).

Formula for number of subjects in each group (n):

$$\frac{(u+v)^2 \times (sd_1^2 + sd_2^2)}{(x_1 - x_2)^2}$$

u = 1.28, v = 1.96,

sd = standard deviation

x = mean

Using the formula and results from previous work in our institution in patients with heart failure to calculate the number required in each group, n = 53:

$$\frac{(1.28+1.96)^2\times(178^2+266^2)}{(710-568)^2}=53.3$$

The standard deviations were large in that study, and reflect the large differences in exercise capacity among patients with heart failure. It was not possible to perform a pilot study in post-CAS patients, due largely to the restraints of time. Using results from a study of post-MI patients and the same equation, n = 16:

$$\frac{(1.28+1.96)^2\times(15^2+20^2)}{20^2}=16.4$$

I had to combine statistical principles with logistics and expediency in reaching a decision to study a total of 81 patients. It took 32 months to follow up that number of patients. The tests that were done had to be arranged in conjunction with busy clinical departments and the patients involved.

In trials of exercise training after CAS involving between six and two hundred and ten patients, 19 - 29% increases in exercise capacity have been reported (Oldridge et al 1978; Hartung & Rangel 1981; Dornan et al 1982; Waites et al 1983; Murray & Beller 1983; Stevens & Hanson 1984; Froelicher et al 1985; Nakai et al 1987) Most of these studies did not even have a control group. It was expected that the proposed study of 81 patients in three groups would show similar changes in exercise capacity.

STATISTICAL ANALYSES

The results were analysed on an intention-to-treat basis, unless specified otherwise.

Results were analysed using SPSS/PC+ version 4.0 statistical data analysis programme. Descriptive statistics were done initially, followed by tests of normality using normal probability plots for all the data. Within and between group differences in the measured variables were assessed by analysis of variance (ANOVA) with application of the Scheffe test for normal data, and Kruskal-Wallis test for non-normal data. When this was significant i.e. $p < 0.05$ and with Scheffe test indicating actual difference between two groups, the analysis was taken further.

Paired 't' test or Wilcoxon test was done for within group data and unpaired 't' test or Mann - Whitney U test was done for between group data. Two-tailed p values are noted where relevant.

The results are expressed as the mean with its 95% confidence interval or standard error, for normal data and as the median with 95% confidence interval or range for non-normal data.

SECTION V

THE EXERCISE PROGRAMME

The programme was devised in conjunction with the Physiotherapy department to include movements involving all major muscle groups in exercises that are simple to perform.

The aerobic exercises were based on the Canadian Airforce XBX physical fitness programme. Aerobic exercises performed were arm circling, arm raising, step-ups, trunk rotation, star or stride jumps, crook-lying with trunk rotation and bridging, hip abduction while lying on side, side lying or standing trunk curls, trunk side flexion, and running on the spot.

Power exercises were based on a universal Multigym system. This consists of a group of apparatus in which weights are connected by appropriately placed pulley systems designed to allow movement of the weights in specific directions.

Power exercises performed were bench press, military press, biceps curl, upright row, pull down, push down, pulley row, quadriceps curl, hamstrings curl and sit ups.

Each patient ended the session with a ride on a stationary bicycle.

The exercise programme used in the study is in line with recommendations of the American Society of Sports Medicine (1990) for exercise in the promotion of fitness in healthy persons. Persons with initial low levels of fitness, such as would be expected in cardiac patients, achieve more, in terms of maximal oxygen consumption (VO2 max), than highly trained persons, after low to moderate intensity exercise programmes.

The recommendations are: 20-60 minutes of any activity that uses large muscle groups and can be maintained continuously i.e. aerobic exercises, to be done 3 - 5 days a week, at 60 - 90% of maximum heart rate, or 50 - 85% of maximum oxygen uptake.

Resistance or strength training of moderate intensity sufficient to develop and maintain fat-free weight - one set of 8 - 12 repetitions of eight to ten exercises that condition the major muscle groups at least 2 days a week is the recommended minimum.

The patients attended sessions up to three times weekly in the same location and were supervised by a Physiotherapist, Cardiac Rehabilitation sister and a physician.

The duration of each session was 12-40 minutes depending on the patient's stage of training. It was anticipated that by the end of the training period, each patient should have been exercising at his perceived maximum level of exertion.

In the aerobic group, the number of repetitions of each exercise was increased over time to increase the intensity of work performed in a graded manner.

In the power group each exercise was done, starting with the lightest weight (2 - 5kg), in 3 sets of 10 repetitions with 45s periods of rest between each element. The weight load was increased gradually, depending on individual's progress and symptoms.

Heart rate and other cardiovascular monitoring were not done during the exercise sessions. Perceived exertion based on visual analogue scales has been

shown to be an acceptable surrogate for heart rate monitoring in exercise rehabilitation programmes. Most studies do report using 70 - 85% target heart rate or percentage of their maximum voluntary effort as a guide to the limits to which patients are exercised. I believe that symptomatic status during the training sessions can be used in a similar way to visual analogue scales. It was hoped that the men would continue unsupervised exercise in the community after the rehabilitation programme, relying on their symptomatic status rather than heart rate to decide on their limits of exercise. In retrospect, however, heart rate monitoring during the exercise sessions would have provided further information on the intensity to which the patients exercised.

AEROBIC EXERCISE PROGRAMME

ARM CIRCLING

Stand with feet slightly apart. Abduct arms and rotate at shoulders, first forwards and then backwards. Start with 5 in each direction.

STEP UPS

Stand facing 20cm step. Step up and down at moderate pace, alternating left and right legs. Start with 10 repetitions.

TRUNK ROTATION

Stand with feet slightly apart, hands on hips. Rotate trunk to left and right alternately. Start with 5 to each side.

CROOK LYING TRUNK ROTATION

Lie on back, arms at side, with knees flexed. Rotate hips from side to side. Start with 5 to each side.

STAR JUMPS

Stand with feet together. Jump up abducting legs and arms fully. Return to starting position. Start with 3 repetitions.

SIDE LYING HIP ABDUCTION

Lie on right side, right arm stretched above head, left arm supporting upper

body at chest level, right knee flexed. Abduct left leg to 90°. Return to starting position. Repeat on left side. Start with 5 on each side.

STANDING TRUNK CURLS

Stand with feet together, arms at side. Bend knees with arms stretched forwards, and lower the body towards mat. Return to starting position. Start with 3 repetitions.

CROOK LYING BRIDGING

Lie on back with knees flexed. Raise hips while keeping feet and shoulders on the mat. Return to starting position. Start with 5 repetitions.

ARM RAISING

Stand with feet together, arms at sides. Raise arms forwards above head, return to starting position. Start with 5 repetitions.

TRUNK SIDE FLEXION

Stand with feet slightly apart, arms at sides. Flex trunk to right, sliding the right hand down right leg. Return to starting position. Repeat on left side. Start with 3 on each side.

RUNNING ON THE SPOT

Raise feet at least 10-20cm off mat, while running on the spot for one minute.

POWER EXERCISE PROGRAMME

BENCH PRESS

Lie on back on the bench, feet on the floor, with the apparatus behind head. Raise weights by pulling bar towards head. Return to starting position.

MILITARY PRESS

Kneel facing the apparatus. Raise weights by pushing the angled bar from chest level to above your head, fully extending your arms. Return to starting position.

BICEPS CURL

Stand facing the apparatus. Bend forearms to 90°, palms upwards, elbows tucked into sides. Raise weight by pulling the bar up, till arms are fully flexed. Return to starting position.

UPRIGHT ROW

Stand facing apparatus. With arms extended, palms downwards, pull the bar up towards your chin, and move elbows outwards at the same time to raise the weights. Return to starting position.

PULL DOWN

Sit on stool, with apparatus behind body. Raise the weights by pulling the bar down toward shoulders. Return to starting position.

PUSH DOWN

Stand facing the apparatus. Bend arms to 90° with palms facing downwards. Raise the weights by pushing bar downwards until arms are fully extended. Return to starting position.

PULLEY ROW

Sit on the mat, legs fully extended facing the apparatus. Reach for the bar and raise the weights by pulling the bar towards the body. Return to starting position.

QUADRICEPS CURL

Sit on the edge of the bench with the cushioned bar at your feet and the apparatus behind body. Hold bar with flexed ankles and raise weights by extending the knees. Return to starting position.

HAMSTRINGS CURL

Lie prone on the bench, with the cushioned bar resting on back of ankles. Raise the weights by flexing at the knees. Stabilise upper body by holding onto the sides of the bench. Return to starting position.

SIT UPS

Lie supine on the mat, with legs fully extended. Grip fixed cushioned bar with flexed feet. Raise upper body and try to touch knees with your forehead and return to starting position.

Attendance records were kept for each patient. The patients also recorded the level of the programme they had reached after each session. Their performance was assessed by the physiotherapist, their symptomatic status was assessed by the doctor, and they were then given appropriate advice about moving on to the next stage.

The patients in the power group attended 63% of the sessions; those in the aerobic group attended 64% of the training sessions.

SECTION VI

INTERVENTIONS

Both exercise training groups attended the exercise sessions held in the same gymnasium supervised by the same physiotherapist, rehabilitation sister and doctor. The programme did not include specific instructions about diet or other changes in lifestyle. We did not record any such changes that may have taken place during the period of follow-up. General advice was available to the patients and would have been the same for all concerned.

The study was aimed at comparing the effects of different forms of exercise training i.e. "treatments" on selected cardiovascular factors. The primary end-point was exercise time on a treadmill.

Patients were assessed at baseline with two treadmill tests and the average of these was used as baseline treadmill performance.

Thereafter they were assessed at three and six months. History, clinical examination and weight, resting ECG, chest Xray, M-mode and 2D - echocardiography, Holter monitoring, lipid and lipoprotein analysis, haemostatic factor assays, were done at each assessment. Height was recorded at the first visit. Exercise thallium-201 scintigraphy and radionuclide ventriculography were done at baseline and six months.

THE SUBJECTS

There are only a few studies on exercise training after coronary artery surgery. These patients are forming a larger and larger proportion of cardiac

patients, as the operation rates rise exponentially. It is necessary to study post-CAS patients as a single group, rather than as part of a mixed bag of cardiac patients. This would help to establish their particular response to exercise rehabilitation. In terms of its effects on lipids and coagulation factors, this may be of special relevance to this group of patients with respect to graft patency.

At the time of the study, the majority of patients requiring coronary artery surgery in the Victoria Infirmary were referred to a particular surgeon at the Western Infirmary. In that regard, the patients form a homogeneous group. The study was confined to men because it was more practicable in terms of available facilities for exercise training sessions.

The patients were recruited from Cardiology clinics in the Victoria Infirmary and asked to take part in the study. They gave their informed consent and were free to withdraw from the study at any time.

The study was approved by the Ethical Committee at the Victoria Infirmary, Glasgow.

Randomisation was done by using the method of opaque sealed envelopes containing the letters 'C', 'A', or 'P'.

Those who dropped out before they had attended an exercise session were replaced, otherwise they were not. Eighty one male patients were asked to take part in the study. Four had dropped out by the end of the study period. Demographic details at baseline are shown in table 1. There were no significant differences between the groups.

Table 1

DEMOGRAPHIC DETAILS AT BASELINE

	Control	Aerobic	Power
Number	27	27	27
Mean age (years)	56.6	56.5	59.2
Grafts (mean)	3.2	3.0	3.3
IMA grafts (no. of patients)	22	17	16
Time since surgery (weeks) median (range)	12 (6-28)	12 (6-48)	12 (6-44)
Mean weight (SEM) kg	80.5 (2.1)	76.3 (2.7)	72.6 (2.0)
Previous MI	11	17	15
Smoking - current	4	3	1
previous	14	15	17
non	8	9	6
Work - employed	8	6	6
off work	7	9	6
retired	11	12	12
Drugs:			
Aspirin	19	15	18
Dipyridamole	18	13	16
anti-ischaemia	5	2	1
diuretic	5	2	4
ACE inhibitor	1	2	0

Their ages ranged from 32 - 70 years. Fifty six percent had previous infarcts, and 60% were ex-smokers. Seventy four percent were not in full-time employment, most were retired. The majority of patients had internal mammary artery grafts, and there was an average of 3 bypass grafts per patient. Most were enrolled around three months post-surgery, and were on anti-platelet drugs, as would be expected.

One patient in the control group was lost to follow up after eight weeks. Two patients in the power group dropped out after two weeks because of problems with their surgical scars; another moved away after five weeks. There were no drop outs in the aerobic group. The data that follow are on 77 patients who completed the study.

SECTION VII

CLINICAL EXAMINATION

At each assessment, the patients had a clinical examination consisting of resting pulse and blood pressure measurement, auscultation of heart and lungs, and measurement of body weight, body mass index and skin fold thickness. Blood pressure was measured manually using a mercury sphygmomanometer. Heart rate was measured from a resting ECG.

Body mass index was derived from the standard formula: weight/height^2. Skin fold thickness was measured with Harpenden calipers at four sites: biceps, triceps, scapula and abdomen. The biceps and triceps measurements were taken midway down each muscle, scapula measurement was taken halfway down the medial aspect of the scapula, and the abdominal measurement was taken at the anterior superior iliac spine. The sum of these was used as an measure of body fat. This method is a well recognised means of assessing body fat in nutritional and exercise training studies. With increasing obesity, a higher proportion of fat is deposited subcutaneously. A 10mm increase in the sum of four skin folds corresponds to an increase in fatness of 4.8% (Lohman 1981). The relative fat pattern does not change much after weight loss from food restriction, though the same may not be true of weight loss associated with exercise.

Results

Heart rate and blood pressure readings are presented in the section on exercise test data.

Results for weight (WT), body mass index (BMI), and skin fold thickness (SFT) are in table 2.

The control group was heavier than the other two at all assessments. At baseline, this difference failed to reach statistical significance (ANOVA $p = 0.07$). The average weight increased slightly in the control and aerobic groups with time, while that in the power group remained almost static. Therefore, the mean weights at three and six months became significantly different (ANOVA $p = 0.02$ and 0.03 respectively). Applying t-tests shows the relevant differences clearly. Between control and power groups at three months and at six months $2p = 0.002$ for each, and for the interval change at three months, $2p = 0.013$ (control group gained 1.3kg, power group lost 0.3kg). Between aerobic and power groups at three months, the interval change was significant with $2p = 0.016$ (aerobic group gained 0.9kg, power group lost 0.3kg). There were no other differences reaching statistical significance. The changes had taken place by three months.

By definition, the patients were overweight, since their mean BMI exceeded 25. This is not surprising, considering the population being studied: middle-aged men from the West of Scotland with coronary artery disease. Body mass index followed a similar pattern to that of body weight. At three months, the control group increased BMI by 0.4, aerobic group increased by 0.3 and power group decreased by 0.1, making the interval change at three

months significant with 2p = 0.016 for control vs power and 2p = 0.024 for aerobic vs power. The difference remained for control and power groups at six months, 2p = 0.019.

Skin fold thickness at baseline was similar in the groups. The power group improved, with lower skin fold thickness values and a greater fall with time than occurred in the other two groups. At three months, ANOVA p = 0.038 (control vs power 2p = 0.007, acrobic vs power 2p = 0.043). At six months, ANOVA p = 0.021 (control vs power 2p = 0.002, aerobic vs power 2p = 0.032). The changes represent at the most 1% reduction in fatness.

The weight gain in the control group is not reflected by a concomitant increase in skin fold thickness as would be expected. The aerobic group also gained weight but it was associated with a small drop in SFT. This is usually explained in terms of a gain in muscle tissue as a result of exercise training. It is supported by the pattern of lower SFT in the power group without much change in body weight. One could assume that the control group either also gained muscle tissue or gained fat in areas that were not measured in the study. Having said that, one must remember that the changes were really rather small and may not be of the same order of clinical as of statistical significance.

Table 2

WEIGHT (kg), BODY MASS INDEX (kg/m^2) and SKIN FOLD THICKNESS (mm) mean (95% CI)

	CONTROL	AEROBIC	POWER
WT1	80.5 (76.1 to 84.8)	76.3 (70.7 to 81.9)	72.6 (68.5 to 76.6)
WT2	81.8 (77.4 to 86.1)	77.2 (71.6 to 82.8)	72.3 (68.2 to 76.4)
WT3	81.6 (77.6 to 85.6)	77.1 (71.4 to 82.8)	72.7 (68.6 to 76.7)
BMI1	27.5 (26.2 to 28.9)	26.9 (25.6 to 28.3)	25.8 (24.4 to 27.1)
BMI2	27.9 (26.6 to 29.3)	27.2 (25.9 to 28.6)	25.7 (24.3 to 27)
BMI3	27.9 (26.6 to 29.2)	27.2 (25.8 to 28.6)	25.8 (24.5 to 27)
SFT1	47.5 (41.5 to 53.4)	46.6 (40.6 to 52.6)	40.4 (36.8 to 44)
SFT2	48.9 (43 to 54.8)	46.4 (40.5 to 52.2)	39.7 (36.8 to 42.6)
SFT3	47.4 (42.3 to 52.5)	45.1 (39.3 to 50.9)	38 (35 to 41)

'1' baseline; '2' three months; '3' six months.

SECTION VIII

THE EXERCISE TEST

Exercise tests were done using the Marquette Case II computerised system. The treadmill is connected to electrocardiographic (ECG) monitoring and display equipment. Leads II, V1 and V5 are continuously displayed, with single complexes of the other leads shown alongside on screen. Full 12-lead electrocardiographs, with automatic ST segment analyses are printed every three minutes. The ST segment is measured 60ms from the J-point, and values exceeding 0.1 mV are considered positive for ischaemia. In addition to the automatic analysis, each exercise ECG is checked manually for artefact, such as that created by poor quality recordings, or movement.

The system records heart rate, exercise time, maximum ST segment depression and the time at which this occurred, estimated workload in metabolic equivalents (mets; 1 met = 3.5ml O_2/kg/min), percentage of target heart rate reached, and number of ventricular ectopics. The final report also displays leads in which 0.1 mV ST depression occurred. The number of ventricular ectopics is unreliable because of artefact, and has not been included in the results.

A modified Balke II protocol was used. This consists of three minute stages. The speed and gradient increase after the first stage from 3.2kph, 0% to 4.8kph, 4%. The speed stays constant from the second to the sixth stage, while the gradient increases by 4% per stage. At the seventh stage, the speed increases to 7.2kph and gradient remains at 20%. This protocol was chosen because most of the patients were already familiar with it. The modified Balke

protocol is the one used for clinical assessments in our department and most of the patients would have had pre-surgery treadmill tests using it. In terms of workload, there is a gradual increase in this with each stage, and so is a physiologically sound means of testing exercise capacity.

Stage	Speed (kph)	Gradient (%)	Mets
1	3.2	0	3
2	4.8	4	5
3	4.8	8	7
4	4.8	12	8
5	4.8	16	10
6	4.8	20	12
7	7.2	20	15

The exercise tests were done between 09.00h and 11.00h. Resting ECG was done after the patient had been sitting for two to three minutes. The blood pressure was measured manually then and at two minutes into each stage of exercise, and entered into the computer.

Each patient had four exercise tests for the purposes of exercise test data and parameters during the programme: two at baseline, and one each at three and six months. The average of the two baseline tests was taken as baseline performance.

The tests were symptom-limited. A note was made of the symptom and also entered into the computer. A fall in systolic blood pressure of greater than

10mmHg from the previous reading, or significant ventricular arrhythmias were other reasons for stopping the test.

The following parameters were recorded for each patient at each assessment:

Resting heart rate (RHR), resting systolic blood pressure (RSBP), submaximal heart rate (SMHR), submaximal rate-pressure product (SMRPP), maximum rate-pressure product (MRPP), maximum heart rate (MHR), maximum treadmill time (MTT), maximum workload (MMET), maximum ST segment depression (MSTD), time to 1mm ST segment depression (TSTD) if any, percentage of target heart rate achieved (PTHR) and heart rate at 5 minutes into recovery (FHR). Target heart rate is calculated as 220 minus age of patient.

These are measures of both physical fitness and residual myocardial ischaemia. A resting bradycardia and rapid recovery of heart rate after exercise are taken as indicative of a fit person. Low submaximal heart rate and rate-pressure product are also a measure of fitness. Submaximal heart rate and rate-pressure product were measured at the end of the first stage of the protocol. In this context, 'submaximal' refers both to the stage reached in exercise testing, and indirectly, to the effort used. Almost all the patients completed stage 1 of the modified Balke protocol, and went on to exert maximal effort until symptoms limited their performance of the treadmill test. The maximum rate pressure product is commonly taken as an indication of myocardial oxygen demand at peak exercise (Kitamura et al 1972; Clausen 1976; Gobel et al 1978). Maximum treadmill time and workload are indicators of fitness, severity of disease, and in some, motivation.

It is difficult to be certain of the extent to which motivation is a factor, without the use of cardiopulmonary exercise testing, to provide an objective assessment of oxygen consumption, and treadmill time at the anaerobic threshold. Assuming that the patients' characters did not change during the study, the uncertainty can be reduced by the fact that each patient acted as his own control during the programme so that the "motivation factor" remains constant.

ST segment depression is the indicator of ischaemia, and its absence on exercise testing is said to imply a good prognosis. In very simplistic terms, the greater the degree of ST depression the greater the ischaemia, and the quicker it comes on during exercise, the graver the outlook. This is the basis of the exercise test as it is commonly used in diagnostic and prognostic cardiology. There are however some doubts about the significance of ST segment changes during exercise tests after coronary artery surgery, with particular regard to the prognostic implications (Dubach et al 1989; Lavie et al 1991; Yli-Mayry et al 1992). The simple statement mentioned above about ST segment depression may not hold true after coronary artery surgery. Certainly in this study, I witnessed several episodes of severe but asymptomatic ST depression, that made me wonder about the patency of the grafts and native coronary arteries in the patients involved.

The time to 1mm ST depression, if any, was recorded manually. If this was a transient occurrence, then it was subsequently ignored. If there was no ST depression during the test it was assumed to occur after the maximum exercise time, and was recorded as such, rather than at infinity, which would

be impossible to fit into any analysis.

The heart rate five minutes into recovery was used as a measure of fitness; a recovery rate (RR) was derived as the difference between maximum heart rate and five minute heart rate divided by five (MHR -FHR/5), and expressed in beats/min. The higher the recovery rate, the fitter the patient. A recovery rate fraction (FRR) was calculated as the difference between maximum heart rate and five minute heart rate, divided by maximum heart rate (MHR - FHR/MHR), and expressed as a ratio. The higher the ratio, the fitter the patient.

Interval changes in submaximum (DSM) and maximum rate-pressure product (DM), maximum treadmill time (DTT) and maximum workload (DMET) were calculated for each group. Interval change from baseline to 3 months is denoted '1', baseline to 6 months, '2'. From 3 to 6 months the prefix 'int' is used. This notation applies whenever interval changes are mentioned.

RESULTS

In all tables the suffix '1' is used for results at baseline, '2' for three months, and '3' for six months, unless otherwise specified. Results are shown as the mean with 95% confidence intervals.

Symptoms

Common symptoms limiting the test were fatigue, dyspnoea, leg ache and chest pain. In a small number of cases the exercise test was stopped because of other complaints such as dizziness (tables 3 - 5).

TABLE 3

REASONS FOR STOPPING EXERCISE TESTS : CONTROL GROUP

Symptom/No.of cases	Baseline	3 months	6 months
Dyspnoea	13	13	9
Fatigue	8	5	11
Leg ache	4	7	5
Chest pain	0	0	0
Other	1	1	1

TABLE 4

REASONS FOR STOPPING EXERCISE TESTS :AEROBIC GROUP

Symptoms/no. of cases	Baseline	3 months	6 months
Dyspnoea	7	9	6
Fatigue	7	8	10
Leg ache	8	6	5
Chest pain	4	4	5
Other	1	0	0

TABLE 5

REASONS FOR STOPPING EXERCISE TESTS : POWER GROUP

Symptoms/no. of cases	Baseline	3 months	6 months
Dyspnoea	10	6	5
Fatigue	6	6	6
Leg ache	6	12	11
Chest pain	1	0	0
Other	1	1	0

As would be expected, 99% were cured of chest pain by coronary artery surgery; only five patients stopped the test because of chest pain. Most were limited by dyspnoea and fatigue. This pattern did not change over the training period. I would have expected more patients to develop a recurrence of angina in that time; on the other hand, those in the aerobic group who had persistent angina were not cured of it by the programme. The numbers involved are too small for more meaningful comment to be made on this issue.

Exercise performance (table 6)

There were significant differences in exercise performance between the control and aerobic-trained groups at three and at six months ($2p = 0.037$ at three months; $2p = 0.002$ at six months; $2p = 0.05$ between three and six months). In the power group, their exercise performance at six months was better than that of the control group ($2p = 0.031$), and interval change at six months was in keeping with this ($2p = 0.075$).

Table 6

EXERCISE PERFORMANCE IN THE THREE GROUPS AT EACH ASSESSMENT AND INTERVAL CHANGES (s)

	CONTROL	AEROBIC	POWER	P
MTT1	683.8 (558.6 to 809.1)	650.5 (549.7 to 751.3)	784.2 (657.8 to 910.5)	NS
MTT2	718.2 (585.3 to 851)	780.8 (673.2 to 888.4)	867.3 (743.6 to 991)	NS
MTT3	710.8 (575.6 to 846)	846.9 (746.5 to 947.3)	906.8 (785.3 to 1028.3)	* 0.031
DTT1	34.3 (-1 to 69.6)	130.3 (46.4 to 214.2)	83.1 (0.9 to 165.3)	** 0.037
DTT2	27 (-40.4 to 94.4)	196.4 (112.2 to 280.7)	122.7 (37.7 to 207.6)	** 0.002
INTTT	-7.3 (-60.6 to 45.9)	66.2 (13 to 119.3)	39.5 (5.6 to 73.5)	** 0.05

Two-tailed 't' test: * power vs control; ** aerobic vs control

The results for estimated maximum workload in metabolic equivalents (mets), follow a similar pattern to that of treadmill time, but the differences are more striking. Thus, the interval change at three months was significantly better between aerobic and control groups ($2p = 0.009$), and maintained at six months ($2p = 0.002$). Between three and six months, there was no significant change between those two groups ($2p = 0.12$). In the power group, the workload at six months was higher than that in the control group ($2p = 0.03$), interval change from baseline to six months was higher ($2p = 0.064$), as was the interval change from three to six months ($2p = 0.05$) (table 7).

These results support the view that exercise training improves exercise performance. In addition, the results suggest that aerobic exercise training in this group of post-CAS patients causes earlier benefit in treadmill performance than does power exercise training, when compared to a control group. However, there were no discernable differences in treadmill performance between the two types of exercise training at the end of the six month training period. This would imply that in the long run, the two types are equally beneficial, but that the effects of power training are slower in onset.

There were no differences in resting heart rate, resting systolic blood pressure, submaximum and maximum heart rates, time to ST segment depression, maximum ST segment depression, submaximum rate-pressure product, five minute heart rate, or percentage target heart rate between the groups at any time (tables 8 to 16).

The degree of ischaemia as measured by maximum ST segment depression during the exercise test did not change with exercise training. In no

group, however, did it reach the critical 2mm, usually taken as the cut-off for an unequivocally positive exercise test. This merely indicates that the operation may have improved myocardial perfusion, but more evidence for this may come from the results of thallium myocardial perfusion scans.

The power-trained group achieved a higher maximum rate-pressure product compared to the control group (2p = 0.023), but there was no difference in that achieved by the two exercise groups or between the aerobic and control groups. When looked at as the interval change from baseline and from three months, the significant difference remains for the power and control groups (DM2 2p= 0.02; INTM 2p= 0.027). This is because in the control group, the maximum rate-pressure product fell with time, while in the aerobic group, it did not rise by much. This may be interpreted as the power group having a higher myocardial oxygen consumption at the end of the period of training, the aerobic group achieved only a modest increase while perhaps not surprisingly, the control group had a drop in myocardial oxygen consumption (table 17). The confidence intervals do overlap, and include zero for the exercise groups, making the clinical relevance of this finding doubtful.

Table 7

ESTIMATED WORKLOAD IN THE THREE GROUPS AT EACH ASSESSMENT AND INTERVAL CHANGE BETWEEN THEM (mets)

	CONTROL	AEROBIC	POWER	P value
MMET1	7.5 (6.1 to 9)	7 (6.2 to 7.9)	8.6 (7.3 to 10)	NS
MMET2	7.8 (6.3 to 9.2)	8.4 (7.3 to 9.5)	9.3 (8 to 10.5)	NS
MMET3	7.8 (6.3 to 9.3)	9 (7.9 to 10.2)	10 (8.6 to 11.3)	* 0.03
DMET1	0.2 (-0.2 to 0.7)	1.4 (0.7 to 2.1)	0.6 (-0.2 to 1.5)	** 0.009
DMET2	0.2 (-0.5 to 1)	2 (1.2 to 2.8)	1.3 (0.4 to 2.3)	** 0.002
INTMET	0 (-0.6 to 0.6)	0.6 (0.1 to 1.2)	0.7 (0.3 to 1.2)	* 0.05

Two-tailed 't' test: * power vs control; ** aerobic vs control

Table 8

RESTING HEART RATE (beats/minute)

	CONTROL	AEROBIC	POWER
RHR1	80.6 (76.8-84.4)	77 (71.5-82.4)	82 (78.2-85.9)
RHR2	83.2 (77.6-88.7)	77.7 (71.4-83.9)	78.9 (74.3-83.4)
RHR3	80.2 (74.8-85.6)	79.8 (72.6-87)	79.3 (74-84.6)

Table 9

RESTING SYSTOLIC BLOOD PRESSURE (mmHg)

	CONTROL	AEROBIC	POWER
RSBP1	131.2 (122.5-139.8)	130.4 (122.6-138.1)	128.1 (121-135.3)
RSBP2	127.3 (119.8-134.8)	125.2 (118.2-132.2)	128.8 (120-137.5)
RSBP3	122.1 (115.4-128.9)	125.2 (118.1-132.3)	125.8 (117.2-134.5)

Table 10

HEART RATE AT SUBMAXIMUM EXERCISE (beats/minute)

	CONTROL	AEROBIC	POWER
SMHR1	104.1 (97.4-110.8)	106.7 (99.1-114.2)	106.2 (101.2-111.2)
SMHR2	104.1 (97.2-106.1)	99.5 (92.9-106.1)	98.2 (93.5-102.9)
SMHR3	99.7 (93.9-105.7)	99 (91.5-106.4)	97.7 (91.8-103.5)

Table 11

RATE-PRESSURE PRODUCT AT SUBMAXIMUM EXERCISE (beats/min mmHg)

	CONTROL	AEROBIC	POWER
SMRPP1	15151.54 (13432.09-16870.98)	15186.73 (13584.23-16789.23)	17060.83 (12012.04-22109.63)
SMRPP2	14206.58 (12922.41-15490.74)	13145.19 (11776.65-14513.73)	13381.25 (12246.67-14515.83)
SMRPP3	13059.04 (12000.13-14117.94)	13045.58 (11723.97-14367.18)	13114.58 (11943.24-14285.93)

Table 12

MAXIMUM HEART RATE (beats/min)

	CONTROL	AEROBIC	POWER
MHR1	149.5 (139.4-159.6)	144.8 (134.4-155.2)	154.8 (147.5-161.9)
MHR2	149.9 (139.4-160.5)	148.5 (137.9-159.2)	152.3 (144.1-160.6)
MHR3	145.4 (134.8-156)	150.9 (140.6-161.2)	157 (149.6-164.5)

Table 13

TIME TO 1mm ST SEGMENT DEPRESSION (s)

	CONTROL	AEROBIC	POWER
TSTD1	526.2 (389.6-662.9)	543.5 (439.9-647.2)	538.6 (405.2-672)
TSTD2	534.4 (410.1-658.8)	525.3 (408.5-642.1)	609.6 (472.3-747)
TSTD3	579.4 (444.4-714.4)	695.5 (565.5-826.6)	641.7 (491.1-792.4)

Table 14

MAXIMUM ST SEGMENT DEPRESSION (mm)

	CONTROL	AEROBIC	POWER
MSTD1	1.23 (0.96-1.49)	1.19 (0.92-1.45)	1.44 (1.05-1.83)
MSTD2	1.24 (0.99-1.48)	1.4 (1.08-1.72)	1.58 (1.19-1.97)
MSTD3	1.13 (0.92-1.35)	1.24 (0.93-1.55)	1.52 (1.09-1.95)

Table 15

HEART RATE FIVE MINUTES INTO RECOVERY PERIOD (beats/min)

	CONTROL	AEROBIC	POWER
FHR1	98.2 (92-104.5)	92.4 (85.3-99.5)	101.8 (96.8-106.7)
FHR2	97.8 (91.8-103.8)	95.2 (88.3-102.1)	97.8 (92.5-103.2)
FHR3	93.2 (85.2-101.2)	96.9 (85.7-108.2)	98.9 (92.6-105.2)

Table 16

PERCENTAGE TARGET HEART RATE ACHIEVED (%)

	CONTROL	AEROBIC	POWER
PTHR1	92.2 (86-98.4)	87.9 (82.2-93.6)	95.7 (91.5-99.9)
PTHR2	92.4 (86.5-98.3)	90.4 (84.5-96.2)	95.3 (90.2-100.3)
PTHR3	91.4 (85.4-97.5)	92.1 (86.4-97.8)	97.5 (92.7-102.4)

Table 17

MAXIMUM RATE-PRESSURE PRODUCT AND INTERVAL CHANGE
(beats/min mmHg)

	CONTROL	AEROBIC	POWER	P value
MRPP1	25079.8 (22732.3 to 27427.3)	23281.9 (21156.4 to 25407.4)	25646.3 (23571.3 to 27721.2)	NS
MRPP2	25212.1 (22449 to 27975.2)	23427.2 (20821.2 to 26033.1)	26003.1 (23821.3 to 28185)	NS
MRPP3	23181.2 (20944.8 to 25417.5)	23527.3 (21028.9 to 26025.7)	26568.1 (24620.9 to 28515.4)	0.023
DM1	132.3 (-1722 to 1986.6)	145.2 (-1797.3 to 2087.6)	356.9 (-1155 to 1868.8)	NS
DM2	-1898.7 (-3193.7 to -603.6)	245.4 (-1371.7 to 1862.5)	921.9 (-1098.4 to 2942.2)	0.02
INTM	-2031 (-3720.6 to -341.3)	100.2 (-1496.2 to 1696.5)	565 (-1057.4 to 2187.4)	0.027

Looking at fitness levels using recovery rate and the recovery rate fraction, the power group was fitter than the control group after six months (RR3 2p = 0.01; FRR3 2p = 0.032). There were no significant differences between the control and aerobic groups or between the two exercise-trained groups. There was a fall in the recovery rate in the control group, while that in the power group rose, and the aerobic group stayed static. Once again, there appears to be a gradation from control to aerobic to power. Those in the aerobic group improved their exercise performance early on, while the improvements in exercise performance in the power group were slower in onset. Both exercise-trained groups may have slightly improved their level of fitness. This is shown by increased exercise performance in the two groups, and better recovery rate, particularly in the power group (table 18).

Table 18

RECOVERY RATE (beats/min) and RECOVERY RATE FRACTION

	CONTROL	AEROBIC	POWER	P value
RR1	10 (8.9 to 11.3)	10.5 (9.6 to 11.4)	10.6 (9.6 to 11.6)	NS
RR2	10.2 (8.9 to 11.6)	10.7 (9.5 to 11.9)	11 (9.9 to 12.2)	NS
RR3	9 (7.3 to 10.7)	10.3 (8.6 to 12)	11.8 (10.6 to 13)	0.01
FRR1	3.3 (3 to 3.6)	3.6 (3.4 to 3.8)	3.4 (3.2 to 3.7)	NS
FRR2	3.4 (3.1 to 3.7)	3.6 (3.3 to 3.8)	3.4 (3 to 3.8)	NS
FRR3	3.2 (2.7 to 3.6)	3.4 (3.1 to 3.8)	3.7 (3.4 to 4)	0.032

DISCUSSION

Exercise performance on the treadmill was the primary endpoint of the study. This did improve with exercise training, and to a different degree with the two types of exercise.

In summary, the main findings from the exercise test data were:

a) early and sustained improvement in treadmill time and workload in aerobically trained patients, with no changes in level of fitness or maximum myocardial oxygen consumption.

b) delayed improvement in treadmill time and workload in power trained patients, associated with increases in the level of fitness and maximum myocardial oxygen consumption.

There was a 20% increase in treadmill time in the aerobic group after three months' training, with a further 10% increase at the end of six months, resulting in a 30% improvement in treadmill time at the end of training.
In the power group, there was an 11% increase after three months and a further 5% increase after six months. The effect of power exercise training was therefore a 16% improvement in treadmill time. These compare with a 5% overall increase in the control group. Figure 1 shows the results of treadmill performance in graphical form. The asterisks represent the significant differences in exercise capacity discussed earlier.

There were small falls in resting heart rate (3 beats/minute) submaximum heart rate (8 beats/minute) and submaximum rate-pressure product (3946 beats/minute mmHg) in the power group. Had these other markers of physical

fitness been more prominent, they would have lent more support to the changes in recovery rate observed in the power group.

It is known that exercise training induces a 'training response'. This comprises a resting bradycardia, reduced heart rate and rate-pressure product at submaximum exercise, increased maximum exercise duration, maximum oxygen consumption and cardiac output and a shorter recovery time.

This effect is often described in exercise training studies (Ehsani et al 1981; Ehsani et al 1982; Laslett et al 1985; Oberman 1988; Ades et al 1989; Wenger 1989). There may also be an increase in the exercise test workload at which ischaemia occurs (Ehsani et al 1981; Laslett et al 1985; Opasich et al 1988).

The exercise trained groups in this study achieved this to a varying degree. Perhaps the intensity of training was not high enough to enable them to achieve all the elements of the training response. Oxygen consumption and cardiac output were not measured in this study.

The use of the treadmill to assess those undergoing power training may have been unfair. It is said that the effect of training is very specific (Jones 1992). One could say that the assessment that was used tested endurance and not strength. This would mean that the aerobically trained patients would be at an advantage. It may have been fairer to incorporate an assessment of strength such as the one-repetition maximum test. Despite this possible limitation, the power group showed significant improvements in exercise capacity on a treadmill. The power exercise programme did include leg exercises, and the repetitive nature of the movements could have improved

endurance. Specific tests of strength may have shown even greater benefits.

It has not yet been possible to deduce the mechanisms of the highly significant improvements in treadmill time and workload achieved by the aerobically trained patients. Nevertheless this can be translated into major gains in terms of physical capacity in the performance of everyday activities, which would occur early in the training programme.

I would suggest that aerobic training may be the preferred type of exercise early after coronary artery surgery, while for more protracted programmes, power exercise training could be introduced later on. An additional point in this regard concerns problems with surgical scars in patients using weight-training equipment soon (i.e. 6 to 12 weeks) after the operation. In this study, two patients had to drop out because of such problems. One had excessive pain in the scar, and the other had difficulty in healing of the lower end of the wound.

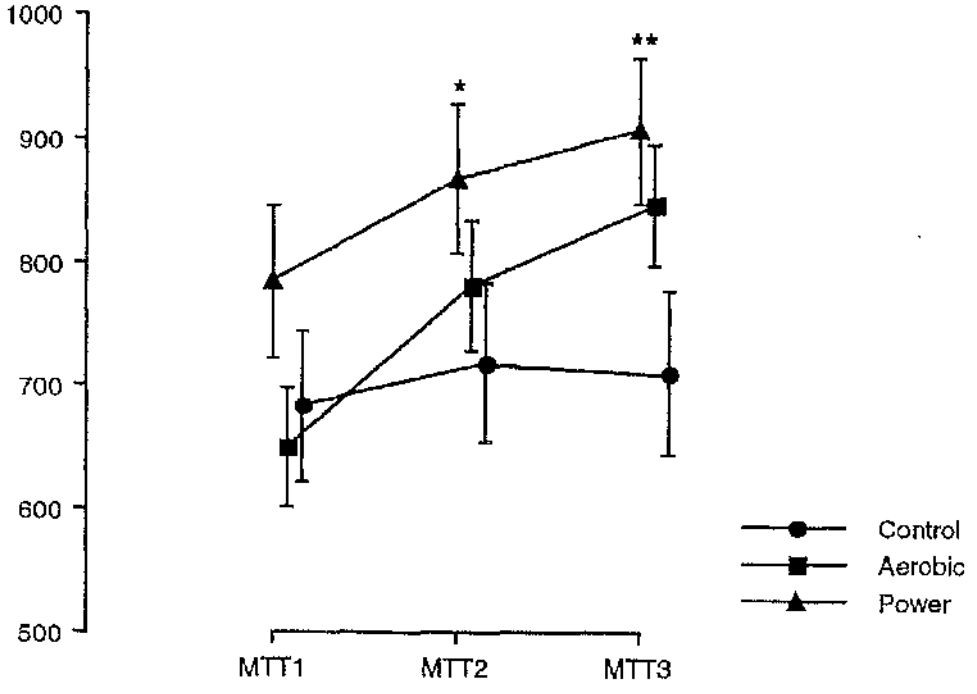


Figure 1

Maximum treadmill exercise performance at each assessment(s) mean (SEM)

STUDIES ON EXERCISE TRAINING AFTER CORONARY ARTERY SURGERY

To date, there have been reports on exercise training after coronary artery surgery in around 400 patients.

In a study of 45 subjects reported by Adams et al (1974), there were four CAS patients, 11 were post MI and the rest normal. The CAS patients achieved as much as post-MI patients after aerobic training.

Six patients and six controls had a pre-operative exercise test and another 16 weeks after surgery. After 32 months of exercise sessions 45 - 60 minutes daily, there were no significant change in resting heart rate or blood pressure. Maximum oxygen uptake increased by 28% in the exercise group and by 3% in the controls. Ninety percent of the total improvement in functional capacity had occurred by 4 months (Oldridge et al 1978).

In 51 patients eight to ten weeks after surgery, attending 16 minute training sessions three times a week, there was a significant improvement in duration of exercise and maximum work load after 8 weeks (Horgan et al 1980).

In a non-randomised study involving 27 post-CAS patients, there was a significant increase in maximum oxygen uptake and maximum heart rate after an in-patient programme of bedside exercise and early ambulation, followed by 3 times weekly monitored callisthenics for 6 weeks (Soloff 1979).

Hartung and Rangel (1981) found that maximum oxygen uptake increased in 10 post-CAS patients who had 20 - 40 minutes aerobic exercise sessions three times weekly for three to six months.

In the largest of the studies, Dornan et al (1982) reported on 210 males referred consecutively to a rehabilitation programme after coronary artery surgery. They had a submaximum exercise test at 8 weeks, followed by 12 weeks training and a repeat exercise test. The patients were divided into those who were on drugs and those who were not. Age and extent of revascularisation did not appear to influence exercise tolerance. Both groups improved significantly after training, but those who were on drugs performed worse.

In a retrospective study of 22 patients, it was found that those who dropped out of a rehabilitation programme did worse in terms of exercise performance, employment status and re-hospitalisation rates (Waites et al 1983).

In the PERFEXT study, post-CAS patients formed a third of the group, and they showed the haemodynamic benefits, such as higher maximum oxygen uptake, that were demonstrated in the other types of patients. This was particularly so in the subgroup with angina (Froelicher et al 1985).

All of these studies therefore show that exercise training does improve exercise capacity after coronary artery surgery.

As mentioned before, most of them included CAS patients as part of a larger group of cardiac patients. None of these previous studies addressed the effects of power training.

The present study was concerned with establishing the effects of exercise rehabilitation on a group comprising only surgical patients.

The main results of the exercise test data are in keeping with what has gone before. It also adds a new dimension and extends our knowledge by assessing the effects of power (strength) training after coronary artery surgery.

STUDIES INVOLVING STRENGTH TRAINING IN CARDIAC PATIENTS

Power or strength training is usually recommended in cardiac patients only after a period of aerobic training has been completed (Crozier Ghilarducci et al 1989; Sparling et al 1990; McKelvie & McCartney 1990). There are limited reports on its effects in normal subjects and cardiac patients (Effron 1989; Stewart 1989; Kelemen 1989; Hill & Butler 1991; Verrill et al 1992; Stewart 1992). Most would recommend circuit weight training as was used in this study (Kelemen et al 1986).

Nine stable aerobically trained cardiac patients had strength training 30 minutes a day, three times a week for 10 weeks. They exercised at 80% maximal voluntary contraction at five stations. Heart rate and blood pressure were monitored during exercise. No signs or symptoms of ischaemia, abnormal heart rate or blood pressure responses occurred. Body weight, skin fold thickness, girth and maximal voluntary contraction were measured. Quadriceps girth increased by 11%. Maximal voluntary contraction increased by up to 53% (Crozier Ghilarducci et al 1989).

Sixteen men in cardiac rehabilitation had circuit training at twelve stations as a supplement to their aerobic exercise for six months. Significant improvement in strength was observed, with 22% increases for all 12 exercises. There were no changes in body weight or percent fat (Sparling et al 1990).

Where direct comparisons have been made between aerobic and strength training, the physiological responses to the latter have been less alarming than expected (McCartney et al 1993).

Collins et al (1991) studied 15 men. During circuit weight training at 40, 50, 60 and 70% of one repetition maximum, percent VO_2 max was consistently lower than that predicted for dynamic exercise such as running or cycling, for a given percent of maximum heart rate. They concluded that using heart rate to prescribe the intensity of weight lifting exercise results in a lower level of aerobic metabolism than during dynamic exercise.

Twelve men with CAD exercised to fatigue at four stations in a circuit. The responses were compared to that on a treadmill. There was less ischaemia, lower peak heart rate and rate pressure product, similar peak systolic pressure, but higher diastolic pressure (Featherstone et al 1993).

After a six week period of aerobic exercise, 25 patients were divided into two groups. Thirteen patients continued with the aerobic programme for another six weeks. Twelve patients performed 15 minutes of aerobic exercise in addition to upper body circuit weight training. Peak heart rate and rate pressure product were similar, but peak systolic blood pressure was higher during aerobic exercise than circuit training. Treadmill time increased in both groups, but upper body strength increased only in the circuit weight training group (Butler et al 1992).

Combined weight lifting and aerobic exercise training (10 patients) resulted in greater improvements in both cycle ergometer performance and one repetition maximum than did aerobic training alone (8 patients). After aerobic training the one repetition maximum increased by 4 - 13%, compared to 21 - 43% after combined training; cycle ergometer power output increased by 2% and 15% respectively and cycling time also increased significantly more in the combined training group (McCartney et al 1991).

Power training therefore improves aerobic capacity. The results of the present study are in keeping with this view. Muscular strength is also improved by power training; this was not assessed in the study.

SECTION IX

HAEMOSTATIC FACTORS

There have been many reports on the effects of acute exercise on platelets and their function, clotting factors and fibrinolysis in normals and in those with CAD. These have yielded varying results: increased platelet count and adhesiveness potentiation of coagulation by increased factor VIII levels, and enhanced fibrinolysis (Iatridis & Ferguson 1963; Menon et al 1967; Ferguson & Guest 1974; Davis et al 1976; Sarajas 1976; Speiser et al 1988). Prolonged aerobic exercise causes strong activation of the fibrinolytic system, slight increase in platelet count, and no change in platelet function, or in prothrombin time. Static exercise of short duration has no effect on platelet function, coagulation and fibrinolytic activity. Repeated bouts of maximum exercise with acidosis, causes a significant increase in platelet count and function, and fibrinolytic activity (Drygas 1988).

In contrast, little is known about the effects of chronic exercise training on haemostatic factors (Ferguson & Guest 1974; Sellier et al 1988; Connelly et al 1992; Wosornu et al 1992). The effects of physical conditioning on fibrinolysis are known. After training on a treadmill for ten weeks, the fibrinolytic response to venous occlusion is augmented (Williams et al 1980). Regular vigorous sporting activity enhances blood fibrinolysis by reducing plasminogen activator inhibitor capacity in normals, but not always in post-MI patients in a rehabilitation class (Estelles et al 1989). Marathon runners have greater increases in fibrinolytic activity compared with that achieved by joggers

and previously sedentary persons (Ferguson et al 1987).

This part of the study was concerned with establishing the effects of the training programme on haematological factors that could influence subsequent cardiovascular events.

METHODS

Forty five millilitres (ml) of venous blood were drawn through indwelling cannulae, after an overnight fast. The first 30 ml were used for lipoprotein analysis. Haemoglobin, platelet count and haematocrit were all measured in five ml of blood in the standard way using a Coulter counter.

Five ml were for assays of factor VII and fibrinogen , and the remaining five ml for assay of fibrinopeptide A. The technicians performing the assays were not aware of the patients' groups. Samples were stored at -85°C in plastic containers and tested in batches. Factor VIIc and fibrinogen samples were stored for up to two weeks, fibrinopeptide A samples were stored for up to six weeks.

Factor VIIc assay.

This was done by bioassay of the activity of VIIc in plasma, and measured by the amount of correction of the one-stage prothrombin time obtained when the patient's plasma was added to factor VII-deficient plasma. The reagents required are available commercially and include factor VII-deficient plasma, saline extract of brain, Owren's buffer (pH 7.35), 0.025M calcium chloride, patient's citrated platelet-poor plasma, and reference plasma containing 100iu/dl of factor VII. After preparing serial dilutions of the reference plasma in Owren's buffer, 0.1 ml of factor VII-deficient substrate plasma, 0.1 ml of normal plasma dilution and 0.1ml of saline extract of brain are placed in a glass test tube in a water bath at 37°C. The mixture is incubated for 30s , and 0.1ml of 0.025M calcium chloride is added. The clotting time is recorded. Each dilution is so tested twice, and the average clotting time is plotted on a double-log graph paper against calculated plasma factor VII level. The 1 in 10 dilution of normal plasma is considered to contain 1 unit of factor VII activity per ml. The patient's plasma is similarly assayed, with dilutions tested depending on the approximate expected factor VII levels. The clotting time of the dilution of patient's plasma is converted to factor VII activity by extrapolation from the standard graph.

The normal range is 60 - 150iu/dl.

Fibrinogen assay

This is also a bioassay and a standard procedure. It is done using Multifibren (Behring) and a modification of the Clauss method. Multifibren consists of lyophilised alpha-thrombin from bovine plasma. The principle is that citrated plasma is clotted by the addition of a relatively large amount of thrombin, clotting time depending mainly on the fibrinogen content of the blood sample. Plasma is diluted 1 in 9 with barbital buffer solution (pH 7.6) and the assay performed within 15 minutes. 0.2 ml of citrated plasma solution and 0.2 ml of Fibrintime are placed in a prewarmed test tube at 37°C, incubated for 60s, and 0.2 ml of Multifibren added. The clotting time is recorded. The result is converted to g/dl using a standard table of values supplied in the kit. Reference curves are checked using supplied control plasma (lyophilised human plasma).

The normal range is 1.8 - 3.5g/dl.

Fibrinopeptide A assay

The assay is based on enzyme linked immunosorbent assay (ELISA) techniques (Boehringer Mannheim). Incubation of constant amounts of fibrinopeptide A (FPA) antibody with the sample leads to the formation of antigen-antibody complexes. The concentration of residual excess antibody is inversely proportional to the amount of FPA in the sample. To determine the concentration of antibody, aliquots of the incubation mixture are transferred

into reaction vessels coated with excess FPA, for subsequent incubation. The wall-bound antigen-antibody complexes obtained form sandwich complexes with peroxidase labelled anti-immunoglobulin G antibodies. The amount of these complexes provides a direct measure of FPA concentration in the sample. The sandwich complexes obtained are determined by enzymatic reaction of peroxidase with hydrogen peroxide/orthophenylene-diamine (a chromogen), and subsequent spectrophotometric measurement at 492nm. Due to the inverse relationship of bound enzyme activity and antigen concentration, the measured absorbances decrease as FPA concentration increases. The results are further evaluated by constructing a reference curve with standards of known concentration. Normal values are < 3 ng/ml.

RESULTS

The results presented are on 55 patients (71.4%) in whom the full complement of haematological results are available. In the remainder, some samples were clotted, or otherwise unsuitable for assay (e.g. delay in reaching the laboratory).

There were 20 patients each in control and power groups, and 15 in the aerobic group.

There were no significant changes in haemoglobin, haematocrit, or platelet count (table 19).

Fibrinopeptide A levels were positively skewed, and the results were therefore analysed by non-parametric methods. There were no significant

changes in FPA with time, and the results are presented as median and range (table 20).

At baseline, 69% of controls, 74% of aerobic and 87.5% of power groups had levels in the normal range. At three months, these figures were 50%, 81.5% and 79.2% respectively. At six months, they were 69.2%,59.3% and 70.8%. So apart from the control group at three months, the majority of patients had FPA levels in the normal range.

The abnormal values ranged from 3 to 66 ng/ml. In the aerobic group, a patient, A.C., developed angina during the course of the study. His FPA levels were 0.5 ng/ml, 14 ng/ml and 44ng/ml at baseline, three and six months respectively. In the power group, J.C. developed angina after three months. His FPA level rose from 0.8ng/ml then to 18ng/ml at six months. From these two examples, one wonders if the levels could have been related to patients' symptoms or the underlying dynamics of their coronary circulation. Obviously, these are anecdotal in the context of this study, but still worthy of mention in the light of previous studies showing high FPA levels in patients with unstable angina (Eisenberg et al 1985; Theroux et al 1987). The true significance of the abnormally high FPA levels encountered in this study is not, however, entirely clear.

Table 19

HAEMOGLOBIN,(g/dl) HAEMATOCRIT (%) AND PLATELET COUNT

	CONTROL	AEROBIC	POWER
HB1	14.8 (14.1 to 15.5)	14.7 (14.3 to 15.1)	15.1 (14.7 to 15.5)
HB2	14.7 (14 to 15.3)	14.6 (14.2 to 15)	15 (14.6 to 15.4)
HB3	14.6 (13.9 to 15.4)	14.9 (14.5 to 15.3)	15.1 (14.7 to 15.5)
HCT1	43.5 (41.5 to 45.4)	43.1 (41.8 to 44.5)	44.5 (43.2 to 45.8)
HCT2	43.2 (41.5 to 44.9)	42.6 (41.5 to 43.7)	43.7 (42.3 to 45.1)
HCT3	42.5 (40.6 to 44.5)	43.7 (42.6 to 44.7)	43.8 (42.5 to 45.1)
PLT1	286 (257 to 315)	271 (238 to 304)	273 (245 to 301)
PLT2	290 (259 to 321)	260 (230 to 290)	254 (226 to 282)
PLT3	299 (256 to 341)	261 (230 to 292)	255 (230 to 280)

Table 20

FIBRINOPEPTIDE A LEVELS (ng/ml)

	CONTROL	AEROBIC	POWER
FPA1	0.65 (0.2-66)	0.9 (0.2-15)	0.8 (0.2-46)
FPA2	2.55 (0.2-41)	1.0 (0.2-45)	0.9 (0.3-44)
FPA3	1.5 (0.2-40)	1.2 (0.3-44)	1.0 (0.2-50)

Results for fibrinogen levels are in table 21. There was a 12% reduction in fibrinogen levels in the aerobic group at the and of the study. This was evident at three months ($p = 0.01$), and was maintained at six months ($p = 0.04$). At six months, there was a 2% reduction in fibrinogen in the power group, and a 4% reduction in the control group, but these did not achieve statistical significance.

'P' values for interval change in fibrinogen levels between the groups highlights the reduction in the aerobic group. (table 22) At three months, aerobic vs control $p = 0.0004$, control vs power $p = 0.07$, aerobic vs power $p = 0.0002$. At six months, acrobic vs control $p = 0.02$, control vs power $p = 0.09$, aerobic vs power $p = 0.05$. The interval changes in fibrinogen level in the aerobic group at three months and at six months were both statistically significant ($p = 0.01$ and 0.04 respectively).

In this subgroup of patients, aerobic exercise caused an early and sustained fall in fibrinogen levels. Based on results of epidemiological surveys, this change would be considered a favourable one. It was not the purpose of the study to establish the mechanism for this. Smoking increases fibrinogen levels, but does not play a major part here since the majority of the patients were ex-smokers at the start of the study.

Factor VIIc levels rose with exercise training in the aerobic group, but fell very slightly in the power group, so that at the end of training, the difference in the two exercise groups was significant (power vs aerobic $p=0.008$; power vs control $p=0.06$) (table 23).

Table 21

FIBRINOGEN LEVELS (g/dl) mean (SEM)

	Baseline	3 months	6 months
CONTROL	3.48 (0.22)	3.87 (0.30)	3.34 (0.19)
AEROBIC	3.40 (0.21)	2.96 (0.16)	2.98 (0.16)
POWER	3.18 (0.12)	3.33 (0.13)	3.12 (0.12)

Table 22

INTERVAL CHANGE FROM BASELINE IN FIBRINOGEN LEVELS (g/dl)

mean (95% CI)

	3 months	6 months
CONTROL	0.36 (-0.18 to 0.56)	-0.15 (-0.42 to 0.12)
AEROBIC	-0.43 (-0.63 to-0.23)	-0.41 (-0.7 to -0.12)
POWER	0.15 (-0.05 to 0.35)	-0.06 (-0.26 to 0.14)

Table 23

FACTOR VIIc LEVELS (iu/dl) mean (SEM)

	Baseline	3 months	6 months
CONTROL	101.22 (4.31)	107.95 (4.5)	109.6 (4.8)
AEROBIC	100.4 (6.73)	108.2 (6.65)	113.67 (5.62)
POWER	105.8 (4.24)	107 (4.45)	104.4 (3.39)

DISCUSSION

The Northwick Park Heart Study showed that factor VII and fibrinogen are independent risk factors for coronary artery disease (Meade et al 1986). The haemostatic system had previously been associated with CAD (Merskey et al 1960; Chakrabarti et al 1968; Stone & Thorp 1985) and with stroke (Wilhelmsen 1984). There have since been other epidemiological studies confirming the importance of the haemostatic system in arterial disease, transient ischaemic attacks, stroke, angina, myocardial infarction and peripheral vascular disease (Kannel et al 1987; Small et al 1988; Lee et al 1990; Qizilbash et al 1991; Yarnell et al 1991; Elwood et al 1993; Meade et al 1993).

Fibrinogen levels are raised in inflammation, as it is an acute phase protein. It is also raised in smokers, older people, hyperlipoproteinaemia, hypertension, diabetes, obesity, and in sedentary persons (Meade 1987). All these are known risk factors for coronary artery disease.

High fibrinogen levels increase plasma viscosity, and platelet adhesiveness, therefore promoting a tendency to thrombosis. There is a linear relationship between the fibrinogen level and the risk of CAD, and this operates even within the physiological range (Meade et al 1985).

To date, there is no simple and safe drug known to reduce fibrinogen levels. Those tried so far are ticlopidine, nisoldipine, stanozolol, oxpentifylline, calcium dobesilate, propranolol, and the fibrates (Ernst 1991). None can be recommended solely for its fibrinogen-reducing properties. Exercise training might be a more innocuous method of trying to influence haemostatic factors.

Factor VII levels correlate positively with dietary fat, plasma cholesterol and triglyceride levels. It is high in oral contraceptive users, older persons, obesity, diabetes. Factor VII activity is inhibited only slowly in plasma, because unlike other coagulation factors, it is not countered by natural inhibitory activity. Its assay is a good measure of coagulable potential. Its activity influences the rate of thrombin formation (Miller et al 1986).

As applied to CAD, hypercoagulability refers more to pro-coagulatory than to the anti-coagulatory influences. There is little information on this aspect in relation to exercise. Acute exercise has not been shown to affect fibrinogen, factors V, VII, or X levels (Iatridis & Ferguson 1963). Strenuous exercise has been shown to be associated with significantly lower fibrinogen concentrations than mild exercise, in a cross-sectional study, while more frequent strenuous exercise was associated with lower factor VII activity (Connelly et al 1992).

With regard to coronary artery surgery, this could have implications for preventing further cardiovascular events and improving graft patency. Although CAS prolongs life in selected patients, it does not prevent subsequent myocardial infarction, because revascularisation does not in itself halt the progression of atheroma. In addition, venous grafts are particularly prone to thrombosis and occlusion.

If it were possible to influence haemostatic factors favourably by means of exercise, it would provide another mechanism for secondary prevention in CAD.

Thrombin is a potent platelet aggregating agent and vasoconstrictor. Thrombin activity, as measured by fibrinopeptide A (FPA) levels, is increased

in patients with unstable angina, myocardial infarction and sudden death (Meade et al 1984; Eisenberg et al 1985; Theroux et al 1987; Willensky et al 1989). Thrombin is difficult to measure directly, because of its very short half-life. Fibrinopeptide A, which is cleaved from fibrinogen by thrombin, is a reliable indicator of thrombin activity. In the Northwick Park Heart Study, an in vivo correlation between factor VII activity and fibrinopeptide A was shown (Miller et al 1986; Meade 1987).

Haemoglobin concentration, haematocrit and platelet count all contribute to plasma viscosity and the propensity to blood sludging up and clotting especially in large vessels.

Fibrinogen and factor VIIc are now accepted as independent risk factors for CAD. That high levels are associated with an increased incidence of CAD has been shown by several epidemiological studies. As is the case for lipids, the search for non-pharmacological ways of altering the levels of these haemostatic factors is worthwhile. No drug has been found to do this innocuously.

As such, the finding that aerobic exercise training for six months caused a 12% reduction in fibrinogen levels is an exciting one. It would represent a substantial reduction in cardiovascular risk for the patients. The relation between fibrinogen levels and cardiovascular risk is a linear one. For every fall of 0.1g/l in fibrinogen concentration, there is a 15% reduction in cardiovascular risk (Connelly et al 1992). Thus the fall of 0.41g/l in the aerobic-trained group at the end of six months, translates into a 61.5% reduction in risk.

In their cross-sectional study, Connelly et al (1992) found that fibrinogen levels were lower in those who took strenuous exercise (2.7g/l) compared to those who took mild or no exercise (2.77g/l). In that study and in others of similar nature, questionnaires were used to assess the extent to which the subjects exercise, and would be prone to errors of reporting, particularly overestimation of strenuous activity in those reporting that. The authors felt that this would have led to an underestimation of the actual difference in fibrinogen concentrations between the exercise levels. In all these studies, there has been an inverse relationship between level of exercise and fibrinogen concentration. In some, but not all, the differences reached statistical significance, and were independent of smoking.

Reports of longitudinal follow up of fibrinogen and factor VII in cardiac patients after exercise training are scanty. There is a report from Russia of a fall in fibrinogen with training in a group of cardiac patients (Dudaev et al 1986).

Other risk factors for ischaemic heart disease that work through an effect on fibrinogen levels are smoking, old age, obesity, diabetes, stress at work, and retarded growth during infancy. In women, use of the oral contraceptive pill and the menopause are additional factors. Cessation of smoking definitely reduces plasma fibrinogen levels (Meade 1987). It would now appear that exercise training also does the same.

Factor VIIc levels are low in those undertaking strenuous exercise frequently, thereby suggesting that it also is influenced by exercise (Connelly et al 1992). Perhaps the patients in my study did not achieve the level of

exercise required to lower factor VII concentrations, hence the result obtained of an increase in the aerobic-trained group and a very small fall in the power-trained group.

The patients were not given specific dietary advice. Dietary variations could have been a factor in the differences seen in factor VIIc levels.

The rise in factor VIIc levels in the aerobic group is disappointing and may be thought to offset the benefit of low fibrinogen levels. The relationship between fibrinogen and non-fatal ischaemic heart disease is linear, but that for factor VIIc is as yet unknown.

The reduction in risk of ischaemic heart disease associated with vigorous exercise in leisure time is possibly mediated partly through reductions in the levels of these haemostatic factors. Exercise has not been shown to affect total cholesterol levels consistently, but is known to increase high density lipoprotein cholesterol levels, another risk factor in ischaemic heart disease. The next chapter section addresses this issue.

Haemoglobin, haematocrit and platelet numbers were not affected by the exercise training programme. I was unable to perform more sophisticated tests of platelet and red cell function and aggregability, and of blood rheology. These may have provided further insights into exercise training and blood coagulability, and are worth exploring in the future.

Fibrinopeptide A is a marker of thrombin activity and active clotting. Levels are raised in unstable angina and acute myocardial infarction. This study did not demonstrate any change in FPA levels after exercise training in a group with relatively stable coronary artery disease. This is perhaps not that

surprising. One would not expect ongoing clot formation in these men. None of the patients developed myocardial infarction during the study, although as mentioned earlier, two patients had an unstable phase. In addition, there was a wide variation in the FPA levels even within patients making it impossible for between group changes to shine through.

The results shown here have been published (Wosornu et al 1992). They are impressive and worthy of further investigation. The differences between and within the groups reached very high levels of statistical significance. In the case of haemostatic factors in post-CAS patients, this implies high levels of clinical significance as well.

SECTION X

LIPIDS & LIPOPROTEINS

Lipids and their subfractions are known risk factors for coronary artery disease. High total cholesterol (TC), high low density lipoprotein (LDL) and low high density lipoprotein (HDL), especially HDL subfraction 2, are associated with risk of death from cardiovascular causes. This has been shown in several primary prevention studies (Miller et al 1977; Gordon et al 1981; Stamler et al 1986; Martin et al 1986; Canner et al 1986; Frick et al 1987; Manninen et al 1988; Holme 1990). Secondary prevention studies have confirmed these findings with good evidence of regression of CAD following treatment of dyslipidaemia (Arntzenius et al 1985; Blakenhorn et al 1987; Passamani 1987; Carlson & Rosenhamer 1988). For every 1% reduction in cholesterol, an estimated 2.5% reduction in CAD incidence occurs (Holme 1990). In the Lipids Research Clinics Coronary Primary Prevention Trial (1984), there was a 19% reduction in risk of CAD death or non-fatal myocardial infarction in the treated group. The effects of triglycerides and very low density lipoproteins (VLDL) are less clear, but they are being implicated more and more in CAD and in graft occlusion (Scwandt 1990). In addition, raised triglyceride levels are associated with hypercoagulability (Meade 1987). A high proportion of patients undergoing CAS have abnormal lipid profiles (Thompson & Sapsford 1985; Billington et al 1989). Attention should be directed at correcting these abnormalities.

High baseline cholesterol levels are associated with reduced graft patency, as shown by angiographic and post-mortem studies (Campeau et al 1984; Campeau & Sniderman 1985; Bourassa et al 1986; Neitzel et al 1986). Coronary atherosclerosis regresses with treatment of hyperlipidaemia (Kane et al 1990; Brown et al 1990; Loscalzo 1990; Barth & Arntzenius 1991; Watts et al 1992). Progression of atherosclerosis correlates best with total cholesterol and LDL levels, while regression correlates with HDL levels (Barth & Arntzenius 1991). In the Cholesterol Lowering Atherosclerosis Study, aggressive diet and drug therapy (colestipol and niacin) caused significant changes in cholesterol levels (43% reduction in LDL, 37% increase in HDL), and slowed the rate of development and progression of atheroma in coronary arteries and vein grafts (Blakenhorn et al 1987).

Apolipoprotein A-1 (Apo-A1) is the major protein component of HDL. Apolipoprotein B (Apo-B) is a structural protein of chylomicrons, VLDL and LDL (Ball & Mann 1986). They have been shown to be better indicators of the risk of CAD than HDL and LDL. A high level of Apo-B and a low level of Apo-A1 indicate an increased risk of CAD (Kostner 1987; Durrington et al 1988).

In normal persons after exercise training, plasma cholesterol falls by 4 - 13% and triglycerides by 9 - 42% (Sellier et al 1988). Increases in HDL have also been found (Huttunen et al 1979; Danner et al 1984; Blumenthal et al 1991).

Exercise training improves lipoprotein profiles in patients with CAD and after myocardial infarction (Erkelens et al 1979; Streja & Mymin 1979; Ballantyne et al 1982; Heath et al 1983; Schuler et al 1988; Agren et al 1989; Baardman et al 1990). In a meta-analysis of 15 trials involving 490 males, trained on average for four 45-minute sessions per week for 25 weeks, there was a reduction in total and LDL cholesterol, cholcsterol/HDL ratio, and an increase in HDL. The total cholesterol level decreased from 5.99 to 5.71 mmol/l; LDL from 3.75 to 3.62 mmol/l; cholesterol/HDL ratio from 5.7 to 5.0; and HDL increased from 1.06 to 1.16 mmol/l (Vu Tran & Brammell 1989).

Decreases in body weight associated with exercise training exert some influence on the changes in lipid levels in some but not all of the trials (Vu Tran & Weltman 1985; Krauss 1989). Training must be of sufficient intensity and duration to be effective in improving lipoprotein profiles.

The mechanisms by which exercise training modifies lipid levels are uncertain. Increased lipoprotein lipase activity in skeletal muscle, adipose tissue and liver has been suggested (Kiens & Lithell 1989; Weintraub et al 1989). Exercise may also induce increased insulin sensitivity (Jennings et al 1986). Exercise increases the supply of triglyceride-rich lipoproteins to lipoprotein lipase, by enhancing muscle blood flow. This causes increased lipolysis and generation of nascent HDL in muscle capillaries (Ruys et al 1989; Lewis 1990).

To assess the effects of exercise training on lipoprotein levels after coronary artery surgery, the patients in the present study had lipid levels measured at baseline, three and six months.

METHODS

Thirty millilitres of venous blood for lipid analysis were taken after an overnight fast. The serum samples were stored at 4°C for up to three days, and tested in batches. The technicians performing the assays were not aware of the patients' groups.

Total cholesterol and triglyceride were assayed by automated analysis using enzymatic colorimetric tests (Boehringer Mannheim). For cholesterol, after esterification and oxidation, the resultant colour was measured at 500nm. For triglyceride, the reaction involved hydrolysis, with subsequent enzymatic determination of the liberated glycerol, also by colorimetry at 500nm.

Normal ranges: cholesterol <5.2mmol/l; triglyceride <2.3mmol/l

Lipoproteins were measured by beta-quantification. They can be selectively precipitated by adding combinations of sulphated polysaccharides and divalent cations to plasma. Five millilitres of plasma in a thermoplastic ultracentrifuge tube is overlayered with normal saline. The tube is sealed with a cap and spun at 35,000rpm at 4°C for 18 hours. Two fractions are obtained. The top fraction contains VLDL, and the bottom fraction contains HDL and LDL. The

LDL can be precipitated with heparin and manganous chloride, leaving HDL in solution. The individual fractions are analysed to obtain a measure of the lipoprotein levels. Total cholesterol, triglyceride, cholesterol in bottom fraction, HDL in bottom fraction, and cholesterol in the top fraction (VLDL) can be measured directly. Then LDL can be calculated as bottom cholesterol minus HDL cholesterol. A calculated VLDL can also be obtained as total cholesterol minus bottom fraction. The measured VLDL (from the top fraction) should agree with the calculated VLDL by $\pm$ 0.35.

HDL subfraction 2 and 3 masses were estimated by rate zonal ultracentrifugation with ultraviolet scanning (Beckman Instruments). Serum with its optical density specially adjusted, is centrifuged at 42,000 rpm for two hours. Under these conditions, HDL is buoyant and so floats through the centrifuge cell at a rate which is a function of its density. As it does so absorbance at 280nm is monitored periodically by the ultraviolet scanning equipment. This shows a decrease in absorbance at the periphery of the cell. After the allotted time, the cell is scanned, and the change in absorbance within two specified flotation intervals (3.5 to 9 and 0 to 3.5) is recorded. This is compared to a template with previously determined boundaries for the specified flotation intervals, and the height at which they cross the absorption curve is measured in millimetres. The differences between the two flotation intervals are calculated and this is converted, using specific molar absorptivities, to give concentrations of HDL2 and HDL3.

Apolipoproteins A1 and B were measured by immunochemical assay (Orion Diagnostica). It is based on measurement of immunoprecipitation in the liquid phase. In conditions of antibody excess (anti-sera to Apo-A1 and Apo-B), the amount of precipitate is proportional to the apolipoprotein concentration in the serum. The measurements are performed by analysers at wavelength of 340nm. The absorbances are converted to sample concentrations by referring to standard graphs, and reference solutions supplied in the kit.

Reference ranges: Apo-A1 0.20 - 2.50g/l; Apo-B 0.15 - 2.00g/l.

RESULTS

There were sixty nine complete sets of data and these are presented in this section. The results are presented as mean and its 95% confidence interval for each group at each assessment (tables 24 to 33). As in other tables, suffix '1' denotes baseline, '2' three month, and '3' denotes six month assessment. Levels are in mmol/l unless otherwise specified.

Table 24

TOTAL CHOLESTEROL

	CONTROL	AEROBIC	POWER
TC1	6.51 (6.05 to 6.98)	6.2 (5.72 to 6.68)	6.56 (6.19 to 6.92)
TC2	6.41 (5.95 to 6.87)	6.12 (5.74 to 6.51)	6.26 (5.90 to 6.62)
TC3	6.18 (5.69 to 6.66)	6.19 (5.80 to 6.79)	6.39 (5.98 to 6.79)

Table 25

TRIGLYCERIDE

	CONTROL	AEROBIC	POWER
TRIG1	2.09 (1.66 to 2.51)	2.01 (1.6 to 2.42)	1.98 (1.59 to 2.36)
TRIG2	2.34 (1.81 to 2.88)	2.21 (1.79 to 2.63)	1.86 (1.55 to 2.17)
TRIG3	2.16 (1.66 to 2.66)	2.06 (1.66 to 2.46)	1.94 (1.62 to 2.27)

Table 26

VERY LOW DENSITY LIPOPROTEIN

	CONTROL	AEROBIC	POWER
VLDL1	0.99 (0.79 to 1.19)	1.04 (0.7 to 1.37)	0.90 (0.73 to 1.06)
VLDL2	1.09 (0.81 to 1.36)	1.04 (0.81 to 1.28)	0.89 (0.74 to 1.04)
VLDL3	1.01 (0.76 to 1.26)	1.04 (0.83 to 1.25)	0.85 (0.73 to 0.98)

Table 27

LOW DENSITY LIPOPROTEIN

	CONTROL	AEROBIC	POWER
LDL1	4.36 (3.99 to 4.73)	4.06 (3.65 to 4.47)	4.43 (4.15 to 4.7)
LDL2	4.25 (3.86 to 4.64)	3.96 (3.64 to 4.28)	4.28 (3.99 to 4.56)
LDL3	4.04 (3.67 to 4.4)	3.97 (3.64 to 4.31)	4.30 (3.96 to 4.65)

Table 28

HIGH DENSITY LIPOPROTEIN

	CONTROL	AEROBIC	POWER
HDL1	1.16 (1.06 to 1.26)	1.22 (1.12 to 1.32)	1.24 (1.13 to 1.33)
HDL2	1.09 (1.01 to 1.17)	1.15 (1.07 to 1.23)	1.16 (1.04 to 1.28)
HDL3	1.12 (0.98 to 1.25)	1.15 (1.07 to 1.23)	1.23 (1.11 to 1.35)

Table 29

HDL/TOTAL CHOLESTEROL RATIO

	CONTROL	AEROBIC	POWER
RATIO1	0.18 (0.16 to 0.2)	0.2 (0.18 to 0.23)	0.19 (0.17 to 0.21)
RATIO2	0.17 (0.16 to 0.19)	0.19 (0.17 to 0.21)	0.19 (0.17 to 0.21)
RATIO3	0.18 (0.16 to 0.2)	0.19 (0.17 to 0.21)	0.2 (0.18 to 0.22)

Table 30

HDL SUBFRACTION 2 (mg%)

	CONTROL	AEROBIC	POWER
HDL2(1)	58.4 (46.9 to 69.9)	68.0 (52.4 to 83.4)	61.9 (48.7 to 75.1)
HDL2(2)	58.5 (47.1 to 69.9)	64.1 (51.9 to 76.4)	62.1 (47.8 to 76.4)
HDL2(3)	62.7 (49.2 to 76.1)	63.0 (49.7 to 76.2)	65.5 (50.8 to 80.2)

Table 31

HDL SUBFRACTION 3 (mg%)

	CONTROL	AEROBIC	POWER
HDL3(1)	224.5 (203.3 to 245.6)	225.9 (200.5 to 251.3)	240.4 (222.3 to 258.4)
HDL3(2)	221.8 (202.8 to 240.8)	222.9 (207.7 to 238.2)	225.2 (200.2 to 250.2)
HDL3(3)	219.7 (202.0 to 237.4)	227.9 (207.9 to 247.9)	235.9 (212.8 to 259.0)

Table 32

APOLIPOPROTEIN A1 (g/l)

	CONTROL	AEROBIC	POWER
APOA1(1)	1.13 (1.05 to 1.22)	1.16 (1.09 to 1.23)	1.25 (1.07 to 1.43)
APOA1(2)	1.12 (1.03 to 1.21)	1.14 (1.08 to 1.21)	1.22 (1.04 to 1.40)
APOA1(3)	1.14 (1.05 to 1.22)	1.09 (1.03 to 1.15)	1.21 (1.10 to 1.31)

Table 33

APOLIPOPROTEIN B (g/l)

	CONTROL	AEROBIC	POWER
APOB1	1.22 (1.09 to 1.36)	1.13 (1.01 to 1.25)	1.17 (1.07 to 1.26)
APOB2	1.20 (1.08 to 1.33)	1.11 (1.00 to 1.22)	1.11 (1.00 to 1.22)
APOB3	1.13 (1.01 to 1.25)	1.14 (1.02 to 1.26)	1.15 (1.05 to 1.26)

DISCUSSION

The total cholesterol and LDL levels were higher than is ideal in post-CAS patients, but it is not a surprising finding among patients with established coronary artery disease in the West of Scotland. Average levels of total cholesterol reported in Scottish studies are 6.48 to 6.95 mmol/l (Scottish Society of Physicians 1971; Isles et al 1989).

There were no statistically significant changes in any of the lipid and lipoprotein levels at any time.

There are several possible explanations for this lack of effect of the exercise programmes on lipoprotein levels in these men.

The patients in the exercise programmes may not have exercised sufficiently hard and long to cause such changes. This is borne out by their failure to achieve a full training effect. It has been suggested that improvements in lipoprotein profiles with training may be due to the training effect. They were found to correlate best with changes in VO_2 max, and are maximal in patients with initially low VO_2 max, high LDL and low HDL (Heath et al 1983). However high density lipoprotein has been shown to increase after thirteen weeks of exercise training without changes in diet, smoking or the achievement of training effect (Streja & Mymin 1979). It is therefore not clear exactly what the relation is between lipid changes and cardiovascular fitness. Some investigators suggest that exercise increases the production of HDL cholesterol from peripheral muscles (Ruys et al 1989).

Most of the reported studies make no mention of the level of fitness achieved by the patients.

In a previous study from the Victoria Infirmary, nineteen men post myocardial infarction were trained for six months by aerobic exercise. There was a reduction in LDL and triglycerides, and an increase in HDL, apoA1 and HDL2, compared with no change in twenty three control patients. There was no change in total cholesterol levels, and no relationship was found between treadmill performance and lipid levels (Ballantyne et al 1982).

In a cross-sectional study of exercise training after MI from Seattle, the only reported change was an increase in HDL in the 83 trained post-myocardial infarction patients (1.2 mmol/l) compared to 103 controls (1.03 mmol/l) (Erkelens et al 1979).

After a year of high intensity exercise training in eighteen patients with stable coronary artery disease, total cholesterol, LDL, VLDL, and triglycerides fell in association with increased work capacity and a reduction in stress-induced ischaemia (Schuler et al 1988). In another group, HDL increased after three months of exercise training, but there was no effect on total cholesterol and LDL. There was a high correlation between HDL and estimated maximum oxygen uptake (Hartung et al 1981).

Seventy seven cardiac patients, nine of whom had coronary artery surgery, underwent three months of cardiac rehabilitation comprising physical fitness, psychosocial wellbeing and risk factor modification. The control group showed no changes in lipids, but total cholesterol fell from 7.1 to 6.8 mmol/l in the rehabilitation group. It remained high in those with initial values above 6.5 mmol/l. There was no change in HDL, LDL and cholesterol/HDL ratio. Those who followed the diet strictly had greater reductions in cholesterol levels

(Baardman et al 1990). All these studies showed only minor changes in lipids.

In this study, the aerobic group had gained an average of a kilogramme in weight by the end of training. As mentioned earlier in most studies where exercise training was associated with changes in lipid levels, there was decrease in weight in the trained patients. It would appear that the slight weight loss and reduction in skin fold thickness in the power group were not enough to influence lipid levels. In a meta-analysis of ninety five trials on exercise training, Vu Tran & Weltman (1985) report that changes in body weight are relevant to lipoprotein levels. Thus, those in which there was no change in body weight, total cholesterol fell by 0.19 mmol/l and LDL levels fell by 0.08 mmol/l. The reductions in lipids were more significant with reductions in body weight - 0.34 mmol/l and 0.29 mmol/l respectively; with increases in weight, cholesterol and LDL increased by 0.07 mmol/l each.

Specific dietary advice or intervention were not included in the rehabilitation programme in this study. This was in order to assess the effects of the two types of exercise training without the influence of other interventions. It is therefore impossible to judge to what extent, if any, each group of patients altered its dietary habits. One would have thought though that, if anything, the patients would have adopted healthier eating habits.

In a study of only post-CAS patients (Agren et al 1989), eighteen underwent exercise training for twelve weeks. Preoperative, post-operative, post-training and one year lipoprotein levels were compared with those in nineteen control patients. There were no changes in body weight with training, and a constant diet was encouraged. Training was by cycling for sixty minutes

three times a week. Plasma cholesterol did not change. Triglycerides decreased by 23% in the training group after two months. In the control group, there was a slow spontaneous decrease in triglyceride levels, so that by one year there was no significant difference between the two groups. High triglyceride levels are associated with hypercoagulability. Lowering triglyceride levels after coronary artery surgery may therefore reduce the risks of thrombosis and graft occlusion. Initial mean LDL levels were high and did not change. Initial mean HDL levels were low. At two months after surgery, HDL levels rose in both groups, but did so more with training. In the trained group, there was a 20% increase in the first 26 weeks, and 23% by one year. In the control group, the HDL level rose by 10-15% post-operatively, and at one year were 20% higher than preoperative values. At that time, there was no difference between the two groups. ApoA1 increased by 5% in both groups two months after operation, and by 10% at one year. ApoB did not change in the trained group, but the control group showed an early increase of 6%. Coronary artery surgery itself seems to influence lipid levels. The exercise trained group showed some additional benefits which were not sustained at one year. That study had a different slant from the present one: it included preoperative assessments and was thus able to determine the effects of the operation itself.

Sixteen untrained men with abnormal lipid levels had twenty weeks of strength training. Despite 50% increase in upper body strength and 37% increase in lower body strength measured by the one repetition maximum test, there were no changes in lipids or lipoprotein levels (Kokkinos 1991).

In strength trained athletes, some reports suggest a fall in HDL cholesterol or a rise in the ratio of total cholesterol to HDL cholesterol. However various factors such as age, body weight, diet and anabolic steroid use could also influence the lipid levels in these studies. (Hurley 1989; McKelvie & McCartney 1990) In a previous study by Hurley et al (1988), weightlifting training caused an increase in HDL cholesterol and a decrease in LDL cholesterol with no change in percent body fat.

Previous studies of weight lifting training in untrained healthy middle-aged men caused reductions in total cholesterol to HDL cholesterol ratio, and LDL cholesterol levels. This was accompanied by a reductions in body fat (McKelvie & McCartney 1990).

The conclusion remains that the exercise training programmes used in this study failed to influence lipid levels after coronary artery surgery in these men. This suggests that for the purposes of influencing lipoprotein profiles, it would seem appropriate to include dietary intervention and aggressive drug treatment, if necessary, in such patients. In so doing the chances of development and progression of atherosclerosis in the future would be reduced.

SECTION XI

ASSESSMENT OF LEFT VENTRICULAR FUNCTION: GATED TECHNETIUM EQUILIBRIUM BLOOD POOL ANGIOGRAPHY

This technique is widely used in the measurement of left ventricular function at rest, and in response to stress (Burow et al 1977; Wackers et al 1979; Port et al 1981; Borer et al 1984). The patient's red blood cells are labelled in vivo with 800 MBq of 99m technetium 20 minutes after the injection of stannous pyrophosphate, which is used to increase the binding of technetium to the red blood cells. A parallel hole general purpose collimator acquires a scan of the left ventricle. The patient rests supine with the camera positioned 35 - 45° LAO with 10° caudal tilt to give maximum separation between left and right ventricles and the atria. The heart rate is monitored and the R wave is used to gate the scan into 16 parts within each R-R interval. An R-R interval window of 20% is used so that any beats outside of this, e.g. ectopics, are excluded from the analysis. The acquisition time is six minutes, with an average count number of 100,000 per second. The acquired beats are stored in frame mode in a 64 x 64 matrix to produce a summated representative cycle.

The stress test chosen for this study was the cold pressor test. This has previously been used and validated in the Victoria Infirmary (Northcote & Cooke 1987). Exercise radionuclide ventriculography is generally preferred as a stress test, since it has been shown to indicate the presence of severe coronary artery disease quite clearly (Borer et al 1977). In patients with CAD, ejection fraction falls with exercise; it rises in normal persons. The cold pressor test

is also useful in detecting CAD and left ventricular dysfunction (Wainwright et al 1979; Manyari et al 1982; Vojacek et al 1982; Rootwelt et al 1982; Buonanno et al 1983). The cold pressor test can cause a fall in ejection fraction even in normal persons, but this is more pronounced in patients with CAD: 5.8% and 8.6% respectively (Wasserman et al 1983). For the purposes of the present study, it was simply a matter of determining the effects of training on left ventricular function in patients with established coronary artery disease who had had coronary artery surgery. The cold pressor test was deemed an adequate and reproducible test for the follow up of these patients.

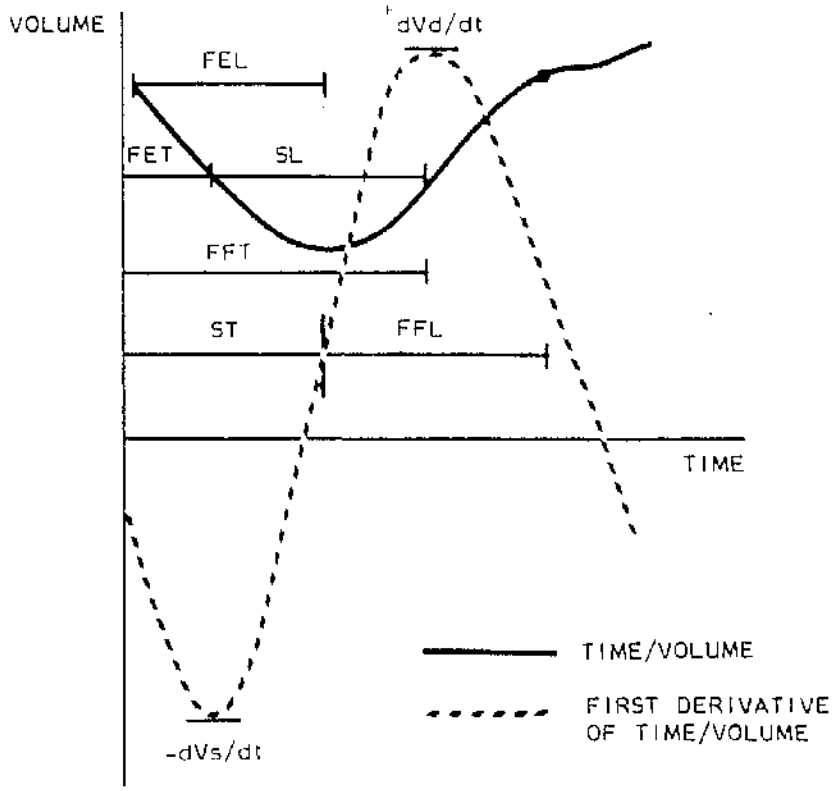
The patient's right forearm is immersed in a mixture of crushed ice and water at 4°C, and the scan is repeated. The acquisition time for this is five minutes.

In the Nuclear Medicine department, Victoria Infirmary, the coefficient of variance for resting ejection fraction in normals is 5%. Two separate mean ejection fractions differed by 1.2 $\pm$ 6.2%. For patients with coronary artery disease, the coefficient of variance for ejection fraction response to cold pressor is 9% (Northcote & Cooke 1987).

The Stanford automatic left ventricular function analysis programme is used for image analysis to construct a time activity curve from which indices of left ventricular function can be derived (figure 2). Global ejection fraction, regional ejection fraction, fast filling time and length, fast ejection time and length, systolic time and length can be calculated.

The method was originally described by Goris et al (1981). The automatic programme performs a comprehensive analysis of left ventricular

function. It constructs functional images of stroke volume, regional ejection fraction, amplitude, and phase. The edge detection algorithm is based on a one dimensional La Placian filter applied to the end-diastolic image vertically, horizontally, and along both diagonals. A search is made for the first edge which completely encloses the left ventricle, which is located by calculation of the x-y coordinates of the centre of gravity of an amplitude image constructed by the system. The programme transforms the data to frequency domain, and retains the zero, first, second, and third harmonics, as well as the diastolic image. The left ventricle is located on the left edge of the stroke volume image, and the edges of the ventricle are identified on the diastolic image. A left ventricular area of interest is created and used for interpolative background subtraction. The area of interest is also used to create a 100-point volume curve using the frequency components. It is from this curve that the system calculates ejection fraction. Time and length for fast filling, fast ejection, and systole and dV/dt are derived from the curve.



F.E.T: FAST EJECTION TIME

-VM/SV: RATE OF NEG CHANGE

FEL: FAST EJECTION LENGTH

ST: SYSTOLIC TIME

SL: SYSTOLIC LENGTH

FFT: FAST FILLING TIME

+ VM/SV: RATE OF POST CHANGE

FFL: FAST FILLING LENGTH

EF: GLOBAL EJECTION FRAC.

Figure 2: Left ventricular time activity/volume curve, its first derivative and report parameters.

Since a number of the patients had had previous infarcts, this needs to be considered in the analysis of regional left ventricular function, and the effects that training might have on this. Detecting wall motion abnormalities in response to stress tests tends to add little to the sensitivity of rest scans. But any changes in regional left ventricular function after an intervention can be considered to be a result of that intervention. Thus for the follow up of patients with exercise training, it might be a useful test.

I sought permission from the Department of Health and Social Security to use radiopharmaceuticals in the study. This relates to this section using 99m technetium, and to the next part, using thallium-201. Permission was granted for nuclear cardiology scans in sixty patients under the supervision of Professor N Mackay who is an ARSAC certificate holder. Copies of the relevant documents form the appendix.

In order to reduce their exposure to radiation to a minimum, the patients had scans at baseline and after the intervention period; the three month assessment was omitted.

RESULTS

Fifty seven patients had a full set of scans for analysis. Of the remainder, 1 scan was not suitable for analysis due to errors in scanning or processing, 2 patients had incomplete scans due to inability to tolerate the cold pressor test. The fifty seven were made up of 16 controls, 25 in the aerobic group, and 16 in the power group. The results of global ejection fraction are presented first followed by those regional ejection fraction. The results

reported in % and expressed as the mean with its 95% confidence interval. Baseline parameters of global ejection fraction in the three groups did not differ from each other significantly (table 34).

In patients with significant coronary artery disease, the ejection fraction falls during the cold pressor test. The influence of the cold pressor test on the other parameters have not been established.

In these patients, there was a trend towards lower ejection fraction in all the groups during the cold pressor test. The value in the power group was significantly higher than that in the other two groups, ANOVA $p = 0.04$. The other parameters were not affected by the cold pressor test at baseline (table 35).

After the training period, the resting systolic length was significantly shorter in the power group as compared to the other two groups, (ANOVA $p = 0.01$). Aerobic and power training in these patients had no effect on resting ejection fraction or that in response to cold pressor.

There was a trend towards shorter systolic length in response to cold pressor (ANOVA $p = 0.07$) and towards shorter fast filling time at rest and in response to cold pressor in the power group (ANOVA $p = 0.08$ and 0.06 respectively) (tables 36 and 37).

The interval changes between baseline and six months in the different parameters are shown in the tables 38 and 39. Changes achieving statistical significance are marked by asterisks in the tables.

As mentioned earlier, the actual ejection fraction during cold pressor at baseline was higher in the power group than in the others . The 't' test was

used to assess the difference.

Between aerobic and power groups 2p = 0.008; and between control and power groups, 2p = 0.05. There was no difference between control and aerobic groups in baseline ejection fraction during cold pressor (2p = 0.8). The differences in ejection fraction shown in the table did not achieve statistical significance.

The data on systolic length and fast filling time were not normally distributed, therefore the Mann-Whitney U test was used in their further analysis, to determine the exact differences between the groups.

For resting systolic length at six months, the difference between the power and aerobic group was significant at 2p= 0.03, and between power and control groups at 2p = 0.01. The difference between control and aerobic groups was not statistically significant, 2p = 0.14.

The only interval change in the other parameters of global ejection fraction reaching statistical significance was a fall in fast filling time during cold pressor in the power group (ANOVA p = 0.04)

Between control and aerobic groups, the difference was not significant 2p = 0.08; between aerobic and power groups, 2p = 0.3; and between power and control groups, 2p= 0.04.

Table 34

BASELINE RESTING PARAMETERS OF GLOBAL EJECTION FRACTION

	CONTROL	AEROBIC	POWER
EF	51.5 (40.4 to 62.7)	49.6 (41.1 to 58.2)	59.2 (54.6 to 63.8)
FET	17.6 (15.9 to 19.4)	19.9 (17.0 to 22.8)	17.9 (14.9 to 21.0)
-VM/SV	4.5 (4.1 to 4.9)	4.5 (4.2 to 4.8)	4.4 (3.9 to 4.8)
FEL	35.4 (31.9 to 38.9)	37.4 (33.2 to 41.6)	36.3 (32.8 to 39.8)
ST	39.9 (37.0 to 42.9)	41.8 (38.3 to 45.4)	41.6 (38.6 to 44.5)
SL	50.7 (44.4 to 56.9)	48.1 (42.5 to 53.7)	45.2 (39.7 to 50.7)
FFT	68.3 (61.5 to 75.1)	68.4 (62.2 to 74.6)	62.2 (57.4 to 66.9)
+VM/SV	3.5 (3.2 to 3.9)	3.6 (3.3 to 4.0)	3.5 (3.1 to 3.8)
FFL	38.7 (32.8 to 44.7)	37.0 (32.4 to 41.6)	33.5 (27.5 to 39.5)

ABBREVIATIONS IN TABLES 34 - 37

EF: ejection fraction

FET: fast ejection time

-VM/SV: rate of systolic shortening

FEL: fast ejection length

ST: systolic time

SL: systolic length

FFT: fast filling time

+VM/SV: rate of diastolic lengthening

FFL: fast filling length

Table 35

BASELINE EJECTION FRACTION PARAMETERS DURING COLD PRESSOR TEST

	CONTROL	AEROBIC	POWER
EF	45.7 (33.9 to 57.5)	44.1 (36.4 to 51.4)	58.6 * (51.1 to 66.2)
FET	18.9 (14.5 to 23.4)	19.7 (15.6 to 23.8)	19.4 (15.5 to 23.3)
-VM/SV	4.4 (3.8 to 5.1)	4.2 (3.9 to 4.6)	4.0 (3.6 to 4.4)
FEL	38.3 (33.2 to 43.5)	42.2 (37.2 to 47.1)	41.3 (37.8 to 44.7)
ST	43.1 (38.2 to 48.0)	46.5 (42.0 to 51.1)	45.1 (41.1 to 49.0)
SL	46.3 (38.8 to 53.9)	54.1 (47.7 to 60.6)	48.1 (40.9 to 55.3)
FFT	65.3 (58.2 to 72.4)	73.9 (68.1 to 79.7)	67.4 (62.0 to 72.9)
+VM/SV	3.7 (3.3 to 4.3)	4.2 (3.7 to 4.7)	3.6 (3.1 to 4.0)
FFL	34.2 (27.5 to 41.1)	32.0 (26.5 to 37.4)	36.6 (29.8 to 43.5)

Table 36

RESTING PARAMETERS OF GLOBAL EJECTION FRACTION AFTER TRAINING

	CONTROL	AEROBIC	POWER
EF	52.9 (40.3 to 65.4)	50.0 (42.4 to 57.6)	55.6 (48.5 to 62.7)
FET	18.4 (15.5 to 21.3)	19.6 (17.0 to 22.1)	21.3 (15.0 to 27.5)
-VM/SV	4.3 (3.9 to 4.7)	4.2 (3.9 to 4.6)	4.4 (3.9 to 4.8)
FEL	35.7 (32.1 to 39.3)	37.1 (33.9 to 40.3)	36.8 (30.9 to 42.6)
ST	40.1 (37.1 to 43.0)	41.9 (38.5 to 45.3)	41.3 (35.8 to 46.7)
SL	52.5 (43.9 to 61.1)	47.1 (42.2 to 52.0)	39.3 * (35.3 to 43.1)
FFT	69.8 (61.9 to 77.7)	65.5 (60.4 to 70.6)	60.0 (55.2 to 64.8)
+VM/SV	3.2 (2.8 to 3.6)	3.6 (3.2 to 3.9)	3.5 (3.1 to 4.0)
FFL	36.9 (29.8 to 44.0)	35.8 (31.5 to 40.2)	30.3 (25.7 to 35.0)

Table 37

EJECTION FRACTION PARAMETERS DURING COLD PRESSOR AFTER TRAINING

	CONTROL	AEROBIC	POWER
EF	48.2 (37.2 to 59.2)	45.1 (38.1 to 52.0)	55.2 (46.1 to 64.3)
FET	18.3 (14.4 to 22.1)	18.8 (15.6 to 22.1)	19.8 (15.8 to 23.9)
-VM/SV	4.4 (4.0 to 4.8)	4.1 (3.7 to 4.4)	4.4 (3.8 to 4.9)
FEL	37.9 (32.6 to 43.2)	41.7 (37.5 to 45.9)	36.6 (32.2 to 40.9)
ST	44.9 (40.6 to 49.1)	45.5 (42.2 to 48.7)	42.2 (38.6 to 45.7)
SL	57.6 (47.5 to 67.7)	55.7 (49.6 to 61.7)	45.6 (37.4 to 53.9)
FFT	75.9 (67.7 to 84.1)	73.9 (68.0 to 79.8)	64.9 (58.7 to 71.1)
+VM/SV	3.7 (3.2 to 4.3)	4.1 (3.7 to 4.5)	3.5 (3.2 to 3.9)
FFL	39.4 (30.9 to 47.9)	35.4 (30.2 to 40.6)	30.6 (25.5 to 35.6)

Table 38

INTERVAL CHANGES IN EJECTION FRACTION AT REST AND IN RESPONSE TO COLD PRESSOR

	CONTROL	AEROBIC	POWER
DEF1	-5.8 (-11.5 to -0.1)	-5.5 (-9.2 to -1.8)	-0.6 (-5.8 to 4.6)
DEF2	-4.7 (-10.0 to 0.7)	-4.9 (-8.8 to -1.1)	-0.4 (-7.4 to 6.5)
DEF3	1.3 (-4.0 to 6.7)	0.4 (-4.4 to 5.1)	-3.6 (-9.6 to 2.4)
DEF4	2.4 (-3.4 to 8.3)	1.0 (-3.6 to 5.5)	-3.4 (-10.5 to 3.7)

ABBREVIATIONS

DEF1: Difference in baseline resting and cold pressor ejection fraction

DEF2: Difference in six month resting and cold pressor ejection fraction

DEF3: Interval change in resting ejection fraction

DEF4: Interval change in cold pressor ejection fraction

Table 39

INTERVAL CHANGES IN OTHER PARAMETERS OF GLOBAL EJECTION FRACTION

	CONTROL	AEROBIC	POWER
DFET1	0.8 (-2.3 to 3.9)	-0.3 (-3.0 to 2.3)	3.3 (-3.6 to 10.2)
DFET2	-0.7 (-7.8 to 6.5)	-0.9 (-5.9 to 4.2)	0.4 (-5.8 to 6.6)
DDS1	-0.2 (-0.7 to 0.4)	-0.3 (-0.6 to 0.1)	0 (-0.4 to 0.4)
DDS2	0 (-0.7 to 0.7)	-0.2 (-0.6 to 0.3)	0.4 (-0.3 to 1.0)
DFEL1	0.3 (-4.8 to 5.5)	-0.3 (-4.5 to 3.9)	0.4 (-5.2 to 6.0)
DFEL2	-0.4 (-5.5 to 4.7)	-0.5 (-6.2 to 5.2)	-4.7 (-11.1 to 1.7)
DST1	0.1 (-4.2 to 4.4)	0.1 (-4.3 to 4.4)	-0.3 (-4.8 to 4.2)
DST2	1.8 (-4.6 to 8.2)	-1.0 (-6.7 to 4.5)	-2.9 (-8.8 to 3.0)
DSL1	1.8 (-6.2 to 9.8)	-1.0 (-7.8 to 5.7)	-5.9 (-11.7 to -0.2)
DSL2	11.3 (-0.8 to 23.3)	1.6 (-4.1 to 7.2)	-2.5 (-13.7 to 8.7)
DFFT1	1.5 (-6.2 to 9.2)	-2.9 (-9.6 to 3.8)	-2.1 (-7.6 to 3.3)
DFFT2	10.6 (1.3 to 19.9)	0 (-5.1 to 5.0)	-2.5 * (-11.6 to 6.6)
DDD1	-0.3 (-0.8 to 0.1)	-0.1 (-0.5 to 0.4)	-0.1 (-0.4 to 0.6)
DDD2	0 (-0.5 to 0.5)	-0.1 (-0.7 to 0.6)	0 (-0.5 to 0.5)
DFFL1	-1.8 (-7.1 to 3.5)	-1.2 (-6.7 to 4.3)	-3.2 (-10.8 to 4.4)
DFFL2	5.1 (-2.7 to 13.1)	3.4 (-3.2 to 10.0)	-6.1 (-15.0 to 2.9)

ABBREVIATIONS

DFET1: Interval change in fast ejection time at rest

DFET2: Interval change in fast ejection time during cold pressor

DDS1: Interval change in -VM/SV at rest

DDS2: Interval change in -VM/SV during cold pressor

DFEL1: Interval change in fast ejection length at rest

DFEL2; Interval change in fast ejection length during cold pressor

DST1: Interval change in systolic time at rest

DST2: Interval change in systolic time during cold pressor

DSL1: Interval change in systolic length at rest

DSL2: Interval change in systolic length during cold pressor

DFFT1: Interval change in fast filling time at rest

DFFT2: Interval change in fast filling time during cold pressor

DDD1: Interval change in +VM/SV at rest

DDD2: Interval change in +VM/SV during cold pressor

DFFL1: Interval change in fast filling length at rest

DFFL2: Interval change in fast filling length during cold pressor

DISCUSSION

In most studies, coronary artery surgery has been shown to have a neutral effect on resting left ventricular function, as measured by radionuclide or contrast ventriculography. This is perhaps not surprising. Coronary blood flow even through stenosed arteries, may be adequate for resting left ventricular contractility which need not alter with revascularisation. It becomes critical when demand increases. In contrast therefore, in most studies, coronary artery surgery has been shown to improve left ventricular function during exercise and stress.

In one of the earlier studies using angiocardiography, Chatterjee et al (1972) found that in five patients with stenoses of the left coronary system, left ventricular ejection fraction at rest was depressed before surgery, and improved post-operatively. One patient with right coronary artery disease showed no change in ejection fraction. Hamby et al (1974) studied 104 patients with patent grafts one year after CAS, and concluded that reversibility of left ventricular function depends on clinical state and pre-operative LV function, such as the presence of wall motion abnormalities. In 30 patients studied before and five months after CAS, Brundage et al (1977) concluded that the most important determinant of LV function after CAS is the state of the native coronary circulation at repeat cardiac catheterisation. Wolf et al (1978) studied 37 patients with biplane left ventriculography before and 13 months after CAS. They found that LV function and segmental dysfunction were related to graft patency. This is similar to findings by Rees et al (1971) in 14 patients. Eight had patent grafts and improved LV function, the remainder did not. In 51

patients studied before and one to two years after CAS, LV function was unchanged in 72%, deteriorated in 3% and there was a 5% incidence of new wall motion abnormalities (Zir et al 1979).

In one of the earlier studies using radionuclide ventriculography, Kent et al (1978), studied 23 patients before and two to six months after CAS. There was no change in resting ejection fraction. In the 17 patients with the most symptomatic benefit, exercise ejection fraction improved from 39 + 3% to 59 $\pm$ 4%. In six, there was no change or a fall in ejection fraction during exercise. Exercise induced LV dysfunction improved. In 14 patients studied before, eight days and three months after CAS, there was no change in resting ejection fraction. Exercise ejection fraction increased more at eight days, and persisted at three months (Austin et al 1981). Ejection fraction fell with exercise pre-operatively, but not 23 weeks after CAS in 36 patients. The results were most impressive in those with pre-operative evidence of exercise induced LV dysfunction (Kronenberg et al 1983). Resting ejection fraction and regional wall motion score were unchanged by CAS in 56 patients studied before and six weeks post-operation. Exercise ejection fraction increased from 64% to 72% and exercise induced wall motion abnormalities were abolished (Taylor et al 1983). Where resting ejection fraction was measured in the early post-operative period (24 hours and one week), it was found to have improved from 49 $\pm$ 2% to 56 $\pm$ 2% in 53 patients. This held true regardless of the pre-operative ejection fraction, and was associated with a decrease in end diastolic volume, suggesting improved myocardial contractility (Tchervenkov et al 1985). Austin et al (1981) suggested that studies of LV function post-CAS

should be delayed till at least three months presumably to allow perioperative factors such as excess adrenergic drive to subside. Dilsizian et al (1988) suggest that subclinical LV dysfunction due to ischaemic or hibernating myocardium is improved by revascularisation. In their study of 31 patients, both resting and exercise ejection fraction improved after CAS; 27 patients had patent grafts. On the other hand, De Nardo et al (1989) found no change in global ejection fraction in 34 patients, despite the development of paradoxical septal motion in 14 of the patients.

A few studies have considered the effects of CAS on diastolic function. In 23 patients LV compliance improved in the 15 with patent grafts. The post-operative biplane ventriculography was done 19 weeks after CAS (Miller et al 1975). In 24 patients with stable angina, ejection fraction increased in response to exercise after CAS. Left ventricular end diastolic pressure was reduced, but still rose with exercise (23 to 37 mmHg pre-op, 17 to 25 mmHg post-op). Early diastolic peak filling rate was greater after CAS, 1260 ml/s pre-operatively, 950ml/s post-operatively (Carroll et al 1985). Kawasuji et al (1988) found no change in resting ejection fraction in the four weeks after CAS. Ejection fraction at peak exercise increased, as did peak ejection rate. Peak filling rate, and peak filling rate during the first third of diastole were unchanged.

Studies on the effects of exercise training on left ventricular function in patients with CAD have also shown inconsistent results. In normals, there is an increase in end diastolic volume and peak cardiac output after training (Clausen 1976; Rerych et al 1980).

In the PERFEXT study, there was no significant change in ejection fraction, end diastolic volume, stroke volume or cardiac output after the one year training programme. The exercise group had lower percentage changes in end systolic volume at varying workloads (Froelicher et al 1984).

In 25 patients with CAD, Ehsani et al (1986) showed that after a year of progressive and intense aerobic training, there was a rise in ejection fraction during maximal supine bicycle exercise (52 $\pm$ 3% vs 58 $\pm$ 3%, $p < 0.01$). This was so despite a higher rate pressure product and systolic blood pressure. Resting ejection fraction was unchanged. There was smaller end systolic volume during exercise, but no change in end diastolic volume. Before training, ejection fraction decreased from rest to exercise in 15 patients, was unchanged in three and increased in seven. After training, ejection fraction decreased from rest to exercise in four, was unchanged in two and increased in 19. They suggest that there was improved contractile function after training. Overall, there was also an improvement in exercise induced regional wall motion abnormalities. Measured VO_2 max increased by 37% in the trained group. The control group of 14 patients showed no changes. In a report on 11 patients using the same training programme, stroke volume during upright exercise requiring 35 - 65% VO_2 max was 18% higher after the training period. Mean blood pressure was unchanged , therefore left ventricular stroke work increased (Hagberg et al 1983).

After six to twelve months of exercise training in 53 patients, there was no change in resting and peak ejection fraction. Ejection fraction at pre-training peak exercise increased from 50 $\pm$ 17% to 54 $\pm$ 17%, $p = 0.002$.

There was a correlation with the magnitude of training bradycardia, but not with the degree of left ventricular impairment before training. The end systolic volume at equivalent workload was smaller after training. The relation to training bradycardia suggests that lower myocardial oxygen demand contributed to the higher submaximal ejection fraction (Williams et al 1984).

Similar results were found by Jensen et al (1980) in 19 patients. Resting and maximal ejection fraction did not change with six months' training, but there was an increase in submaximal ejection fraction.

DeBusk and Hung (1982) report an slight increase in submaximal ejection fraction after 12 weeks' training in 21 post-infarct patients, with no change in resting or maximal ejection fraction.

Verani et al (1981) found that 12 weeks of training increased resting ejection fraction from 52 $\pm$ 4% to 57 $\pm$ 4% in 16 patients with CAD. In 15 patients with recent MI, after six months training, there was no change in resting or exercise ejection fraction (Cobb et al 1982). Stroke volume increased by 10% after one year of high intensity exercise training in 37 post-MI patients, whilst 42 who had low intensity exercise showed no changes, not even in exercise performance (Paterson et al 1979).

The form of stress used here was the cold pressor test. It was described in the 1930s (Hines & Brown 1936) and the haemodynamic responses to it were studied in the 1960s with varying results (Boyer et al 1960; Greene et al 1965). More recently, Buonanno et al (1983) showed that the cold pressor test invokes the sympathetic nervous system, with a rise in systolic pressure, heart rate, double product, and left ventricular end diastolic pressure. There is an increase

in myocardial oxygen consumption due to increased afterload. Vasoconstriction also increases peripheral vascular resistance. Left ventricular ejection as measured by fast ejection length and systolic time is prolonged by cold pressor, and peak rate of left ventricular ejection is reduced and delayed.

There have not been any reported studies on the effects of coronary artery surgery on the performance of the cold pressor test, nor was that part of this study. Given that both the cold pressor test and exercise increase the demands on the myocardium, I think that it is reasonable to extrapolate from the studies on exercise radionuclide ventriculography. It has been shown that exercise stress is more sensitive than cold pressor in detecting CAD (Rootwelt et al 1982; Manyari et al 1982). Wherever possible therefore, exercise stress tends to be used in the detection of CAD. The cold pressor test is useful in the follow-up of such patients, and is an alternative to exercise when this cannot be performed for mobility and technical reasons. In the presence of CAD, the ejection fraction tends to fall with cold pressor stress as it does with exercise (Vojacek et al 1982). It was reasonable to use the cold pressor test in studying the effects of exercise training on ejection fraction. None of the studies mentioned above have used it.

In a study from this department of 40 patients with angina, 20 had aerobic training for one year. The exercise group showed an improvement in ejection fraction during cold pressor test from 48 $\pm$ 8.4% to 54.9 $\pm$ 10.1%, while in the control group it fell from 49.4 $\pm$ 14.2% to 45.1 $\pm$ 12.1% ($p < 0.01$). There was no change in resting ejection fraction. The fall in ejection fraction with cold pressor was less in the exercise group after training

(control -6 ± 6.9%, exercise -2.4 ± 8.4%).

Before addressing the results of the present study, the meaning of the parameters that were measured in this section should be discussed. Global ejection fraction depends on heart rate, preload, afterload and intrinsic myocardial contractility. It is a widely used but composite measure of left ventricular function. In equilibrium radionuclide angiography, it is the difference between end diastolic and end systolic counts divided by end diastolic counts, in the left ventricular region of interest. The other parameters are mathematically derived from a time/activity curve of left ventricular function (figure 2). Fast ejection reflects systole and fast filling, diastole. A brief period of isovolumetric contraction marks end diastole and a brief period of isovolumetric relaxation marks end systole. Fast ejection length is between the end of isovolumetric contraction and end systole. At end systole, fast filling begins. Fast filling ends with diastasis. As well as the lengths of fast ejection and fast filling, the maximum rate of change of volume during those periods (DVs/Dt and DVd/Dt) and the time at which these maximum changes occur (FET and FFT) are measured automatically from the time/activity curve and its first derivative. Systolic length (SL) is not obtained from systole; it is FFT minus FET, the time from maximum rate of volume change in systole to maximum rate of volume change in diastole.

In a study of normal persons using isoprenaline and propranolol, Sapru et al (1980) found that left ventricular ejection and filling times and rates are sensitive indicators of changing inotropic state. In CAD, peak filling rate is reduced and time to peak filling is prolonged, and in some studies this is

proportional to disease severity (Bonow et al 1981; Polak et al 1982; Reduto et al 1982; Mancini et al 1983; Miller et al 1983; Dymond et al 1984).

There have been no reported studies comparing the effects of aerobic and power exercise training on measures of left ventricular systolic and diastolic function after coronary artery surgery.

In this study there were no changes in rest or stress ejection fraction nor in the ejection fraction response to cold pressor in any of the groups. Indeed the values were rather consistent. Power and aerobic training had no influence on most of the derived measures of left ventricular contractile function.

The only statistically significant changes were in the power group. There was shorter systolic length at rest ($p = 0.01$) and during cold pressor ($p = 0.05$) after the training period. Fast filling time was also shorter in the power-trained group. This may suggest improved efficiency of contraction, but the clinical and physiological relevance of these isolated responses are unclear. As well as that, since neither translates into improved global ejection fraction, perhaps other determinants of ejection fraction such as heart rate and blood pressure which were not analysed in this part of the study might have been helpful in unravelling the significance (if any) of the isolated changes that occured in the power group.

REGIONAL EJECTION FRACTION

Regional ejection fraction abnormality is a marker of CAD. It is derived in the same way as is global ejection fraction (Maddox et al 1979). In the present study, the left ventricle is divided into eight equal segments, numbered 1 to 8, in a clockwise direction starting from 12 o'clock (figure 3). The end diastolic and end systolic counts in each region are used to determine the regional ejection fraction.

In the tables, the letters A to D are used to indicate the type of scan, such that A represents baseline resting scan, B, six month resting scan C, baseline cold pressor scan D, six month cold pressor scan.

There are no reported studies of the effects of exercise training on regional ejection fraction.

Twenty seven of the patients in whom a full set of scans was available for analysis had not had previous myocardial infarctions. The analysis of results of regional ejection fraction takes account of this.

The results are shown as comparisons made between the two resting scans and between the two cold pressor scans, rather than between resting and cold pressor scans at each assessment. In this way, the two types of scan become two separate tests of regional ejection fraction. In the previous section, it was shown that the cold pressor test did not make any difference to parameters of global ejection fraction, and indeed there was no significant

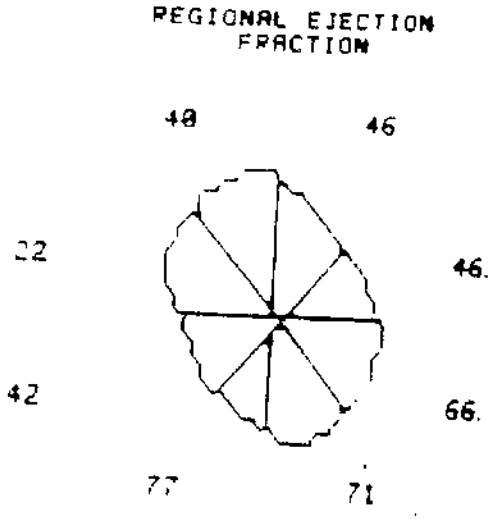


Figure 3: Regional ejection fraction: left ventricular segments.

rest to stress changes in regional ejection fraction either.

Results are expressed as mean with the SEM, and 'p' values mentioned in the text or shown in the table if indicated. They are first presented for the groups as a whole (tables 40 and 41).

In looking at the interval changes within groups, the interval change in resting and cold pressor scans in region 7, and resting scan in region 8 reached significance, with ANOVA p = 0.02, 0.04, and 0.004 respectively (table 42).

In region 7 at rest, the difference was between power and control groups with 2p = 0.034. There was a reduction in ejection fraction in the power group and an increase in the control group. In region 7 after cold pressor, the difference was between aerobic and control, with 2p = 0.021, a reduction in the aerobic group and a rise in the control group. In region 8 at rest there were significant differences between both exercise trained groups and the control group, with 2p = 0.012 in aerobic vs. control, and 2p = 0.003 in power vs. control. Again, it was the control group that showed an improvement in ejection fraction in that region. Interestingly, the atria and great vessels overlie regions 7 and 8, therefore these findings may well be spurious, and unlikely to be of clinical relevance.

Table 40

REGIONAL EJECTION FRACTION AT REST: BASELINE AND SIX MONTHS. mean (SEM) %

	CONTROL	AEROBIC	POWER
1A	42.7 (3.8)	44.5 (3.8)	48.9 (2.8)
1B	48.1 (4.5)	40.8 (3.0)	44.3 (3.8)
2A	63.6 (4.6)	59.9 (4.1)	64.5 (3.4)
2B	63.8 (4.6)	59.6 (3.2)	57.8 (5.7)
3A	66.6 (4.5)	59.6 (3.7)	64.4 (4.2)
3B	61.3 (4.7)	61.1 (3.6)	61.78 (4.3)
4A	57.6 (6.0)	52.6 (4.5)	58.5 (4.2)
4B	54.7 (6.7)	54.2 (4.9)	59.4 (5.1)
5A	49.9 (6.3)	44.9 (5.0)	57.8 (3.9)
5B	49.1 (7.8)	47.8 (5.8)	54.5 (3.5)
6A	34.6 (4.3)	28.7 (3.8)	40.9 (2.4)
6B	32.1 (5.9)	29.9 (4.0)	36.3 (4.1)
7A	22.5 (3.8)	21.6 (3.9)	34.1 (3.5)
7B	28.3 (4.7)	24.3 (3.5)	25.7 (3.0)
8A	24.1 (3.7)	29.6 (4.0)	38.1 (4.4)
8B	33.0 (4.3)	25.6 (3.1)	30.3 (3.6)

Table 41

REGIONAL EJECTION FRACTION AFTER COLD PRESSOR: BASELINE AND SIX MONTHS mean (SEM)%

	CONTROL	AEROBIC	POWER
1C	37.3 (4.9)	38.0 (4.6)	48.6 (4.0)
1D	45.6 (4.1)	40.3 (3.1)	47.3 (4.6)
2C	57.6 (4.8)	51.4 (5.2)	60.8 (4.5)
2D	59.9 (4.3)	52.6 (4.2)	57.4 (5.7)
3C	58.9 (4.8)	47.4 (5.8)	62.6 (4.5)
3D	59.6 (4.3)	55.7 (4.4)	59.0 (7.0)
4C	52.8 (6.6)	48.0 (4.8)	61.6 (4.1)
4D	51.8 (6.4)	50.6 (4.5)	56.7 (5.8)
5C	42.8 (7.5)	42.6 (4.1)	61.1 (3.6)
5D	45.5 (8.0)	43.7 (5.2)	52.4 (4.2)
6C	29.4 (5.7)	28.7 (3.5)	41.9 (3.9)
6D	35.3 (7.6)	30.6 (3.1)	43.4 (4.8)
7C	16.1 (4.1)	26.5 (3.1)	35.3 (4.3) *
7D	28.4 (6.6)	21.9 (2.7)	35.6 (5.4)
8C	25.8 (5.4)	31.2 (3.4)	38.7 (5.0)
8D	32.3 (4.6)	26.2 (3.0)	35.6 (4.8)

*ANOVA $p = 0.007$

Table 42

STATISTICALLY SIGNIFICANT INTERVAL CHANGES IN REGIONAL EJECTION FRACTION mean (SEM)%

	CONTROL	AEROBIC	POWER
REGION 7 rest	5.8 (2.8)	2.7 (3.1)	-8.4 (3.9)
REGION 7 cp	12.3 (5.9)	-4.6 (3.4)	0.4 (5.2)
REGION 8 rest	8.9 (3.9)	-4.0 (2.8)	-7.8 (3.4)

Table 43

DISTRIBUTION AND SITES OF MYOCARDIAL INFARCTION IN EACH GROUP

	CONTROL	AEROBIC	POWER
NONE	9	10	8
ANTERIOR	1	7	2
INFERIOR	2	7	6
SITE UNKNOWN	4	1	0

The data are now analysed with reference to previous myocardial infarction.

Twenty seven patients had not had myocardial infarctions. The distribution and sites of infarction in each group are shown in table 43.

The following tables show regional ejection fraction at rest and after cold pressor in patients with no history of previous myocardial infarction (tables 44 and 45), anterior myocardial infarction (tables 46 and 47) and inferior myocardial infarction (tables 48 and 49).

In those with no previous myocardial infarction, there were no significant differences between or within the groups.

In comparing those with anterior myocardial infarction and those with no previous myocardial infarction, there was a significant difference within the aerobic group (no MI n = 10, anterior myocardial infarction n = 7) in the following regions:

baseline resting scans region 1, (55.3 vs 27.1, 2p = 0.002) region 3, (70.3 vs 44.7, 2p = 0.006) region 4, (63.7 vs 32.3, 2p = 0.015) region 6, (39.7 vs 13.9, 2p = 0.009) region 7, (33.6 vs 5.4, 2p = 0.003) region 8 (42.3 vs 12.1, 2p = 0.002); six month resting scans region 1 (50.3 vs 29.4, 2p = 0.002) and region 2, (68.6 vs 29.4, 2p = 0.082).

As expected, those with anterior myocardial infarction had lower regional ejection fractions at baseline than those with no previous myocardial infarction. This difference disappears with time and training, and those with anterior myocardial infarction appear to 'catch up' with those with no previous myocardial infarction. In region 1, the difference remains and it appears in

region 2. This could signify an improvement in ejection fraction in the anterior zone of the left ventricle, denoted by regions 3 to 6, in those with anterior myocardial infarction brought about by aerobic exercise training. Alternatively, there could have been a deterioration in regional ejection fraction in those with no previous myocardial infarction. The atria and great vessels lie over regions 7 and 8, and partly over region 1 so the significance of changes in those regions are less clear.

These interval changes do not actually achieve statistical significance, since some patients in each of the two groups improve while others deteriorate. Thus, although the absolute values of ejection fraction in the regions mentioned above differ significantly, the mean interval changes do not (table 50). Nevertheless, the direction of change is positive in those with anterior myocardial infarction and negative in those with no previous myocardial infarction. No firm conclusions can be reached, but the suggestion is that aerobic exercise training could influence the ejection fraction in the anterior zone of the left ventricle in patients with previous anterior myocardial infarction. The type of graft did not make any difference. This would imply that there had been an improvement in myocardial perfusion to that region, and that despite the infarction, there was residual viable tissue.

The numbers in the control and power groups are too small to contribute to the question. Those with inferior myocardial infarction showed no significant changes.

There were 5 patients with myocardial infarction at unspecified sites, 4 in the control group, and 1 in the aerobic group. In this small subgroup of

patients, there was again no significant difference in regional ejection fraction between or within the two groups.

In the previously mentioned study from this department, there were significant improvements noted in regions 3, 4 and 6 in the exercise groups between baseline and 12 month cold pressor scans. There was a small improvement in the control group due mainly to a reduction in resting regional ejection fraction.

It is interesting that the same regions also showed an improvement among a subgroup in the present study, though it was in the resting scan and not the stress scan as had been found in the previous study.

Table 44

REGIONAL EJECTION FRACTION AT REST IN PATIENTS WITH NO PREVIOUS MYOCARDIAL INFARCTION (n = 27) mean (SEM)%

	CONTROL	AEROBIC	POWER
1A	47.9 (4.8)	55.3 (6.7)	50.3 (4.5)
1B	50.1 (7.3)	50.3 (4.2)	46.6 (5.6)
2A	69.2 (5.4)	68.6 (7.0)	68.4 (5.4)
2B	70.0 (6.7)	65.7 (4.0)	70.3 (6.9)
3A	73.8 (5.5)	70.3 (4.9)	69.4 (4.5)
3B	66.8 (7.1)	69.3 (4.0)	71.0 (3.7)
4A	69.9 (6.4)	63.7 (5.9	64.1 (6.2)
4B	64.9 (8.9)	60.6 (7.2)	64.8 (4.5)
5A	60.8 (5.7)	55.2 (6.7)	63.8 (5.4)
5B	65.6 (8.9)	55.3 (8.3)	53.3 (5.0)
6A	42.3 (4.9)	39.7 (5.6)	38.6 (4.4)
6B	43.6 (7.9)	36.8 (5.4)	33.8 (3.0)
7A	28.8 (5.3)	33.6 (6.1)	32.3 (5.2)
7B	35.8 (7.1)	31.7 (5.9)	24.6 (2.1)
8A	29.0 (5.2)	42.3 (6.4)	36.8 (8.4)
8B	36.9 (6.5)	32.9 (4.8)	28.8 (5.5)

Table 45

REGIONAL EJECTION FRACTION AFTER COLD PRESSOR IN PATIENTS WITH NO PREVIOUS MYOCARDIAL INFARCTION (n = 27) mean (SEM) %

	CONTROL	AEROBIC	POWER
1C	41.3 (7.3)	43.5 (6.8)	43.4 (6.7)
1D	50.0 (6.2)	44.0 (4.0)	50.9 (2.5)
2C	64.9 (5.9)	53.6 (7.8)	56.1 (8.3)
2D	60.9 (6.8)	59.2 (4.2)	68.0 (5.9)
3C	67.1 (6.3)	56.7 (7.9)	65.4 (4.9)
3D	64.4 (6.3)	63.9 (5.0)	71.4 (4.5)
4C	65.4 (8.7)	54.4 (7.6)	63.9 (6.3)
4D	63.3 (8.8)	57.5 (6.7)	63.8 (5.4)
5C	56.6 (9.8)	48.8 (9.3)	62.0 (6.2)
5D	57.4 (10.4)	55.6 (5.5)	51.3 (4.7)
6C	39.9 (6.1)	30.0 (6.2)	36.3 (6.0)
6D	41.8 (9.4)	37.0 (4.7)	42.1 (5.4)
7C	21.3 (5.1)	26.4 (4.9)	30.8 (6.3)
7D	35.3 (6.5)	25.5 (4.6)	33.9 (5.9)
8C	31.7 (7.5)	34.9 (6.1)	33.9 (9.1)
8D	38.3 (5.1)	28.1 (5.3)	32.4 (4.9)

Table 46

REGIONAL EJECTION FRACTION AT REST IN PATIENTS WITH ANTERIOR MYOCARDIAL INFARCTION (n = 10) mean (SEM)%

	CONTROL	AEROBIC	POWER
NUMBER	1	7	2
1A	25.0	27.1 (3.3)	45.0 (5.0)
1B	34.0	29.4 (3.5)	38.0 (0)
2A	45.0	44.3 (4.7)	48.5 (2.5)
2B	54.0	49.6 (7.3)	48.0 (6.0)
3A	57.0	44.7 (6.0)	64.0 (11.0)
3B	58.0	50.4 (7.7)	54.0 (0)
4A	24.0	32.3 (9.2)	55.5 (5.5)
4B	30.0	38.6 (10.3)	67.0 (11.0)
5A	12.0	27.3 (9.3)	62.5 (3.5)
5B	16.0	28.1 (12.6)	58.5 (8.5)
6A	11.0	13.9 (6.3)	37.0 (2.0)
6B	12.0	15.3 (8.9)	33.0 (1.0)
7A	8.0	5.4 (5.2)	22.0 (2.0)
7B	20.0	10.7 (5.8)	18.0 (2.0)
8A	2.0	12.1 (4.5)	30.5 (3.5)
8B	9.0	13.9 (4.1)	35.0 (1.0)

Table 47

REGIONAL EJECTION FRACTION AFTER COLD PRESSOR IN PATIENTS WITH ANTERIOR MYOCARDIAL INFARCTION (n = 10) mean (SEM)%

	CONTROL	AEROBIC	POWER
NUMBER	1	7	2
1C	22.0	23.9 (9.5)	50.0 (1.0)
1D	36.0	32.1 (7.7)	41.5 (28.5)
2C	45.0	37.4 (11.3)	70.5 (9.5)
2D	57.0	39.4 (11.1)	42.5 (34.5)
3C	40.0	24.9 (12.7)	68.5 (8.5)
3D	65.0	46.7 (9.4)	39.5 (34.5)
4C	14.0	31.0 (10.2)	69.5 (8.5)
4D	47.0	41.7 (8.9)	44.0 (18.0)
5C	6.0	27.7 (8.1)	68.0 (13.0)
5D	7.0	29.4 (9.4)	49.5 (6.5)
6C	-3.0	22.7 (7.3)	44.0 (16.0)
6D	2.0	21.6 (6.1)	32.0 (3.0)
7C	-6.0	22.7 (6.4)	39.5 (21.5)
7D	3.0	16.1 (4.6)	20.5 (13.5)
8C	13.0	22.4 (6.3)	41.0 (7.0)
8D	0	21.4 (6.4)	25.5 (24.5)

Table 48

REGIONAL EJECTION FRACTION AT REST IN PATIENTS WITH INFERIOR MYOCARDIAL INFARCTION (n = 15) mean (SEM)%

	CONTROL	AEROBIC	POWER
NUMBER	2	7	6
1A	32.0 (13.0)	46.3 (4.6)	48.3 (11.7)
1B	43.5 (14.5)	37.0 (5.7)	43.3 (7.3)
2A	59.5 (24.5)	64.6 (6.9)	64.7 (4.3)
2B	62.0 (11.0)	57.1 (3.4)	44.5 (9.4)
3A	57.0 (24.0)	58.0 (6.7)	57.8 (8.9)
3B	55.0 (17.0)	56.7 (6.7)	51.8 (8.6)
4A	37.0 (24.0)	54.4 (4.8)	52.0 (6.9)
4B	36.0 (29.0)	56.3 (7.1)	49.8 (11.4)
5A	24.0 (32.0)	45.1 (7.2)	57.3 (3.0)
5B	28.0 (28.0)	53.1 (8.3)	54.8 (6.8)
6A	24.5 (17.5)	27.7 (5.8)	45.2 (1.6)
6B	14.5 (8.5)	34.0 (5.6)	40.7 (10.6)
7A	10.0 (8.0)	21.7 (5.6)	40.5 (5.4)
7B	15.0 (10.0)	26.3 (4.8)	29.7 (7.4)
8A	17.5 (14.5)	27.6 (5.1)	42.3 (3.9)
8B	26.5 (12.5)	28.6 (5.5)	30.7 (6.8)

Table 49

REGIONAL EJECTION FRACTION AFTER COLD PRESSOR IN PATIENTS WITH INFERIOR MYOCARDIAL INFARCTION (n = 15) mean (SEM)

	CONTROL	AEROBIC	POWER
NUMBER	2	7	6
1C	25.5 (18.5)	44.7 (7.9)	55.0 (5.2)
1D	41.0 (16.0)	40.9 (4.8)	44.5 (9.9)
2C	47.5 (20.5)	59.6 (8.6)	63.7 (4.2)
2D	52.0 (7.0)	52.3 (5.8)	48.3 (12.1)
3C	46.5 (11.5)	53.4 (8.2)	56.8 (10.1)
3D	48.0 (4.0)	48.7 (8.9)	49.0 (13.9)
4C	31.5 (17.5)	53.7 (6.1)	56.0 (6.8)
4D	33.5 (16.5)	44.9 (7.7)	51.5 (12.7)
5C	24.0 (30.0)	48.0 (7.9)	57.5 (4.0)
5D	38.5 (38.5)	37.0 (11.6)	64.8 (9.8)
6C	20.0 (22.0)	32.1 (5.9)	48.8 (4.6)
6D	46.0 (46.0)	29.7 (5.1)	49.0 (10.5)
7C	4.0 (13.0)	29.7 (6.5)	39.8 (5.7)
7D	50.0 (43.0)	21.9 (5.4)	43.0 (11.3)
8C	2.5 (9.5)	35.9 (5.4)	44.3 (5.4)
8D	38.0 (25.0)	27.3 (4.5)	43.2 (8.7)

Table 50

INTERVAL CHANGES IN RESTING REGIONAL EJECTION FRACTION IN AEROBIC GROUP: NO MI VS ANTERIOR MI

REGION	NO MI	ANTERIOR MI	'2p'
1	-5.0 (7.8)	2.3 (3.7)	0.41
2	-2.9 (5.8)	5.3 (4.6)	0.29
3	-1.0 (3.8)	5.7 (3.9)	0.24
4	-3.1 (5.3)	6.3 (4.5)	0.20
5	0.1 (4.7)	0.9 (6.2)	0.92
6	-2.9 (3.0)	1.4 (5.2)	0.48
7	-1.9 (6.3)	5.3 (3.0)	0.32
8	-9.4 (5.3)	1.7 (3.5)	0.10

SECTION XII

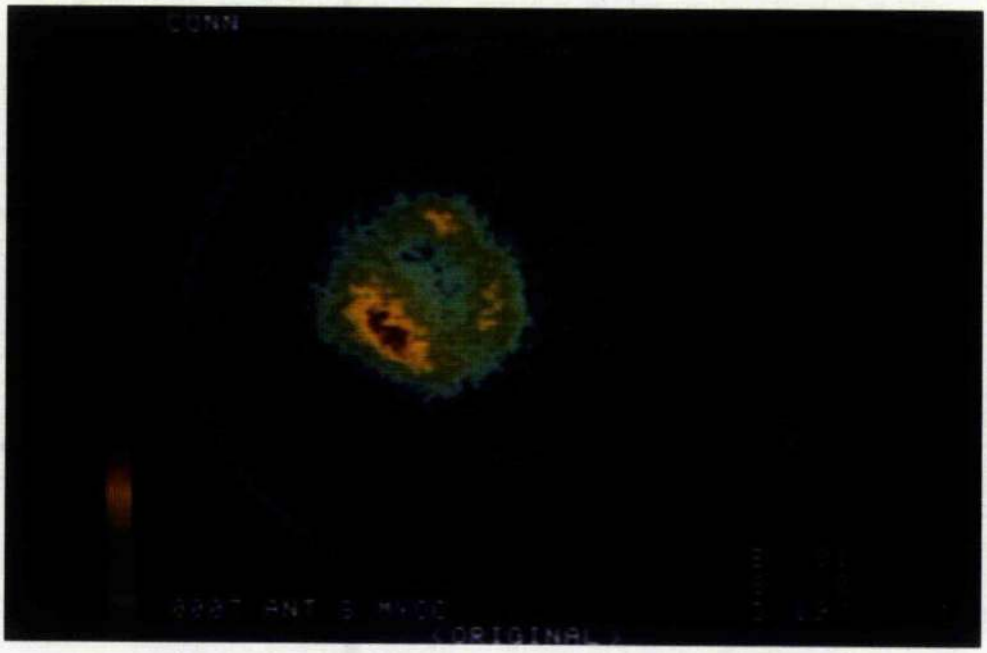
MYOCARDIAL PERFUSION: REST AND EXERCISE THALLIUM-201 SCINTIGRAPHY

Exercise thallium-201 scintigraphy was used in assessing myocardial perfusion. This technique is well established. In the myocardium, thallium-201 acts like potassium and is taken up avidly by well-perfused parts (Strauss et al 1975). In coronary artery disease, obstructive lesions may prevent the uptake of the radionuclide by affected parts of the myocardium particularly under conditions of stress. At rest, these parts are adequately perfused, and any defects that were present during the stress test may disappear. This is the basis of the reversible perfusion defect used in the diagnosis of coronary artery disease (Bailey et al 1977; Ritchie et al 1977; Hamilton 1979; Grunwald et al 1981; McKillop 1982; Verani 1983). In myocardial infarction, the perfusion defects present during stress tend to remain also at rest, and form the irreversible or fixed perfusion defect (Pohost et al 1977; Hamilton et al 1977). After coronary artery surgery, or other means of myocardial revascularisation, one would expect that perfusion defects due to obstructive coronary lesions would be abolished and that the extent of fixed defects may be reduced. This depends on the completeness and maintenance of revascularisation, the emergence of new lesions, including graft occlusion, and the progression of existing lesions, including reinfarction. The maintenance of revascularisation could be due to changes brought about by exercise training.

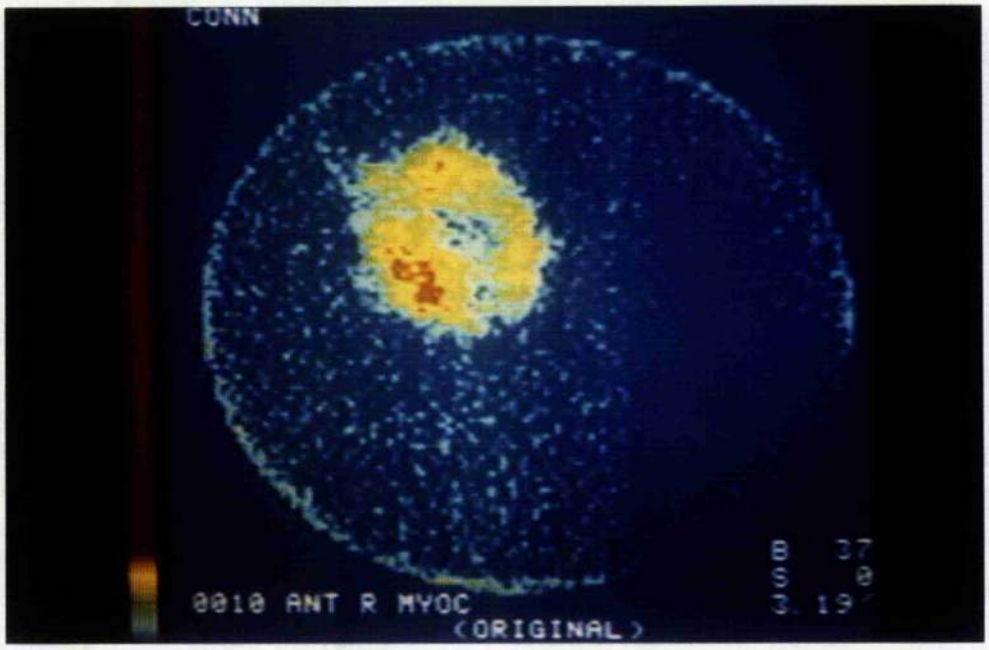
METHODS

The patients had additional treadmill exercise tests using a modified Balke protocol as previously described, at baseline and at the end of their training period. An indwelling venous cannula was inserted in the left antecubital fossa. This was used to obtain the samples needed for haematological and lipoprotein assays, and then flushed with 10ml normal saline prior to starting the treadmill test. The patients had been fasting for at least 12 hours. On these occasions, they were asked to exercise until they estimated that they were one minute from their maximum exercise. At that point, 80 MBq of thallous-201 chloride was injected into the cannula, and flushed with a further 20 ml normal saline. At the end of exercise, the patient was quickly transported in a wheelchair to the scanning room. This was accomplished within 10 minutes in the majority.

A Technicare Sigma 410 gamma camera with a large field of view crystal and general purpose collimator, connected to an ADAC CGR 7310 computer was used to acquire the thallium-201 scans. The scans were obtained in anterior, 45° left anterior oblique (LAO), and 65° LAO positions, (figures 4 to 6). 350,000 counts were acquired in each position. The time taken to acquire these preset counts was recorded. The spleen was masked with a lead shield. Data were acquired and stored in a 128 x 128 x 8 bit matrix on the computer.

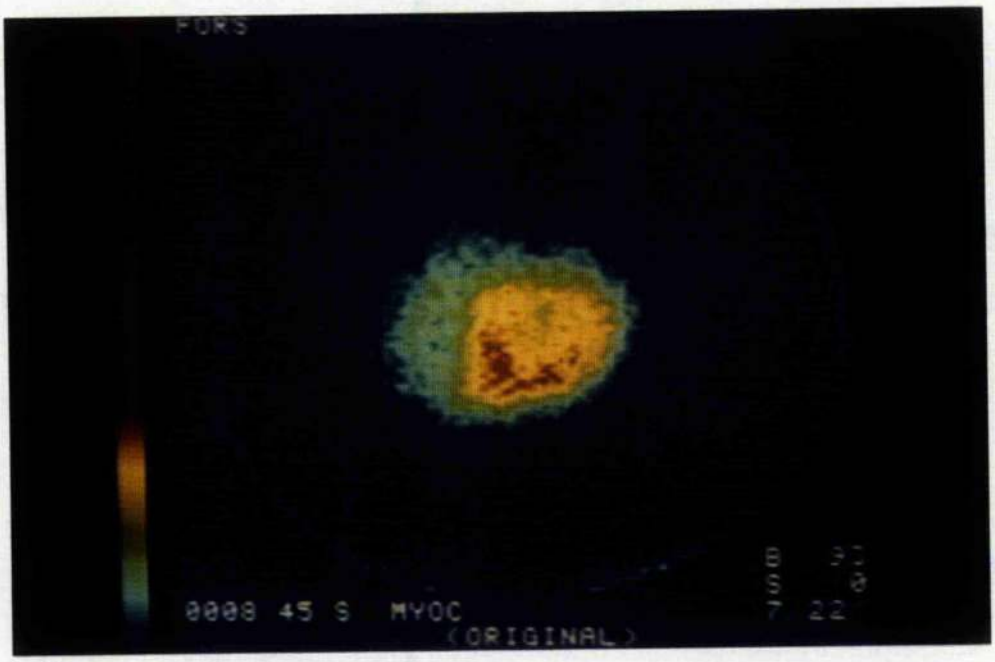


(a)

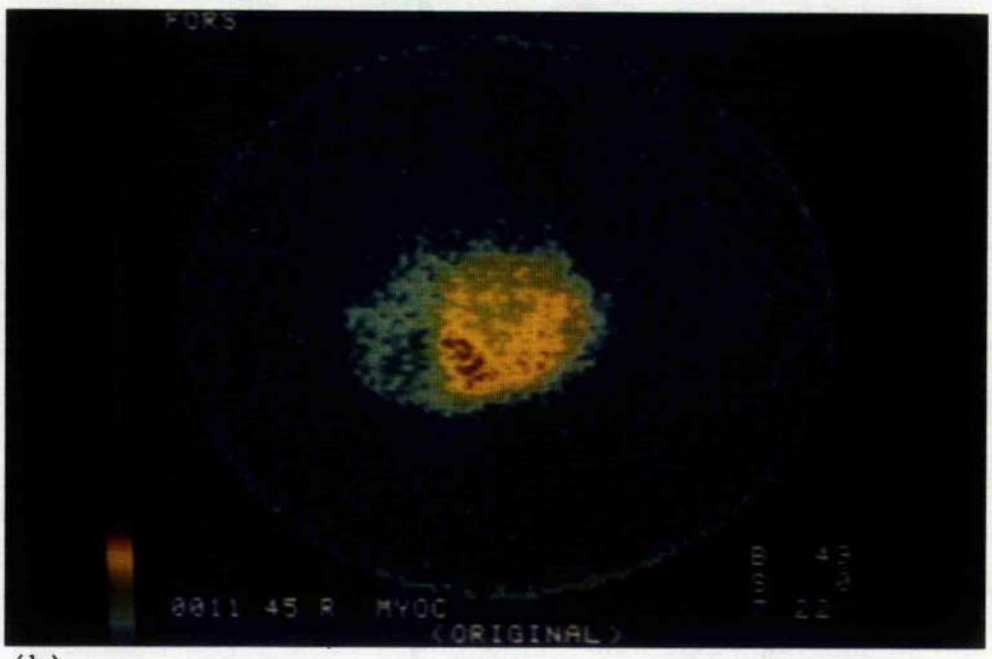


(b)

Figure 4. Planar thallium scan: anterior view after stress (a) and after rest (b)

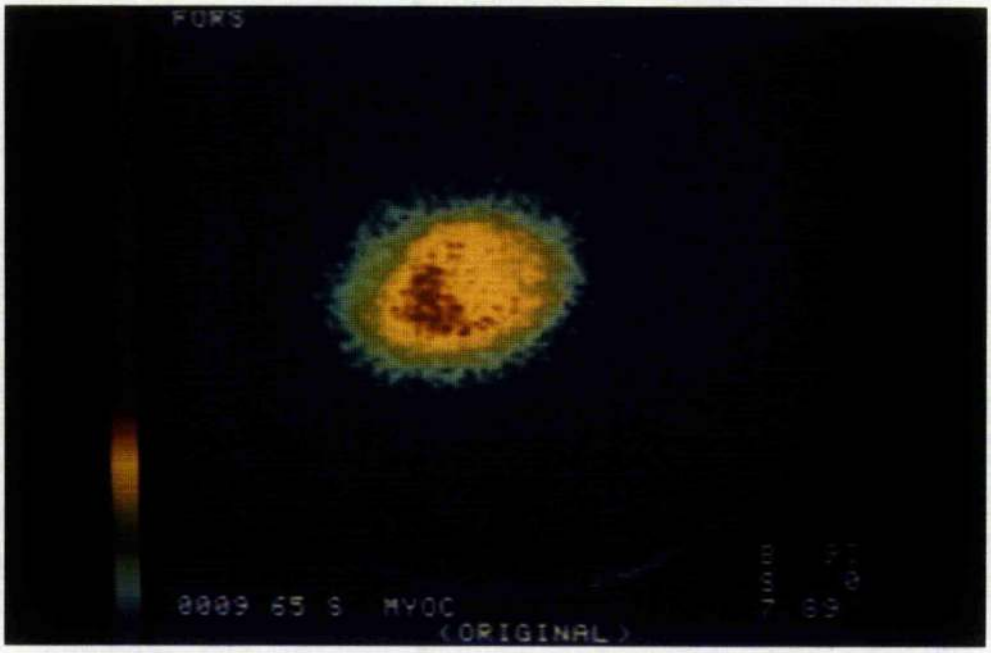


(a)

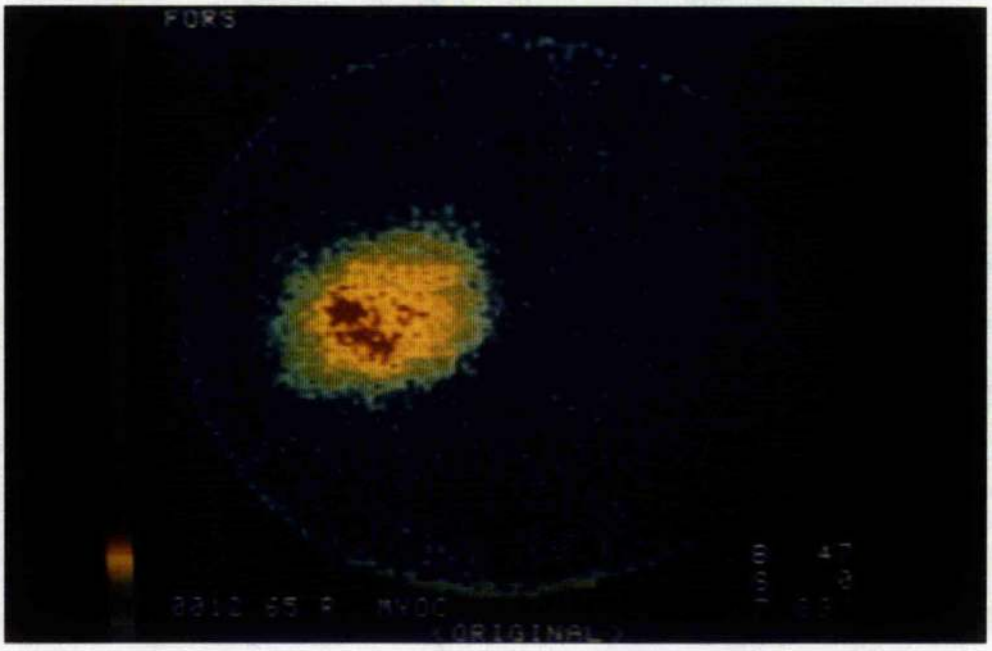


(b)

Figure 5. Planar thallium scan: 45o LAO view after stress (a) and after rest (b)



(a)



(b)

Figure 6. Planar thallium scan: 65° LAO view after stress (a) and after rest (b).

Three hours later, the patient returned for further scans, taken in the same views. Each scan was obtained in the time it had taken to obtain the corresponding view earlier in the day.

There were therefore six scans, three stress and three rest or redistribution scans for processing. This was done using commercially available software and analysis programmes.

The initial processing included background subtraction of non-cardiac activity (which was principally due to pulmonary uptake). Subtraction of non-cardiac activity was done by interpolative background subtraction, as described by Goris et al (1976) and modified by Beck et al (1979). The stored image is recalled onto the monitor, and a lightpen is used to outline the boundaries of the left ventricle, thus creating a left ventricular area of interest (AOI). The interpolative background subtraction then takes place, and the process is repeated for each image. The programme generates a horizontal reference plane i.e. a three-channel profile, across the centre of the AOI. A new set of pixel values (interpolated values) is assigned to the reference plane. A background-computed image is determined as a fraction of the radioactivity in the myocardial region relative to the reference plane. Then, a background corrected image is created by subtracting the computed background image from the original unprocessed one.

The production of raw stress, redistribution and washout profiles is done next. The profiles consist of the maximum number of counts along radii originating at the centre of the left ventricle. Each radius is separated by 6° from the next. The number of counts along the radius is smoothed using a three

point smooth.

The programme quantitates the spatial distribution of thallium in the myocardium on each pair of stress and redistribution images. The centre and apex of the left ventricle are marked by the operator on each pair of images, using a light pen. The system then creates sixty radii extending from the centre, placed at 6° intervals, with the first radius at 90° anticlockwise from the apex. The system searches for the pixel in each radius with the maximum number of counts, within the inner and outer search boundaries of the myocardium. It then averages the pixels and displays the image, with inner and outer boundaries, and hottest pixel marked. Once this is accepted by the operator, each pixel is averaged with the two adjacent pixels on each radius, and the stress and redistribution images are displayed on the screen.

The calculated count profiles can then be plotted, with the highest count value on either image being assigned a value of 100%. All other pixels are assigned a value relative to this. The horizontal axis of the graph represents count location in the myocardium, with the apex always at the 90° position. The vertical axis shows the percentage of the maximum counts in the myocardium. Stress and redistribution curves are plotted on the same graph. The percent washout curve is also plotted, with percent washout calculated as Stress image count value minus Redistribution image count value divided by Stress image count value, multiplied by 100%.

Profiles generated in this way provide information on the relative distribution of thallium around the circumference of the heart (Burow et al 1979). The stress profile will show up ischaemic areas as those of initially low

uptake of thallium, with a tendency to normalise after rest. In normals, the stress and redistribution curves will run parallel to one another. Washout curves are particularly relevant in patients with balanced triple vessel disease, or after intervention. Uptake of thallium may be uniform in all areas in these cases, and therefore plots of relative counts may show no abnormality. Slow clearance of thallium from ischaemic areas may result in redistribution profiles which are higher than expected.

The addition of normal values to the curves provides further enhancement of the above programme and analysis. Maddahi et al (1981) have published normal values for stress and washout curves, which identify lower limits of normal corresponding to two standard deviations below the mean for his group of normal individuals. Abnormal curves can be compared with these values to show up areas which fall below the normal range. For the detection of coronary artery disease, the technique has a sensitivity of 93% and specificity of 91%. It was therefore deemed suitable for the assessment of myocardial perfusion in post-CAS patients.

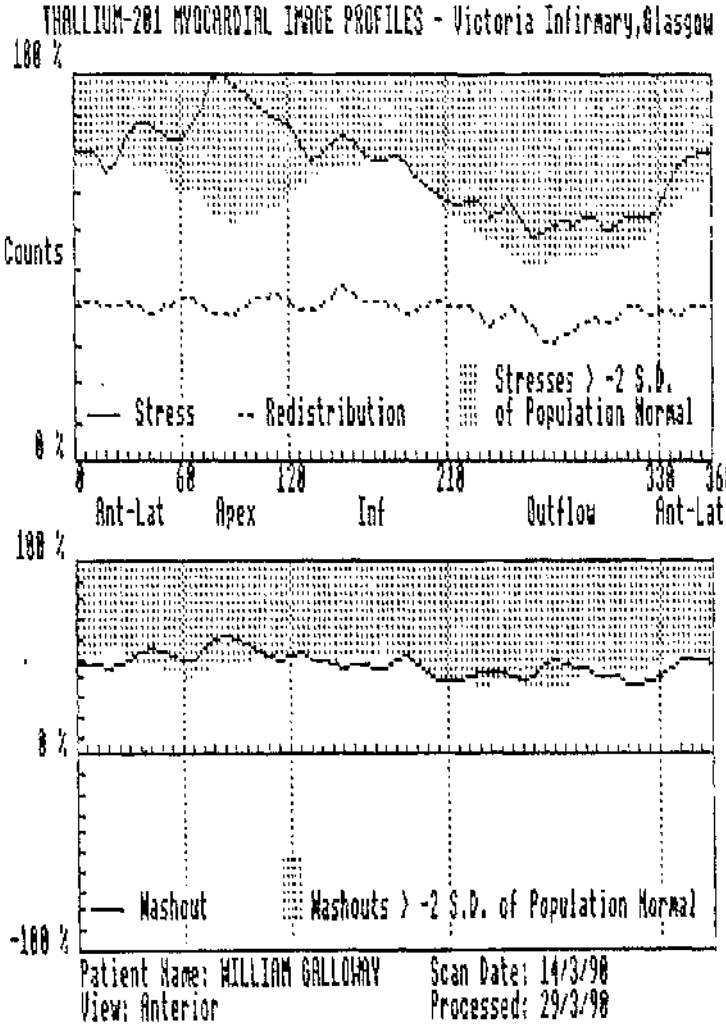
A computer programme had been developed in the Nuclear Medicine Department at the Victoria Infirmary, on a BBC Master computer to superimpose the normal curves from Maddahi's study onto the profiles generated from the patients, and to quantitate any abnormality. Before this is done, a further smoothing of the profiles is carried out. The programme has the feature of automatic alignment of stress and redistribution profiles using cross-correlation. The facility for the operator to override the automatic alignment is available. This may be necessary in the presence of gross

localised perfusion defects.

A printout of the counts for stress, redistribution and washout profiles generated from the ADAC computer is obtained. The stress and redistribution data are entered by hand into the BBC computer, and stored. The stress image is used later as the reference for the cross-correlation routine. The raw data are smoothed using a three point smooth, and then normalised to the new maximum of the stress profile. The redistribution profile is cross-correlated with the stress profile, and the results of these calculations are displayed on the screen. The stress and redistribution profiles are then plotted in the position of maximum cross-correlation. The operator can either accept the automatic alignment, or manually adjust it. This is then stored, and can be printed out. The washout profile is calculated and along with the stress profile, it is compared with the normal range of data (figures 7-9).

Each image is divided into four segments, and for a segment to be considered abnormal, at least one area of 18 degrees or more in either of the profiles has to extend below the normal limit. For a study result to be considered abnormal at least two abnormal segments have to be present in the entire study. The outflow tracts are not included in the analysis.

The use of normal values generated from a different population may not be ideal, but their incorporation into our analysis provides a guide as to the extent of abnormality and differences between the two scans in each patient.

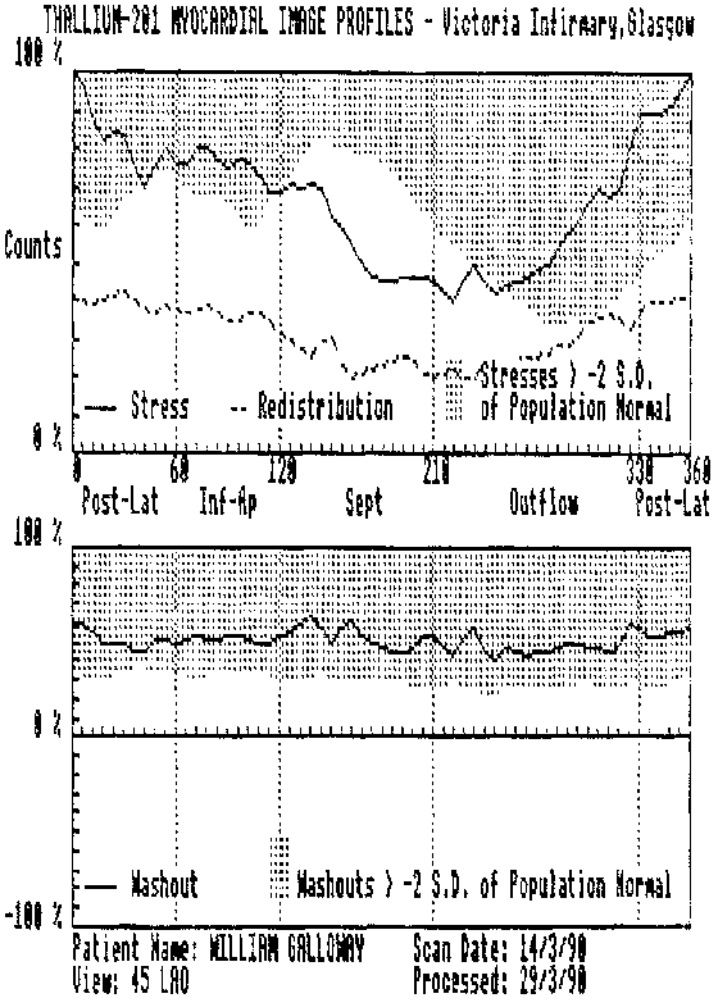


Abnormal Degrees per Region

	Ant-Lat	Apex	Inf
Stress	0	0	0
Washout	36	18	90

No. of abnormal regions is 3

Figure 7: Stress, redistribution and washout curves, anterior view.

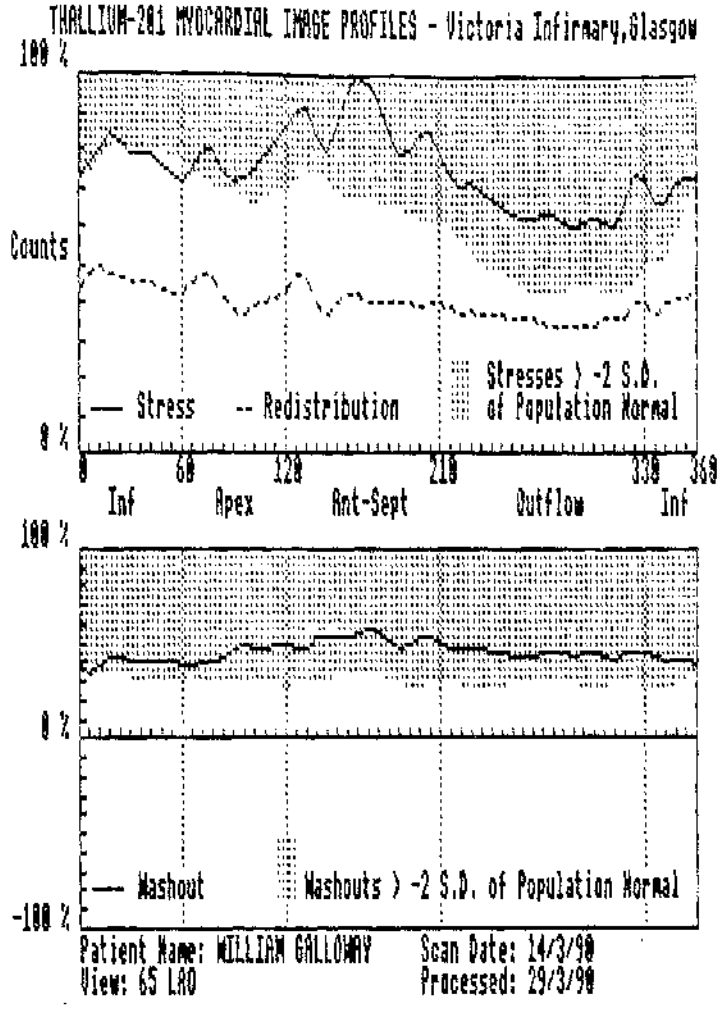


Abnormal Degrees per Region

	Post-Lat	Inf-Ap	Sept
Stress	0	0	96
Washout	0	0	0

No. of abnormal regions is 1

Figure 8: Stress, redistribution and washout curves, 45° LAO view.



Abnormal Degrees per Region

	Inf	Apex	Mnt-Sept
Stress	36	6	0
Washout	0	0	0

No. of abnormal regions is 2

Figure 9: Stress, redistribution and washout curves, 65° LAO view.

RESULTS

Fifty six patients had complete sets of scans for analysis. There were 18 in the control group, 23 in the aerobic group and 15 in the power group. The imbalance in the training groups was due to more patients being randomised to the aerobic than to the power group in the middle part of the study, with the thallium scans being performed on a consecutive basis. There were errors during the acquisition of baseline scans in the remaining four patients.

Three sets of scans from each group were analysed twice to determine the intra-observer variation. This was thought to be relevant because the full analysis involved several steps. The differences in the results were negligible. The anterior views were identical; in the 45° and 65° LAO views, there were 6 - 12° differences in the degrees of abnormality in the stress profiles.

The degrees of abnormality in the stress and washout profiles before and after training were compared between the groups.

Results are presented first as regional stress data in each individual, with the mean and SEM (tables 51 to 59). As is expected following revascularisation, some stress scans were normal. Subsequent tables show mean total degrees of abnormality in stress profiles for each view and mean global stress in the three groups (table 60). Washout data are presented as mean degrees of abnormality of regional washout, mean washout in each view and mean global washout in the three groups (tables 61 and 62).

A number of patients had previous myocardial infarction, causing fixed perfusion defects. It may be suggested that if exercise training has any effect on myocardial vascularity, even such fixed defects may be altered, especially

as they may represent stunned or hibernating myocardium.

In the previous section, those with anterior myocardial infarction had improved anterior regional ejection fraction after aerobic training. Results of their thallium scans were therefore analysed as a subgroup to see if this was related to myocardial perfusion as was speculated. Significant differences were found after training in degrees of abnormality in the washout curves, but not in the stress curves.

The aerobic group tended to have lower degrees of abnormality in washout in the anterior zone after training than the power group. The control group had intermediate values. The significant results are in table 63. None of the other values achieved statistical significance.

A fair number of the patients had normal anterior views, resulting in low mean degrees of abnormality in each region.

Abbreviations used in the tables are:

ALS/W: anterolateral stress/washout

AS/W: apical stress/washout

IS/W: inferior stress/washout

PLS/W: posterolateral stress/washout

IAS/W: inferoapical stress/washout

SS/W: septal stress/washout

INS/W: 65° LAO inferior stress/washout

APS/W: 65° LAO apical stress/washout

ASS/W: Anteroscptal stress/washout

ANTS/W: anterior view stress/washout

FVS/W: 45° LAO view stress/washout

SVS/W: 65° LAO view stress/washout

1 = first scan

2 = second scan

MI code: 1 = none 2 = anterior 3 = inferior 4 = site unknown

There were significant differences between the groups only in IS1 (ANOVA p = 0.02) and IS2 (ANOVA p = 0.04), with the control group having a lower perfusion abnormality in that region than the exercise groups on both scans. This suggests that there was no change in regional perfusion with exercise training in these patients who appear to have been adequately revascularised by coronary artery surgery.

There was a significant difference only in the anterior view, with the control group having a smaller perfusion defect than the aerobic group on both scans. The control group did increase the perfusion defect more than the aerobic group, and in the power group, there was a reduction in the perfusion defect. These interval changes did not reach statistical significance. There was therefore no overall change in global stress perfusion with exercise training in these patients.

A further analysis was done of patients with no history of myocardial infarction. This did not yield any differences between the groups.
The overall low degrees of abnormality implies that revascularisation had been very successful in these patients.

The lack of effect of exercise training on myocardial perfusion is perhaps a reflection of its existing adequacy.

In a further analysis of the stress data, only patients with positive scans in any of the three views were considered. This did not add to the above results in that there was no significant differences within or between the groups at any time.

Table 51

CONTROL GROUP: ANTERIOR VIEW STRESS DATA

PAT.	ALS1	ALS2	AS1	AS2	IS1	IS2	MI
1	0	0	0	0	0	0	4
2	0	0	0	0	0	0	1
3	0	0	0	0	0	0	4
4	0	36	0	0	0	0	1
5	0	0	0	0	0	0	1
6	36	18	0	24	72	66	3
7	0	0	30	24	78	48	2
8	0	30	0	0	0	0	4
9	42	0	0	0	0	0	1
10	0	0	0	0	0	0	3
11	0	0	0	0	0	18	1
12	78	90	12	60	0	36	2
13	0	36	0	0	0	0	1
14	0	0	0	0	0	0	1
15	0	0	0	0	0	54	1
16	0	0	0	0	0	0	1
17	0	24	0	0	0	24	1
18	18	18	0	0	0	0	1
MEAN	9.66	14	2.33	6.0	8.3	13.66	
SEM	5.0	5.5	1.8	3.7	5.7	5.2	

Table 52

CONTROL GROUP: 45° LAO VIEW STRESS DATA

PAT.	PLS1	PLS2	IAS1	IAS2	SS1	SS2	MI
1	0	0	0	0	54	54	4
2	0	0	0	0	48	36	1
3	0	0	0	0	66	72	4
4	0	18	0	0	54	42	1
5	0	0	0	0	0	0	1
6	36	66	24	30	30	54	3
7	36	0	18	36	90	66	2
8	0	0	0	0	0	0	4
9	0	0	0	0	0	48	1
10	0	0	0	0	30	60	3
11	0	0	0	0	0	24	1
12	0	0	0	0	96	90	2
13	0	60	0	0	18	60	1
14	0	0	0	0	96	96	1
15	0	0	0	0	0	66	1
16	0	0	0	0	78	96	1
17	0	0	0	0	60	0	1
18	0	0	0	0	66	102	1
MEAN	4.0	8.0	2.33	3.66	43.6	53.6	
SEM	2.7	4.8	1.6	2.5	8.3	7.6	

Table 53

CONTROL GROUP: 65° LAO VIEW STRESS DATA

PAT.	INS1	INS2	APS1	APS2	ASS1	ASS2	MI
1	0	0	0	0	0	0	4
2	0	48	0	30	0	0	1
3	0	0	0	0	24	0	4
4	0	54	0	0	0	0	1
5	36	0	0	0	0	0	1
6	78	72	30	30	0	0	3
7	48	60	60	60	42	0	2
8	60	36	0	0	0	0	4
9	48	42	0	0	0	0	1
10	78	54	0	0	0	0	3
11	0	48	0	0	0	0	1
12	0	0	48	24	60	72	2
13	36	0	0	0	0	0	1
14	0	0	0	0	0	0	1
15	24	0	0	0	0	0	1
16	30	54	0	0	0	0	1
17	0	0	0	0	0	0	1
18	0	18	0	6	0	18	1
MEAN	24.3	27	7.6	8.3	7.0	5.0	
SEM	6.7	6.4	4.3	3.9	4.1	4.1	

Table 54

AEROBIC GROUP: ANTERIOR VIEW STRESS DATA

PAT.	ALS1	ALS2	AS1	AS2	IS1	IS2	MI
1	48	0	42	0	0	0	4
2	54	0	0	0	84	72	3
3	0	0	0	0	0	0	1
4	18	18	60	24	24	0	3
5	0	0	0	0	84	84	3
6	0	36	0	42	48	78	1
7	42	30	0	0	0	0	1
8	0	0	0	0	0	0	1
9	0	24	0	36	18	90	3
10	18	36	0	0	0	0	2
11	0	24	0	36	36	90	1
12	0	0	0	0	90	90	3
13	0	42	0	0	18	24	3
14	90	84	60	54	18	18	2
15	24	24	36	36	90	90	1
16	0	0	0	0	84	54	2
17	0	0	0	0	36	0	1
18	0	0	0	0	0	36	1
19	18	60	0	12	48	18	2
20	0	30	0	0	66	0	1
21	18	0	42	0	66	54	1
22	36	72	0	12	0	0	2
23	60	0	0	0	0	0	1
MEAN	18.5	20.9	10.4	10.9	35.2	34.7	
SEM	5.3	5.3	4.3	3.6	7.2	7.9	

Table 55

AEROBIC GROUP: 45° LAO VIEW STRESS DATA

PAT.	PLS1	PLS2	IAS1	IAS2	SS1	SS2	MI
1	0	0	0	0	36	0	4
2	0	0	0	0	0	0	3
3	0	0	0	0	0	0	1
4	72	0	18	0	30	0	3
5	60	78	36	6	0	0	3
6	78	0	0	0	0	0	1
7	0	0	0	0	84	84	1
8	36	36	6	0	36	0	1
9	24	0	0	0	0	0	3
10	0	0	0	0	60	102	2
11	0	0	0	0	0	48	1
12	36	72	24	0	18	0	3
13	18	18	0	0	30	84	3
14	18	0	12	60	102	90	2
15	0	0	0	0	0	0	1
16	0	0	0	0	30	48	2
17	0	0	0	0	30	0	1
18	0	0	0	0	0	30	1
19	18	36	54	60	90	90	2
20	0	0	0	0	84	66	1
21	0	0	0	36	90	102	1
22	0	0	0	0	60	42	2
23	0	0	0	0	66	0	1
MEAN	12.3	10.4	6.5	7.0	36.8	34.2	
SEM	4.3	4.8	2.9	3.8	7.4	8.4	

Table 56

AEROBIC GROUP: 65° LAO VIEW STRESS DATA

PAT.	INS1	INS2	APS1	APS2	ASS1	ASS2	MI
1	54	0	60	0	0	0	4
2	72	78	0	12	0	0	3
3	0	0	0	0	0	0	1
4	0	90	48	60	30	18	3
5	90	90	6	12	0	0	3
6	48	24	0	0	0	0	1
7	0	48	0	0	0	0	1
8	30	72	0	24	0	0	1
9	54	60	0	6	0	0	3
10	18	18	0	0	0	0	2
11	72	54	12	0	0	0	1
12	24	72	0	0	0	0	3
13	54	24	0	0	0	36	3
14	36	24	60	60	90	90	2
15	0	0	0	0	0	0	1
16	0	36	0	0	0	0	2
17	36	54	0	0	0	0	1
18	0	0	0	0	0	0	1
19	60	30	60	60	30	84	2
20	0	0	0	0	0	0	1
21	0	66	0	0	0	0	1
22	0	0	0	0	66	84	2
23	0	0	0	0	0	0	1
MEAN	32.1	34.7	11.2	8.9	8.9	12.8	
SEM	6.7	6.2	4.8	3.8	4.8	6.2	

Table 57

POWER GROUP: ANTERIOR VIEW STRESS DATA

PAT.	ALS1	ALS2	AS1	AS2	IS1	IS2	MI
1	0	0	0	0	0	30	1
2	0	0	0	0	0	24	1
3	0	0	0	0	72	0	3
4	0	0	0	0	78	78	3
5	0	0	0	0	0	0	1
6	0	0	0	0	0	0	2
7	0	48	0	60	0	24	3
8	0	0	42	24	66	36	1
9	0	0	0	0	0	0	3
10	54	24	0	0	0	0	1
11	0	0	0	0	24	0	1
12	90	72	60	0	60	18	2
13	0	0	0	0	0	0	3
14	0	0	0	0	0	0	4
15	0	0	0	0	0	0	1
MEAN	9.6	9.6	6.8	5.6	20.0	14.0	
SEM	6.8	5.6	4.7	4.2	8.1	5.7	

Table 58

POWER GROUP: 45° LAO VIEW STRESS DATA

PAT.	PLS1	PLS2	IAS1	IAS2	SS1	SS2	MI
1	0	0	0	0	0	0	1
2	0	0	0	0	18	60	1
3	0	36	0	6	0	0	3
4	0	0	0	0	0	0	3
5	0	0	0	0	0	0	1
6	0	0	0	0	0	54	2
7	0	66	0	0	0	24	3
8	0	0	66	36	90	54	1
9	0	0	0	0	0	0	3
10	72	0	0	0	66	60	1
11	0	0	0	0	0	0	1
12	30	24	0	0	78	102	2
13	0	0	0	0	0	48	3
14	0	0	0	0	0	0	4
15	0	0	0	0	0	0	1
MEAN	6.8	8.4	4.4	2.8	16.8	26.8	
SEM	5.1	4.9	4.4	2.4	8.3	8.6	

Table 59

POWER GROUP: 65° LAO VIEW STRESS DATA

PAT.	INS1	INS2	APS1	APS2	ASS1	ASS2	MI
1	0	0	0	0	0	0	1
2	18	18	0	0	0	0	1
3	90	78	12	24	0	0	3
4	48	36	6	0	0	0	3
5	18	30	0	0	0	0	1
6	24	18	18	0	0	0	2
7	90	54	6	0	0	0	3
8	0	0	0	0	0	0	1
9	18	24	0	0	0	0	3
10	78	72	0	0	0	0	1
11	60	48	24	6	0	0	1
12	36	0	0	18	60	78	2
13	0	0	0	0	0	0	3
14	0	0	0	0	0	0	4
15	24	24	0	0	0	0	1
MEAN	33.6	26.8	4.4	3.2	4.0	5.2	
SEM	8.4	6.8	1.9	1.9	4.0	5.2	

Table 60

TOTAL STRESS PERFUSION ABNORMALITY IN ALL GROUPS

	CONTROL	AEROBIC	POWER
ANTS1 *	20.3 (9.2)	64.1 (10.2)	36.4 (15.5)
ANTS2 **	32.0 (11.6)	66.5 (11.4)	29.2 (10.8)
FVS1	50.0 (9.9)	55.6 (9.8)	28.0 (14.4)
FVS2	61.0 (8.8)	51.6 (11.6)	38.0 (10.8)
SVS1	39.0 (10.7)	52.4 (12.0)	42.0 (10.2)
SVS2	40.3 (9.3)	56.3 (10.5)	35.2 (8.7)
GLOBALS1	109.3 (25.7)	172.2 (24.6)	106.4 (32.1)
GLOBALS2	133.3 (22.7)	174.5 (25.6)	102.4 (23.9)

* ANOVA p= 0.02. ** ANOVA p= 0.04

Table 61

DEGREE OF ABNORMALITY IN REGIONAL WASHOUT IN ALL GROUPS

	CONTROL	AEROBIC	POWER
ALW1	62.6 (7.9)	67.3 (6.5)	67.2 (7.9)
ALW2	74.3 (6.2)	77.7 (4.1)	70.0 (7.2)
AW1	40.3 (4.9)	43.8 (4.1)	44.4 (6.2)
AW2	43.0 (5.1)	54.5 (3.1)	46.8 (5.2)
IW1	55.3 (7.8)	73.6 (5.1)	67.2 (7.5)
IW2	69.6 (7.2)	66.3 (5.7)	70.0 (6.5)
PLW1	2.3 (2.3)	16.7 (5.9)	9.6 (5.7)
PLW2	12.3 (5.7)	12.3 (4.8)	13.6 (7.4)
IAW1	2.3 (2.3)	9.6 (3.5)	7.2 (4.6)
IAW2	12.7 (4.2)	11.2 (4.2)	10.0 (5.6)
SW1	13.0 (5.9)	9.1 (4.3)	6.0 (3.3)
SW2	14.3 (4.9)	15.1 (5.3)	14.4 (8.3)
INW1	7.3 (3.1)	7.3 (3.8)	5.6 (3.4)
INW2	13.0 (5.9)	19.6 (6.3)	16.0 (7.8)
APW1	6.3 (4.4)	3.1 (2.2)	5.6 (3.8)
APW2	10.0 (4.3)	4.9 (2.9)	12.8 (5.3)
ASW1	11.3 (5.6)	8.6 (4.2)	16.8 (7.5)
ASW2	11.3 (4.0)	16.9 (6.6)	21.6 (8.8)

Table 62

DEGREE OF ABNORMALITY IN WASHOUT PER VIEW AND GLOBALLY IN ALL GROUPS

	CONTROL	AEROBIC	POWER
ANTW1	159.4 (19.1)	184.7 (12.5)	176.1 (20.1)
ANTW2	188.1 (16.7)	198.5 (11.4)	184.1 (17.6)
FVW1	17.7 (9.4)	35.5 (12.1)	22.8 (9.6)
FVW2	39.3 (12.3)	38.6 (11.6)	38.0 (20.6)
SVW1	25.0 (11.7)	19.0 (8.2)	28.0 (13.3)
SVW2	34.3 (12.8)	41.5 (12.0)	50.4 (21.4)
GLOBALW1	202.1 (32.8)	239.2 (24.8)	226.9 (30.8)
GLOBALW2	261.8 (33.9)	278.6 (28.2)	272.5 (51.4)

Table 63

THALLIUM WASHOUT IN PATIENTS WITH ANTERIOR MYOCARDIAL INFARCTION - SIGNIFICANT RESULTS

	CONTROL	AEROBIC	POWER	ANOVA
PLW2	57.0 (27.0)	0 (0)	81.0 (9.0)	0.002
SW2	45.0 (9.0)	24.0 (11.1)	90.0 (0)	0.025
APW2	21.0 (21.0)	1.2 (1.2)	54.0 (6.0)	0.008
ASW2	24.0 (24.0)	4.8 (4.8)	90.0 (0)	0.002
FVW2	138.0 (54.0)	40.8 (18.0)	231.0 (9.0)	0.007
SVW2	84.0 (84.0)	30.0 (18.4)	222.0 (18.0)	0.024
GLOBALW2	453.0 (147.0)	276.0 (37.3)	693.0 (27.0)	0.01
DSVW	30.0 (30.0)	2.4 (38.9)	210.0 (30.0)	0.04

DISCUSSION

There have been many studies on exercise and resting thallium-201 scintigraphy before and after CAS (Ritchie et al 1977; Verani et al 1978; Kolibash et al 1979; Robinson et al 1979; Berger et al 1979; Sbarbaro et al 1979; Hirzel et al 1980; Pfisterer et al 1982; Gibson et al 1983). They have confirmed that myocardial perfusion is improved by bypass surgery. In 1978, Verani et al showed that 9 out of twenty three patients had normal thallium scans, and 19 had improved scans post-operatively. Ten years later, using exercise thallium tomography in 25 patients, Fioretti et al (1988) found that transient defects were reduced from 11 to 5 segments per patient, and even persistent defects were reduced from 8 to 4 segments per patient after CAS.

It is generally agreed that thallium-201 scintigraphy is a more sensitive and specific investigation than exercise electrocardiography in the setting of CAS. In 1977, Ritchie et al studied 20 patients by rest and exercise thallium imaging postoperatively. In addition, nine had resting scans and 11 had resting and exercise scans preoperatively. Patients with no new perfusion defect had 87% graft patency, those with a new defect had 54% graft patency, suggesting that pre- and post-operative thallium scans may nonivasively predict graft patency. In a study of 55 patients pre-CAS and two weeks and one year post-CAS, Pfisterer et al (1982) found a sensitivity, specificity and overall accuracy of 80%, 88%, and 86% respectively for detecting graft occlusion. Hirzel et al (1980) reported that 31 patients with normal postoperative scans had 81% graft patency, 16 patients in whom perfusion defects had not changed after surgery had 38% patency, and seven patients with worse perfusion defects after surgery

had 15% patency.

Segments showing total redistribution preoperatively are more likely than those with partial redistribution or persistent defects to become normal postoperatively. Ninety three percent of such segments were normal after surgery, compared with 73% with partial redistribution, and 45% with persistent defects, in a study of 47 patients (Gibson et al 1983).

As with other aspects of exercise rehabilitation, most reported studies on thallium scintigraphy are in patients with angina or previous myocardial infarction with CAS patients forming a small, if any, part of the group.

The results obtained here are in keeping with several previous reports, which conclude that thallium scans and scores are unchanged by exercise training in patients with coronary disease or previous myocardial infarction (Foster 1986). It had been thought that exercise training would encourage the development of collateral vessels and thus improve myocardial perfusion. Verani compared et al (1981) exercise thallium scans before and after twelve weeks aerobic exercise training in 16 patients. There were no controls. Patients exercised to the same level before and after training. Pairs of scans were assessed blindly as to a change in perfusion, and then anatomical regions of individual scans were given a score of 0-4, in a semi-quantitative analysis. Three patients improved, three were worse, and ten unchanged.

Tubau and colleagues (1982) used circumferential profile analysis of thallium scans before and after a mean duration of training of 5.6 months in 17 patients. Five patients improved, one was worse, and 11 unchanged.

The PERFEXT study was a randomised controlled trial of 146 patients

(Froelicher 1987c). The exercise group undertook one year of aerobic training. Side by side analysis of paired thallium scans was used, with any changes scored on a 0-3 scale. There were no significant changes found. Regional scoring was done on a 0-10 scale. The exercise group showed a small improvement in perfusion but this was dependant on the presence of angina. Subgroup analysis of these thallium data was done, using circumferential profile analysis (Sebrechts et al 1986). Global indices were statistically different between the control and trained groups, but regional analysis failed to identify any one vascular territory as being the source of this improvement. The study did not really add to that reported by Froelicher.

The lack of effect could be related to low intensity and short duration of exercise training used in the studies, for there have been one or two training programmes resulting in improved myocardial perfusion.

Eighteen patients with angina and hyperlipidaemia were studied before and after one year of exercise training and low fat diet. There were 18 matched controls. Thallium scans were done after maximal exercise. The trained group achieved a higher exercise level than at baseline. Degrees of circumference of left ventricle with reversible ischaemia were measured from reconstructed cross-sectional images of stress and redistribution scans. Stress induced myocardial ischaemia in the trained group was reduced by 54%, even though they achieved a higher workload (Schuler et al 1988).

Sixteen patients with chronic stable angina showed a 34% reduction in number of degrees of ischaemia on circumferential profile analysis after one year of aerobic exercise training. (Todd et al 1991). There was no change in

17 control patients. View and segmental data showed that the improvement was mainly in left anterior descending artery territory. Thallium scans were again done at maximal exercise and the trained patients achieved a higher cardiac workload. This study was conducted in this department and has been referred to in other sections of this work.

The PERFEXT study included 53 patients with previous CAS, 28 in the exercise intervention group, and 25 controls (Froelicher et al 1985). The mean time from surgery was two years. The exercise group had more evidence of ischaemia than the control group at baseline: exercise-induced angina (32% vs 24%), ST depression (46% vs 32%), thallium ischaemia (44% vs 26%), left main coronary disease (25% vs 8%), thallium ischaemia score (3.7 vs 1.4 units). This would suggest that they had incomplete myocardial revascularisation. The results of thallium-201 scintigraphy before and after exercise training were the same as that reported for the whole PERFEXT group. There was a trend towards improved thallium scans in the exercised patients with angina. Interval change in immediate scores was -0.1 Atwood severity units in controls, -0.8 in exercisers, 0.4 in controls with angina, and -1.6 in exercisers with angina. Interval change in ischaemia scores in controls was 0, in exercisers -1.0, controls with angina -1.2, exercisers with angina -2.1.

Slow myocardial thallium washout rate has been found to increase the sensitivity of thallium stress tests (Maddahi et al 1981; Sklar et al 1982; Gerwitz et al 1983), identifying patients with left main stem and triple vessel disease (Maddahi et al 1986) and in correctly localising the diseased vascular territory (Abdulla et al 1985). Washout rates improve the diagnostic reliability

of thallium scans in the assessment of graft patency (Zimmerman et al 1988). Changes in washout would therefore reflect changes in myocardial ischaemia. The analysis of degrees of abnormality in washout profiles in this study did not yield any relevant findings in the group as a whole. In subgroup analysis of those with anterior MI, the aerobic group fared better after training than the power, and to a lesser extent, the control groups. This result should be interpreted cautiously. It is an indirect assessment of perfusion, not supported by changes in stress profiles. It is based on subgroup analysis involving nine patients. Highly statistically significant differences did occur in several areas and this consistency makes the finding worthy of mention. Thallium washout is affected by various factors including heart rate, activity prior to and timing of redistribution scan, blood glucose and myocardial uptake in relation to other organs (Abdulla et al 1985; Kaud et al 1986; Angello et al 1987).

There are several possible explanations for the lack of more convincing change in the thallium indices measured in the present study.

The most likely one is that there was little improvement to be made on myocardial perfusion in these patients. The vast majority of patients were free of angina during the study. The inclusion of patients with previous myocardial infarction in this study may have reduced the chances of demonstrating reversible perfusion defects, and any improvement or otherwise induced by exercise training. Alternatively, one could speculate that the training programmes were not rigorous enough or that any changes were too minor to be demonstrated by thallium scanning, and the analysis used.

Newer techniques such as quantitative single photon emission computed

thallium-201 tomography (SPECT) may have identified subtle changes in perfusion. It has been found to improve localisation of coronary stenoses, predict multivessel disease and determine perfusion defect size accurately (Maddahi et al 1989; Mahmarian et al 1990). Almost half the patients had normal anterior views at baseline, indicating that revascularisation had been adequate, and not likely to improve further. There have been suggestions that delays in scanning after exercise reduce the detection of transient defects (Rothendler et al 1985). The anterior view was taken first, and any changes might have been identified readily in that view. That was the only view with differences in stress scan abnormalities between the three groups.

SECTION XIII

TWENTY FOUR HOUR AMBULATORY HOLTER MONITORING.

Twenty four hour ambulatory Holter monitoring was used in the study to determine the effects of the training programmes on ventricular ectopic activity, minimum, mean and maximum heart rate and total ischaemic burden. Ventricular ectopic activity was measured in terms of the total number of ectopics per twenty four hours, and the maximum Lown grading in that period. Total ischaemic burden was assessed by maximum ST segment depression, heart rate at onset of maximum ST depression, duration of ST depression greater than 0.1 mV from baseline occurring 80 ms after the J point and episodes of such ST depression.

Each patient had Holter monitoring done at baseline and after six months. The Oxford Medilog 4000 (MARS) ambulatory electrocardiographic recorder was used. This is a frequency modulated recorder with a frequency response of 0.05 to 40 hertz and a signal to noise ratio of over 30 decibels. Each complex is processed in real time and stored on a cassette tape. By playing the cassette through the Oxford Medilog MARS replay system, the information can be retrieved. Recorder heads were cleaned before each use, new batteries were used for each recording and cassettes tapes were demagnetised before use, to help achieve high quality. To this end also, the patient's chest was shaved if necessary, and rubbed with an abrasive paste to remove the stratum corneum. Five electrodes were placed as follows:

1. manubriosternal angle 2. left anterior axillary line, just below the clavicle

3. the sixth rib in the left anterior axillary line 4. the right fourth costochondral joint 5. the sixth rib in the right anterior axillary line. Electrodes 1 and 3 record lead CM5, electrodes 2 and 4 record modified lead II, and electrode 5 is the ground electrode. An impedance meter was used to ensure that the resistance between electrodes was less than 5 kilo ohms. Artefact due to lead movement was reduced by creating stress loops in the leads before attaching them to the patient with surgical tape, and an elastic vest. The recorder was worn in a pouch on a waist belt. A 1 mV calibration signal was fed into the recorder and ECG signal recorded on a conventional ECG machine to ensure adequate quality before the actual recording was started.

Patients were asked to carry on with their normal activities as much as possible during ambulatory monitoring. Each had a diary card on which to record details of events, also marked by the event button. None had recordings done during periods of exercise training.

The cassette was analysed automatically by the Oxford Medilog MARS replay system. This produced trend graphs of heart rate, ST segment analysis (figure 10), ventricular ectopic activity, hourly summary of maximum and minimum heart rates, and arrhythmias. Samples of all types of complex and their relative frequency were also shown. (figure 11) Since the time of each significant event is shown, a manual check can be done to exclude artefacts from the analyses.

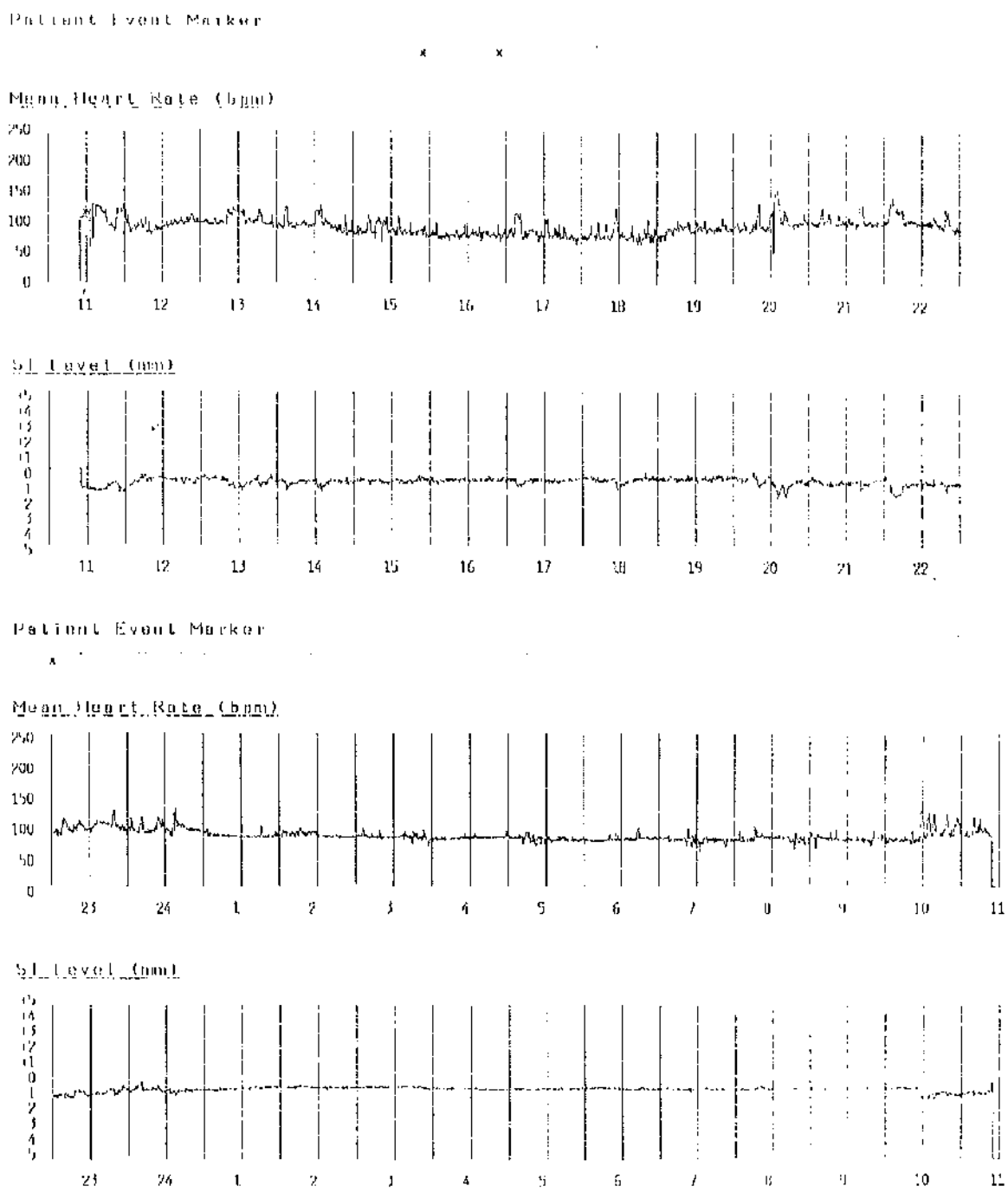


Figure 10: Holter monitoring mean heart rate and ST level.

Minimum Heart Rate 45 at 6:08:00
Maximum Heart Rate 166 at 14:57:07 ST level 2.52 mm

Maximum ST Level 0.12 mm at 5:16 Heart rate 82
Minimum ST Level 2.92 mm at 16:04 Heart rate 148

ARRHYTHMIA SUMMARY Note: ECG Signal Quality Check was Overridden

TIME	MAX RATES	MIN RATES	TOTAL BEATS	TOTAL VEs	PAUSE	VT	IDIOVENTR RHYTHM	COUPLET	BIGEMINY TRIGEMINY	SINGLE VEs	PSVT	SINGLE SVEs	PAROXYSMAL EPISODES
TOTALS	166	45	144361	105	0	0	0	0	1	101	0	99	2
start 15.00	146	71	6276	4	0	0	0	0	0	4	0	0	2
15.00 - 16.00	160	81	6945	9	0	0	0	0	0	9	0	2	0
16.00 - 17.00	166	128	8736	1	0	0	0	0	0	1	0	0	0
17.00 - 18.00	162	114	8908	0	0	0	0	0	0	0	0	0	0
18.00 - 19.00	166	131	8851	5	0	0	0	0	0	5	0	2	0
19.00 - 20.00	158	114	8442	4	0	0	0	0	0	4	0	0	0
20.00 - 21.00	148	84	7257	29	0	0	0	0	1	29	0	2	0
21.00 - 22.00	140	89	6949	21	0	0	0	0	0	21	0	2	0
22.00 - 23.00	152	92	6605	7	0	0	0	0	0	7	0	1	0
23.00 - 0.00	126	76	5611	2	0	0	0	0	0	2	0	1	0
0.00 - 1.00	120	67	5423	1	0	0	0	0	0	1	0	2	0
1.00 - 2.00	111	54	4746	5	0	0	0	0	0	5	0	2	0
2.00 - 3.00	93	62	4476	7	0	0	0	0	0	7	0	1	0
3.00 - 4.00	92	60	4121	5	0	0	0	0	0	5	0	2	0
4.00 - 5.00	88	55	4052	0	0	0	0	0	0	0	0	2	0
5.00 - 6.00	89	49	4091	0	0	0	0	0	0	0	0	4	0
6.00 - 7.00	87	53	3932	1	0	0	0	0	0	1	0	2	0
7.00 - 8.00	105	45	3940	0	0	0	0	0	0	0	0	5	0
8.00 - 9.00	90	45	3817	0	0	0	0	0	0	0	0	2	0
9.00 - 10.00	108	52	4906	1	0	0	0	0	0	1	0	1	0
10.00 - 11.00	181	51	5069	2	0	0	0	0	0	2	0	1	0
11.00 - end	161	59	7644	4	0	0	0	0	0	4	0	0	0
	155	102	8103	0	0	0	0	0	0	0	0	1	0
	142	70	5501	1	0	0	0	0	0	1	0	2	0

CLASSIFICATIONS (S for Supraventricular beats, V for VEs)

Max and Min Rate ..... Average Heart Rate over 4 beats.
SI heart rates ..... Average Heart Rate over the whole minute.
Pause ..... Asystole greater than 1.9 secs (2.4 secs after a VE), and at least 1.9 times greater than average R-R interval of 4 previous beats.
VT ..... 5 or more successive VEs during which 2 R-R intervals exceed 110 BPM.
Idioventricular Rhythm .. 5 or more successive VEs at a heart rate less than 110 BPM.
Couplet .... S V V S Bigeminy .... S V S V S V Trigeminy .... S S V S S V S S V.
Paroxysmal SV Tachycardia (PSVT)... A sudden increase in SV heart rate followed by abrupt cessation.
Artefact ..... Usually the number of beats not analysed.
SI levels ..... Referred to 1mV - 10mm.

Figure 11: Holter monitoring arrhythmia summary.

The Lown ventricular ectopic grading system is shown here.

Figure 12

LOWN VENTRICULAR ECTOPIC GRADING SYSTEM

Grade 0 - None

Grade 1A - Isolated, less than 30 per hour

Grade 1B - Isolated, more than 30/hr, less than 1/min

Grade 2 - Frequent, more than 30/hr

Grade 3 - Multiform

Grade 4A - Repetitive; couplets

Grade 4B - Repetitive; salvoes

Grade 5 - Early ectopics (R on T)

RESULTS

The results are on fifty four patients in whom baseline and six month Holter tapes were fully completed and could be analysed.

A. Heart rate responses

The results for minimum, maximum, and mean heart rate are shown in figures 13 to 19.

There was no consistent change in maximum heart rate over the training period.

The minimum heart rate in the exercise groups was significantly lower after training than in the control group at the following times of day:

time	ANOVA p value
0.00h	0.01
3.00h	0.03
4.00h	0.05
5.00h	0.03
10.00h	0.008
11.00h	0.02
12.00h	0.03
13.00h	0.04
16.00h	0.04
17.00h	0.02
19.00h	0.02
21.00h	0.04

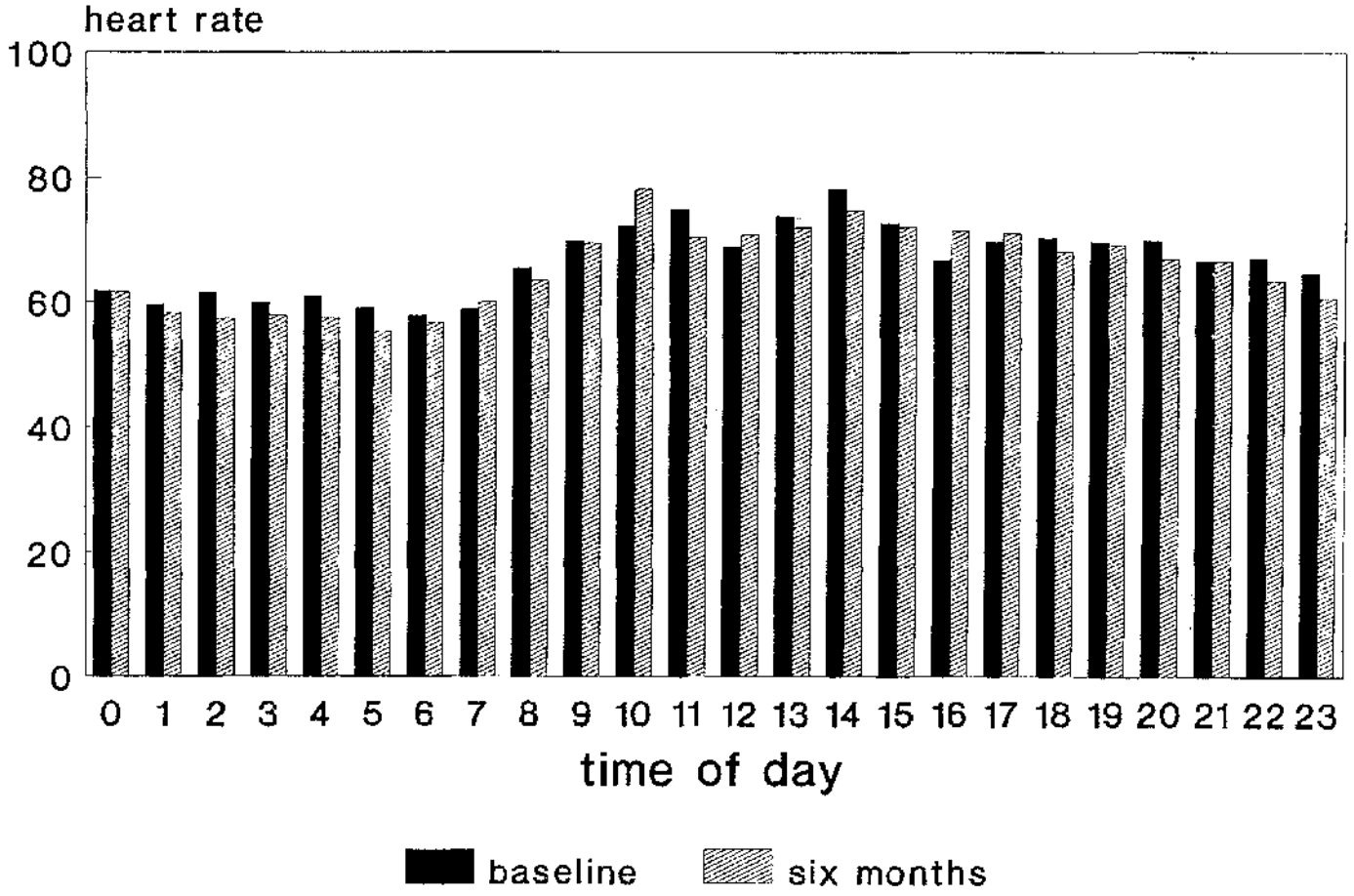


Figure 13: Minimum hourly heart rate: control

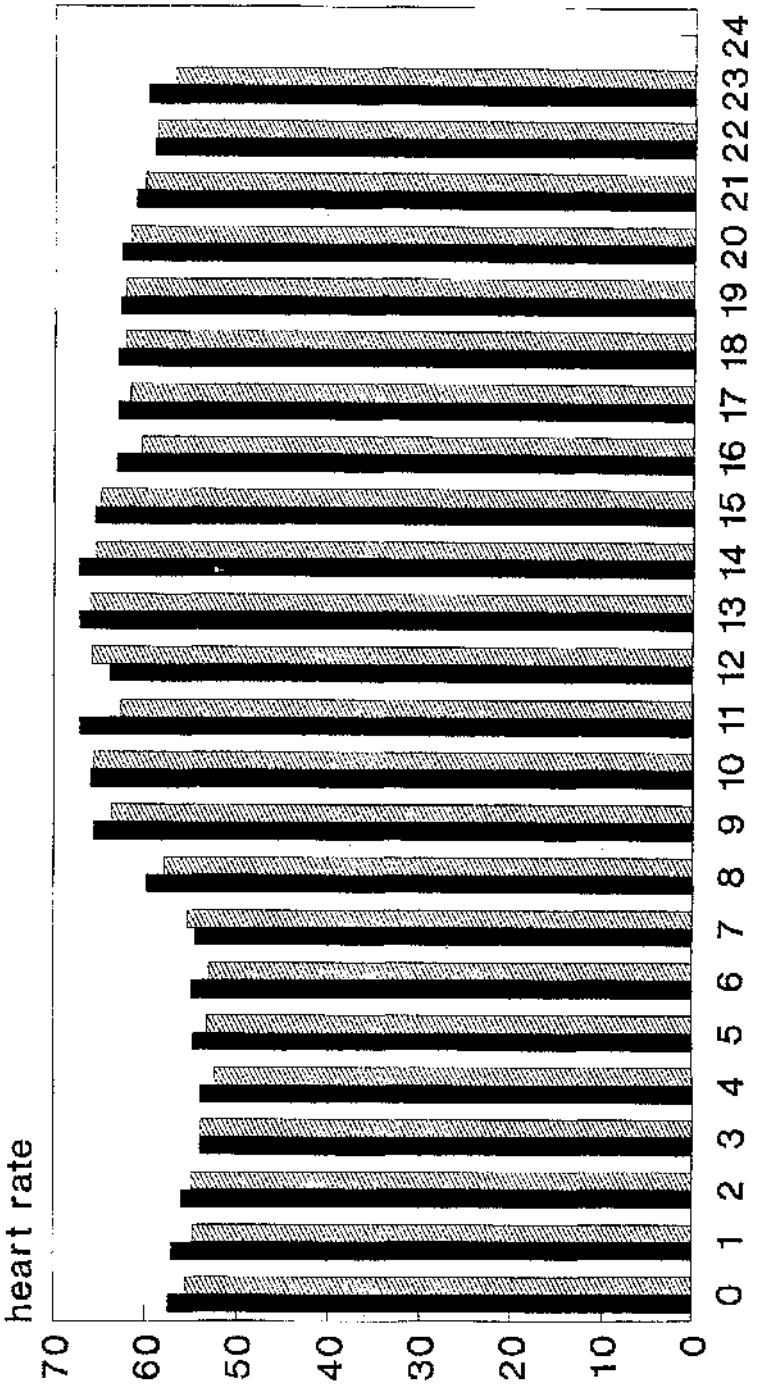


Figure 14: Minimum hourly heart rates: aerobic

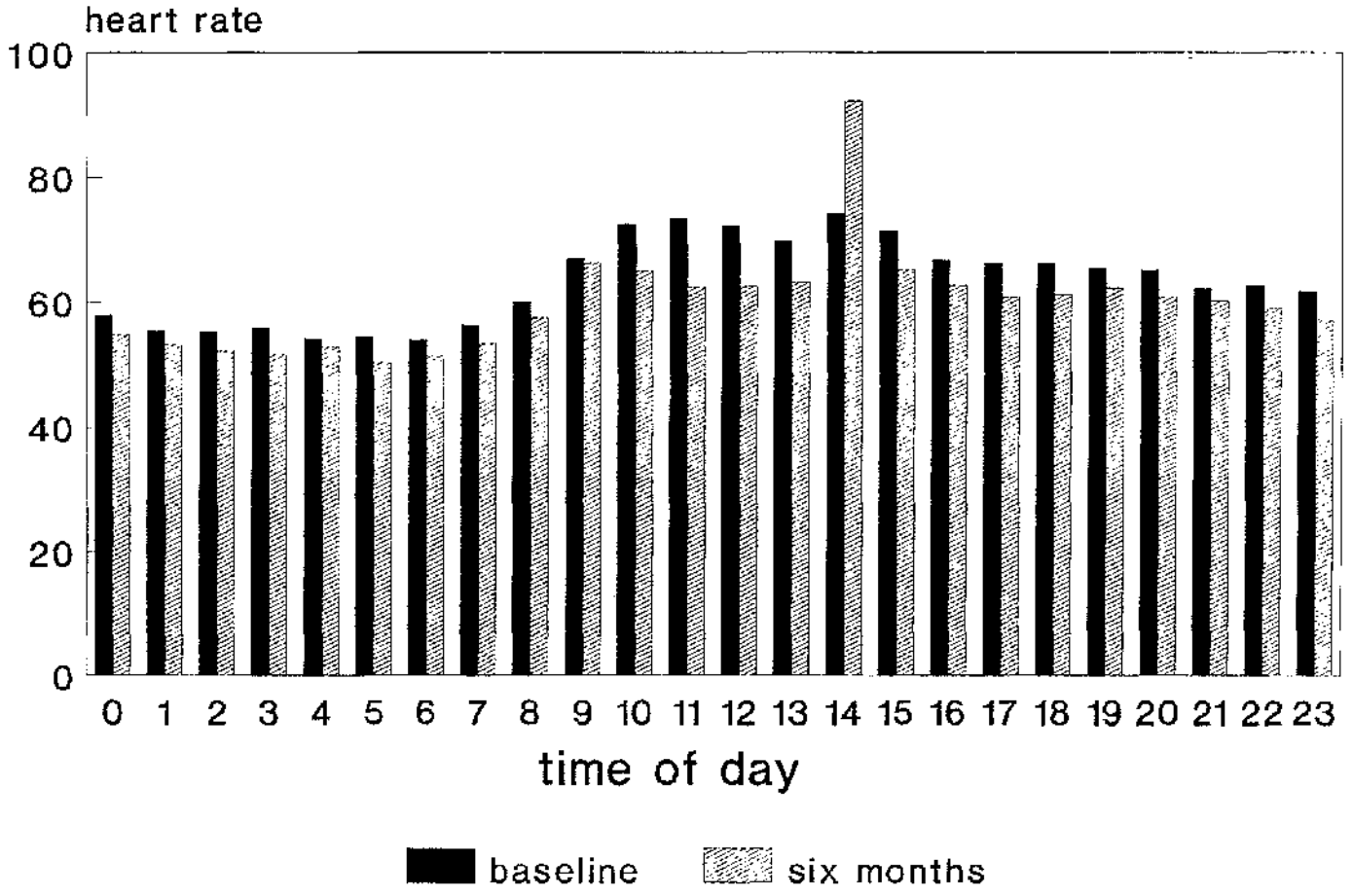


Figure 15: Minimum hourly heart rates: power

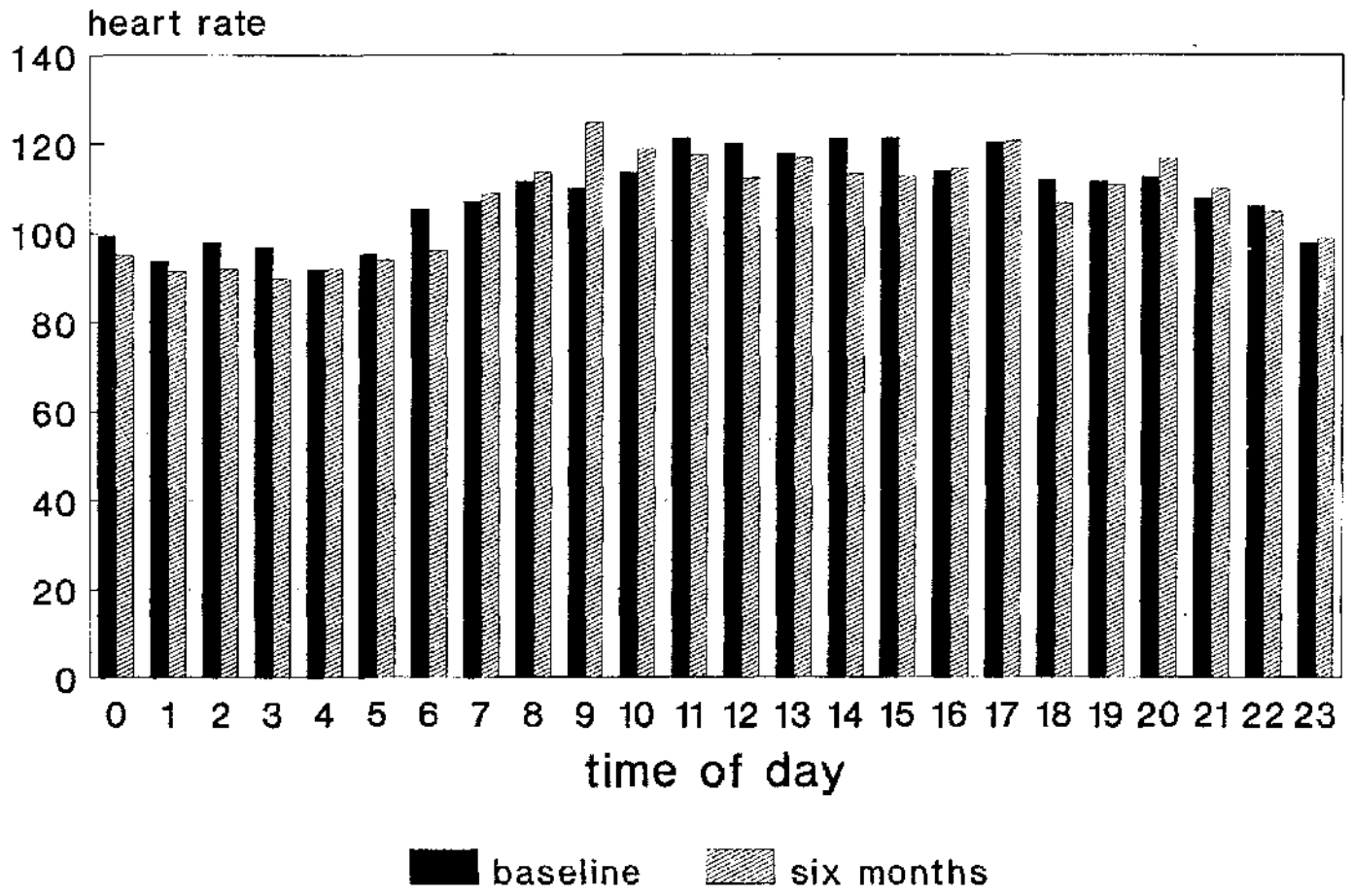


Figure 16: Maximum hourly heart rates: control

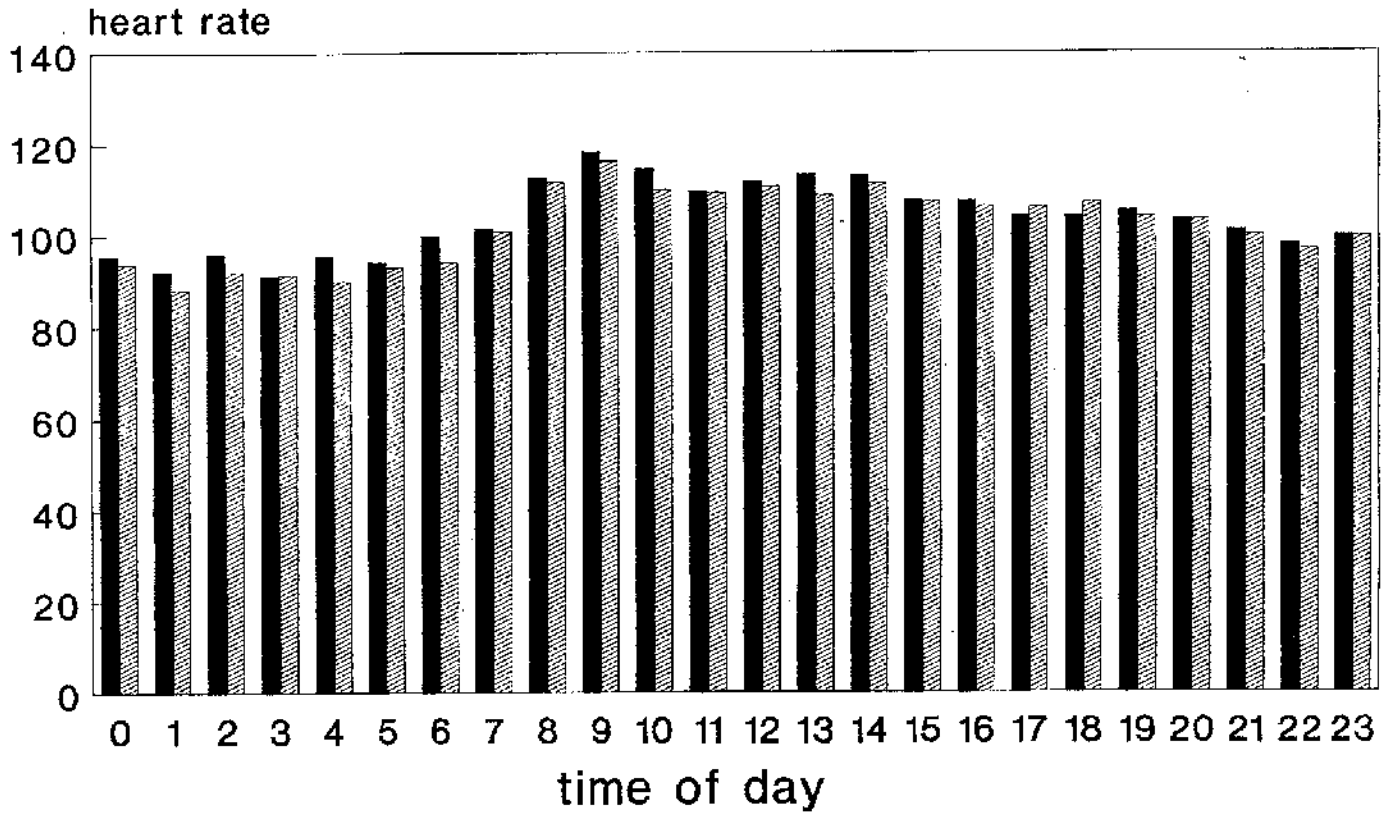


Figure 17: Maximum hourly heart rates: aerobic

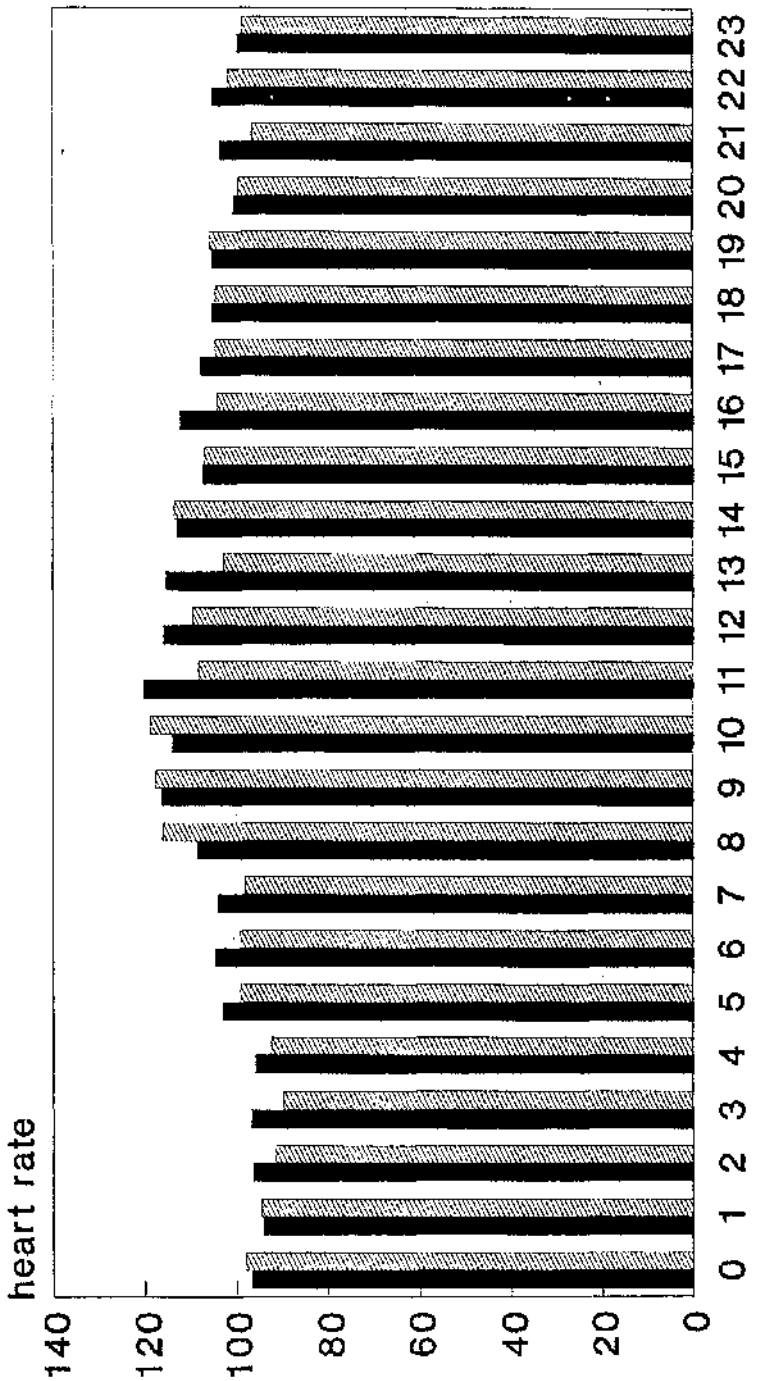


Figure 18: Maximum hourly heart rates: power

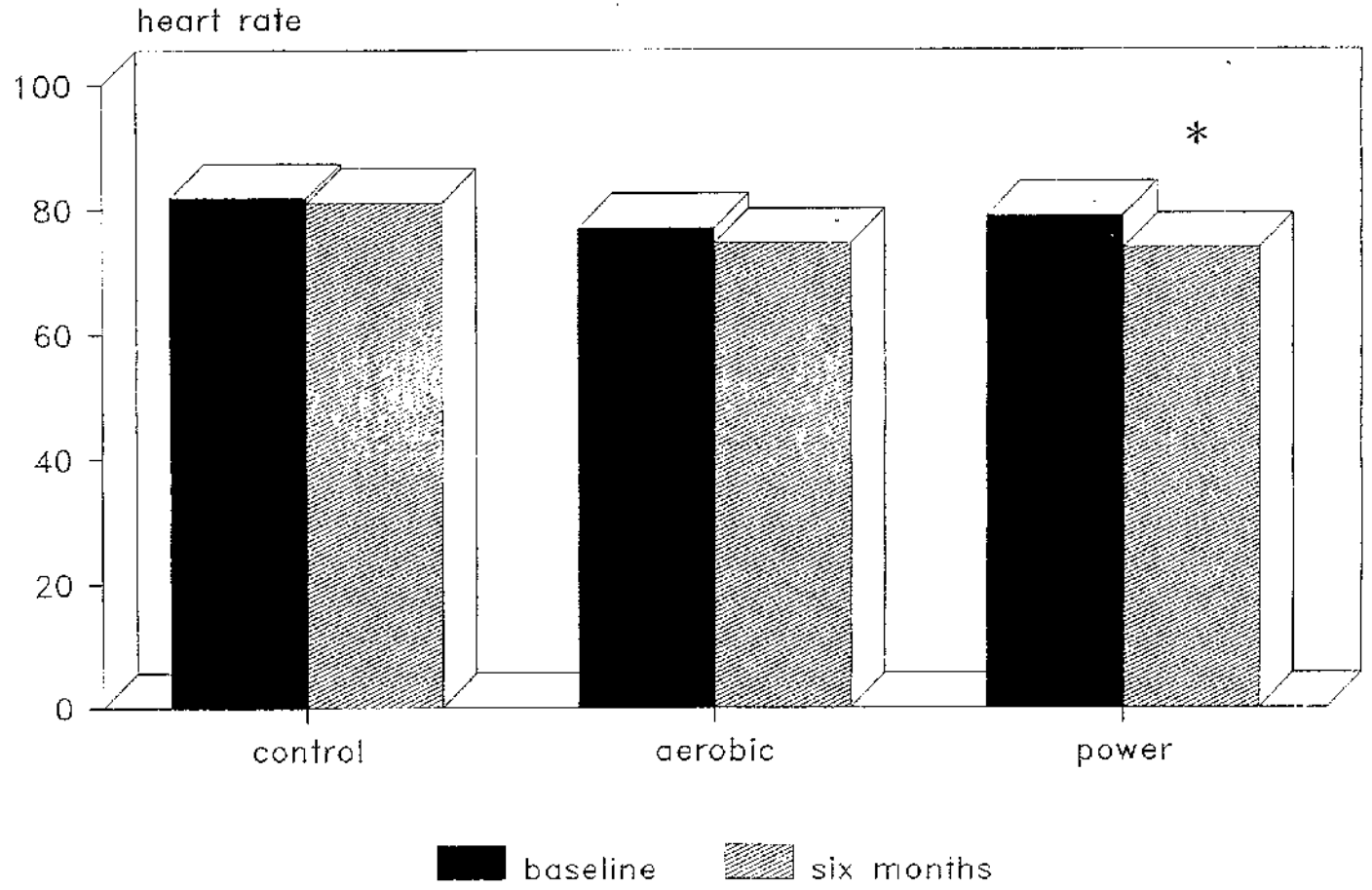


Figure 19: Mean heart rate: all groups

* p = 0.008

The mean heart rate was calculated as the total beats per 24 hours divided by 1440. There was a lower mean heart rate in the power group after training, falling from 78.8 (SEM 2.3) beats/min to 73.6 (SEM 1.5) beats/min ($p = 0.008$). This was significantly lower than the controls' 81.0 (SEM 2.2) beats/min ($p = 0.01$), but not significantly different from that in the aerobic group which was 74.5 (SEM 2.2) beats/min. The difference between the aerobic and control groups also reached statistical significance, $p = 0.05$.

Thus exercise training using both modalities conferred a tendency towards a lower minimum heart rate to the patients. This additional benefit operated particularly mid-morning, lunch-time, early evening, and nocturnally. At other times, there was a trend towards lower minimum heart rates, but it did not reach statistical significance.

B. Ventricular ectopic activity.

The total number of ventricular ectopics per day did not change within or between the groups. Table 64 shows the median number of ventricular ectopics per day in each group at baseline and at six months. The data were not normally distributed, and there was a wide range. Analysis of the number of ventricular ectopic beats per hour did not change the interpretation of the results.

Table 65 is maximum Lown grade at each assessment.

TABLE 64

Ventricular ectopic beats per day

median (range)

	BASELINE	SIX MONTHS
CONTROL	177 (0 - 878)	54 (0 - 4146)
AEROBIC	67 (1 - 2577)	43 (0 - 5471)
POWER	66 (0 - 33847)	65 (3 - 5097)

TABLE 65

Lown grade at each assessment (number of patients)

	CONTROL		AEROBIC		POWER	
LOWN	a	b	a	b	a	b
0	2	1	0	1	1	0
1a	8	9	13	11	7	9
1b	2	3	3	2	3	4
2	2	1	2	1	3	2
3	0	0	1	4	1	1
4a	0	0	2	2	3	2
4b	0	0	0	0	1	1
5	0	0	0	0	0	0

a - baseline b - six month assessment

The table is self-explanatory. The majority of patients had low grade ventricular ectopic activity, which was not altered by exercise training.

C. ST segment analysis.

The following parameters were measured and analysed :

minimum ST level (MINST mm)

heart rate at the onset of minimum ST level (HRST beats/min)

duration of ST depression greater than 1mm (DURST s)

number of episodes of significant ST depression (EPIST)

The results are shown in the tables 66 to 68.

In these tables, suffix '1' denotes baseline, '2' denotes six month assessment. The results are presented for each individual and then summarised for the group with mean, SEM and median values. There were no significant changes in these measurements in the three groups. In addition, there was no circadian pattern in these parameters.

Table 66

ST SEGMENT ANALYSIS - POWER GROUP

PAT	MINS T1	MINS T2	HRST 1	HRST 2	DURS T 1	DURS T 2	EPIST 1	EPIST 2
1	2.36	1.84	88	100	320	140	6	4
2	2.96	3.24	130	134	100	130	4	3
3	2.48	1.48	120	126	10	30	1	3
4	1.20	1.48	68	72	10	250	1	3
5	1.28	1.60	90	94	10	20	1	2
6	2.00	1.16	128	86	50	20	3	1
7	1.04	0.80	54	84	10	0	1	0
8	0	0	100	78	0	0	0	0
9	1.04	1.28	120	122	5	5	1	1
10	1.44	1.04	130	118	20	5	2	1
11	2.24	1.56	130	120	100	50	1	2
12	1.36	0.40	98	120	5	0	1	0
13	1.12	0.80	106	106	5	0	1	0
14	0	0	58	70	0	0	0	0
15	0.56	0.52	92	54	0	0	0	0
16	0.20	1.00	118	134	0	10	1	1
17	0.68	0.48	118	120	0	10	0	1
18	3.00	2.48	110	110	310	80	21	5
19	0.64	0.72	114	98	0	0	0	0
MN	1.27	1.38	107	107	59.6	73.9	2.5	2.1
SEM	0.27	0.23	6	7	23.9	33.7	0.67	0.59
MD	1.5	1.36	103	108	15.0	7.5	2.0	1.0

Table 67

ST SEGMENT ANALYSIS - AEROBIC GROUP

PAT	MINS T1	MINS T2	HRST 1	HRST 2	DURS T 1	DURS T 2	EPIST 1	EPIST2
20	0.88	1.08	104	82	0	10	0	1
21	1.48	0.32	96	142	35	0	3	0
23	2.84	2.40	126	124	160	340	4	7
24	0.40	0.92	70	120	0	0	0	0
25	0.88	0.88	132	102	0	0	0	0
26	0.88	1.28	88	86	0	5	0	1
27	0.60	1.04	128	140	0	5	0	1
28	0.92	1.04	56	58	0	5	0	1
29	3.68	1.00	142	84	70	10	3	1
30	0.56	0.24	108	60	0	0	0	0
31	1.04	0.88	64	96	10	0	1	0
32	0.40	0.40	72	56	0	0	0	0
33	1.04	0.68	120	112	10	0	1	0
34	1.32	1.44	62	58	10	10	1	1
35	0	0.40	92	70	0	0	0	0
36	2.88	3.92	68	66	960	900	6	7
37	0.96	1.32	144	150	0	15	0	1
38	1.52	0.88	134	74	10	0	2	0
39	0.12	0	52	60	0	0	0	0
40	1.52	1.36	124	82	30	5	3	1
41	1.84	2.92	154	148	45	375	5	6
MN	1.21	1.05	101	92	62.1	62.1	1.2	1.05
SEM	0.2	0.18	7	7	23.9	44.9	0.4	0.4
MD	0.96	0.92	104	84	15	0	0	0

Table 68

ST SEGMENT ANALYSIS - CONTROL GROUP

PAT	MINS T1	MINS T2	HRST 1	HRST 2	DURS T1	DURS T2	EPIST 1	EPIST2
42	1.68	1.72	134	114	25	35	3	3
43	2.40	1.88	104	108	290	50	6	4
44	3.20	2.52	86	108	215	240	7	6
45	0.36	0.32	70	78	0	0	0	0
46	0.20	1.04	118	132	0	5	0	1
47	1.92	1.24	96	100	85	5	5	1
48	1.84	1.40	128	122	80	20	4	1
49	0	1.76	106	148	0	10	0	1
50	0	0	102	70	0	0	0	0
51	1.16	1.32	102	96	5	5	1	1
52	1.84	1.88	90	64	85	285	3	5
53	0	0.04	82	68	0	0	0	0
54	1.32	1.28	124	136	5	5	1	1
MN	1.35	1.15	104	102	50.3	38.9	2.3	1.4
SEM	0.21	0.19	6	5	22.5	15.4	1.1	0.4
MD	1.20	1.04	110	106	10	5.0	1.0	1.0

DISCUSSION

ST SEGMENT CHANGES

There are many reports on ambulatory ECG and ST segment analysis in ischaemic heart disease in general, and on the importance of the total ischaemic burden (Chierchia et al 1983; Deanfield et al 1984; Gottlieb et al 1986; Deanfield 1987; Selwyn 1987; Nabel et al 1987; Pepine et al 1987; Epstein et al 1988; Stern et al 1988; Mulcahy et al 1989a; Mulcahy et al 1989b; Deedwania & Nelson 1990; Northcote & Higgins 1990). There is only one published report on Holter monitoring in the setting of exercise training in ischaemic heart disease. In a study of 40 patients with angina, already referred to in this work, Todd & Ballantyne (1992) found that ST segment depression was reduced in extent, frequency and duration in the exercise-trained group at the end of one year. There was also a reduction in the reporting of angina pectoris by the patients. The mean number of episodes of ST depression in the exercise group was 8.3 (SD 8.0) at baseline and 5.2 (SD 7.0) at one year, $p = 0.02$. In the control group it was 5.7 (SD 6.2) and 6.4 (SD 8.4) respectively.

The assessment of ST depression in these post-CAS patients was, like thallium scintigraphy, a means of measuring residual ischaemia. It is gratifying to find that at baseline there was minimal residual ischaemia in all the groups making it hard to show evidence of any change that may have been caused by exercise training. Indeed none was shown. It is generally thought that the higher the total ischaemic burden, the worse the prognosis. It would appear that these patients are fairly well protected in that regard.

Myocardial ischaemia after CAS may be due to different factors. These include early or late graft occlusion, low graft blood flow, anastomotic site stenosis or occlusion, distal stenosis in grafted vessels, progression in native CAD or pre-existing or acquired abnormalities of microcirculation affecting vasodilatory coronary flow reserve (Kennedy et al 1990).

Coronary artery surgery either abolishes ambulatory and exercise-induced ST depression, or converts it to a painless phenomenon. Transient ischaemic episodes, primarily symptomatic episodes, are reduced in 40 - 60% of patients by bypass operations. Total ischaemia duration is also reduced. In a study of 28 patients, Droste found that 17 had at least one episode of transient ST change pre-operatively, compared to 7 post-operatively (Droste & Roskamm 1992). Some workers have found that although the number of patients with ST changes falls post-operatively, the average number of episodes in those with continuing ST changes increases. For example, Crea et al (1987) found an increase from 7.1 to 9.7 episodes per patient. Egstrup (1988) found an increase from 1.8 to 3.25 episodes per patient.

Previous studies have shown that silent myocardial ischaemia on 24 - 48 hour ambulatory ECG monitoring occurs in 13 - 50% of patients from three weeks to one year after CAS. Of these, 80 - 99% of episodes of ST depression are silent (Droste & Roskamm 1992).

In this study, 57% of patients had at least one episode of ST depression. These were silent in all but four patients - one in the control group, two in aerobic group and one in the power group. Exercise training could be a method of reducing transient ischaemia, as assessed by ambulatory monitoring. This

did not occur in this study, and it may be that the patients did not attain the level of training required to show that effect. In most studies, on ambulatory ST segment changes, only episodes lasting at least twenty to thirty seconds are considered to be relevant. In the current study, episodes as short as five seconds were included in the analysis and may have caused an overestimation of such events, and perhaps the inclusion of what some may consider as artefact.

Kennedy et al (1990) reported on 94 patients between one and three months after CAS, and 184 patients a year after CAS. Silent myocardial ischaemia was detected in 20% of the early group and 27% of the late group. The mean frequency of episodes was 6 - 10 per 24 hours, and mean duration was 15 - 23 minutes. There was a circadian variation with peaks between 06.00h and 12.00h, and between 18.00h and 24.00h. Silent myocardial ischaemia was not associated with graft occlusion, low graft flow rates, distal residual stenoses, or ungrafted native vessels.

It has been suggested that ST segment shifts during exercise testing and ambulatory ECG recording may not have the same meaning early after myocardial revascularisation as they have before the intervention. (Ribeiro et al 1984; Quyyumi et al 1985; Kennedy et al 1990; Gohlke-Barwolf et al 1990; Patel et al 1993). There is poor correlation between ambulatory and exercise-induced ST segment changes and graft patency, yet rubidium tomographic perfusion studies suggest that they are still an expression of abnormal myocardial perfusion (Ribeiro et al 1984). In the above study by Kennedy and colleagues, silent myocardial ischaemia was not predictive of adverse clinical

events after follow up of 62 months. This is supported by Dubach and colleagues (1989). In contrast, Egstrup (1988) reported on 36 patients studied by 36 hour ambulatory monitoring before and three months after CAS. Twelve patients had silent ischaemia after CAS and more cardiac events (6 vs 2) than the 24 who had no ST segment changes. Perhaps in the later stages after CAS, signs of myocardial ischaemia will assume the prognostic significance that they hold before revascularisation, since graft attrition and progression of native CAD may then overwhelm the protective factors at play in the early stages.

CHANGES IN HEART RATE

The mean heart rate and hourly minimum heart rates were reduced by training, but it had no effect on hourly maximum heart rates. This is a reflection of the resting bradycardia which is commonly induced by exercise training. It suggests that the training programmes may have increased resting vagal tone but did not blunt the chronotropic response in these patients. In the aforementioned study by Todd & Ballantyne (1992) there were lower nocturnal heart rates and a tendency towards lower hourly minimum and maximum heart rates after training, an effect which was compared to beta blockade (Todd & Ballantyne 1990).

Ventricular and supraventricular ectopic activity were not allowed for in the hourly heart rate measurements. This ectopy would have affected maximum as well as minimum heart rates, so I do not think it altered the results.

VENTRICULAR ECTOPIC ACTIVITY

The wide variability in the ventricular ectopic activity in these patients is supported by previous studies on Holter monitoring for arrhythmias (Hinkle et al 1969; Morganroth et al 1978; Winkle 1980; Smith et al 1992). There was a low level of ventricular ectopy in the group, and perhaps a bigger population would be needed to show up any change induced by exercise training. Low grade ventricular arrhythmias are of uncertain prognostic significance.

It may be postulated that exercise training might alter the balance of sympathetic and parasympathetic tone in favour of diminished propensity to arrhythmogenesis. This was not found to be so in this study. Baseline was at least six weeks after CAS, by which time, any peri-operative influences would have ceased to apply.

It is known that perioperative ventricular arrhythmias are common and often silent. On days 0 to 7 after surgery, ventricular arrhythmias were found in 66% of 50 patients who had continuous two-lead ECG monitoring for ten perioperative days (Smith et al 1992).

As with other aspects of this study, there are no previous published reports on the effects of exercise training after CAS with which to make direct comparisons. There are several studies on the effects of CAS itself on resting and exercise induced arrhythmias. The results have been varied.

Coronary artery surgery may not decrease the frequency or severity of resting or exercise-induced arrhythmias. In a study of 68 patients, 37 of whom had CAS, there was an increase in ventricular arrhythmias after three weeks - mean ventricular ectopic beats, 133 (SD 35) before, 292 (SD 57) at three weeks

and a decrease after 18 months, 283 (SD 45), all not statistically significant. Twenty one patients had percutaneous transluminal coronary angioplasty, which had no influence on ventricular arrhythmias either. The early increase in ectopics could have been due to peri-operative factors such as increased sympathetic drive. The authors conclude that factors other than ischaemia are responsible for ventricular arrhythmias (Rotman et al 1990).

Exercise-induced ventricular arrhythmias were found to occur less often before, than three months after CAS in two hundred patients, 16.0% vs 24.5%, $p < 0.05$ (Yli-Mayry et al 1990). This finding was irrespective of graft patency or left ventricular function. There were ten cardiac deaths in the group after a mean follow-up period of 61 $\pm$ 19 months. None of these had exercise-induced ventricular arrhythmias, but had lower ejection fractions than the remainder.

In another study of 126 patients by the same authors, complex ventricular arrhythmias (> 30 ventricular ectopics/hr, multiform, and repetitive complexes) were found more often three months after (n = 49) than before (n = 30) CAS on 24-hour Holter monitoring. After mean follow-up of 50 months, there were four witnessed sudden cardiac deaths. The ejection fraction was a stronger predictor of sudden cardiac death than was the presence of complex ventricular arrhythmias on Holter monitoring. Patients with normal ventricular function are protected against sudden cardiac death even in the presence of complex arrhythmias after surgery (Huikuri et al 1990).

In an observational study of 400 patients undergoing coronary artery surgery, nine had severe ischaemia and exercise induced ventricular

arrhythmias preoperatively. None were observed during follow-up of one to four and a half years after CAS (Rasmussen et al 1987). The authors concluded that reduction of ischaemic exercise-induced arrhythmias may contribute to the reduction in mortality resulting from CAS, in larger patient series.

Thirty two patients had exercise ECG, 24 hour Holter monitoring and cardiac catheterisation before and again twelve months after CAS (Moller et al 1983). Exercise induced ventricular arrhythmias occurred in only three patients. The prevalence of ventricular arrhythmias during Holter monitoring was 56% and 66% pre- and post-operatively. Complex ventricular arrhythmias occurred in 18% pre- and 28% post-operatively. Graft patency was 77%, and left ventricular performance was not altered significantly by CAS. The conclusion was that the occurrence of ventricular arrhythmias is not affected to any great extent by coronary artery surgery.

SECTION XIV

ECHOCARDIOGRAPHY

Echocardiography was done using a Hewlett-Packard Sonos 1000 ultrasound scanner and 3.5MHz probe. Scans were done at baseline, after three and six months. M-mode and two-dimensional (2D) echocardiography were used to assess the effects of exercise training on cardiac dimensions. The scans were done with the patient in the left lateral position.

It was initially hoped that estimates of ejection fraction could be obtained reliably from the 2D scans to be compared with that obtained by radionuclide ventriculography. It soon became clear that this would not be so. It was difficult to obtain 2D scans that were technically adequate for this purpose in a number of patients. Taking this together with the known limitations of left ventricular ejection fraction derived from echocardiography, it was not pursued, and the 2D scans were not analysed further.

Paradoxical septal motion is common after cardiac surgery, though its mechanism is still debated. A note was made of the pattern of septal motion. Doppler, exercise and dobutamine echocardiography were not part of the study.

The M-mode scans were analysed. The following measurements were taken in the standard way: right ventricular internal dimension in diastole (RVIDD), aortic root (AO), left atrium (LA), left ventricular internal dimension in diastole and systole (LVIDD, LVIDS), interventricular septum (IVS), left ventricular posterior wall (LVPW), fractional shortening (FS). Interventricular septal motion (IVSM) was graded as normal, hypokinetic or paradoxical.

Left ventricular mass was derived from M-mode measurements using the formula:

$$lvm=(lvidd+ivs+lvpw)^3-(lvidd)^3\times 1.04g$$

RESULTS

The scans were stored on videotape for later analysis. This part of the study is perhaps more subject to observer bias than the others. In order to try to reduce this effect, the scans were analysed in random order at the end of the study, and the results tabulated only after all the scans had been reviewed.

Baseline and six month scans were compared in sixty four patients (table 69). In the remainder, technically adequate pairs of scans were not obtained.

There were no significant differences within or between the groups in the measured variables or in the interval changes. There was a trend towards thinner left ventricular posterior wall in the aerobic exercise group at six months compared with the other groups; control 0.08cm, aerobic -0.08cm, power -0.002cm, $p = 0.07$. These differences are highly unlikely to be of any clinical relevance.

Left ventricular mass (LVM) is shown in table 70. There was an increase in left ventricular mass in the control group and a decrease in the exercise trained groups. This is a most unexpected finding. Power exercise training usually causes left ventricular hypertrophy.

Paradoxical septal motion was seen in 25 patients (39.1%) at baseline,

hypokinetic motion in 33 (51.6%) and normal motion in six (9.4%) (tables 71 and 72). In three patients, paradoxical septal motion became hypokinetic after six months.

DISCUSSION

Exercise training has been shown to have variable effects on cardiac dimensions and contraction measured by M-mode and 2D echocardiography. In normal persons, prolonged and intensive endurance exercise causes a modest degree of right and left ventricular chamber enlargement (Gilbert et al 1977; Ehsani et al 1982; Colan et al 1985), increased left ventricular wall thickness, and left ventricular mass, but no change in ejection fraction (Tabakin et al 1965; Hanson et al 1968; Hartley et al 1969). In wrestlers and weight trainers, left ventricular wall thickness increases (Morganroth et al 1975; McKillop et al 1989). Other studies have failed to demonstrate any change in these variables with training (Froelicher 1987a).

In 10 patients with coronary artery disease, Ehsani et al (1981) found that a year's aerobic training resulted in an increase in left ventricular end diastolic dimension, posterior wall thickness, and mass. Conversely, Ditchey et al (1981) did not find any changes in a group of 14 patients. These studies are limited by the lack of control groups. In another study reported by Ehsani et al in 1982, there was an increase in left ventricular end-diastolic diameter from 47mm to 51mm after a year of aerobic training in 8 men. Left ventricular fractional shortening decreased progressively during graded isometric handgrip before training but not after it. In that study, there was a control group of 5

patients who did not show such changes. There have been no previous reports in patients who have been exercise-trained after coronary artery surgery.

This study concurs with the view that exercise training does not directly affect cardiac dimensions. Again, the arguments regarding intensity and duration of training could be invoked. Most exercise rehabilitation programmes in UK practice take place once or twice a week for six to eight weeks. It would be fair to assume that no effect on cardiac dimensions could result from those programmes.

Abnormalities of septal motion are recognised phenomena after cardiac surgery. The exact mechanism is debated. Loss of pericardial restraint by pericardiotomy may allow the heart to move anteriorly in systole. Perioperative ischaemia, pericardial effusions and clot in the right ventricle have also been suggested as possible causes. The incidence of abnormal septal motion is reported as 56-100% by cineangiography, radionuclide ventriculography or echocardiography (Rubenson et al 1982; Ribeiro et al 1985).

In the study by Ribeiro et al (1985) 45 patients were studied by cross-sectional echocardiography before and 8-10 days after bypass surgery. Fourteen developed new septal wall motion abnormalities. Of these, 11 developed hypokinesia (8 with normal CK-MB), 2 developed akinesia (due to infarction), and 1 dyskinesia in a previously akinetic region. They concluded that most new septal motion abnormalities were not caused by transient ischaemia, or perioperative infarction.

Lehmann et al (1990) studied 24 patients by continuous intraoperative

transoesophageal echocardiography during cardiac surgery. They found that mean left ventricular fractional shortening did not vary among regions in the initial stages of surgery, but changed dramatically after the discontinuation of cardiopulmonary bypass. There was an apparent medial hypokinesis and lateral hyperkinesis due to cardiac translation. Pericardiotomy did not affect septal motion. They concluded that new abnormalities in septal motion appear to be directly related to events occurring during cardiopulmonary bypass.

In the present study, 10 patients (7 aerobic, 2 power 1 control) had previous anterior myocardial infarctions, which could have caused septal hypokinesia. Right ventricular enlargement and overload may have contributed in causing paradoxical septal motion. Subgroup analysis failed to find any difference in right ventricular dimensions between those with and those without paradoxical septal motion. (table 73) None of the three in whom septal motion changed during the study had myocardial infarctions, or decreases in right ventricular dimensions. Paradoxical septal motion could concievably influence the left ventricular function and estimates of ejection fraction.

There are obvious limitations to the results on left ventricular mass. Three-dimensional information is derived from a two-dimensional image. There are inherent limitations due to the asymmetry of left ventricular geometry. Since the measurements are cubed, any errors are compounded. The results are contrary to what has been found previously. There is no explanation such as hypertension, for the increase in LV mass in the control group. One would have expected an increase rather than a significant decrease in LV mass in the power-trained group.

Changes in mean body weight in the three groups do not account for the differences in left ventricular mass. The body weight in the power group remained static, while that in the control and aerobic groups increased slightly. Changes in left ventricular mass index follow the same pattern as LVM.

There are limitations to their interpretation, but these results would again suggest that the exercise training programmes used in this study did not cause a direct central or myocardial effect. Its convincing benefits were probably of peripheral origin.

TABLE 69

M-MODE ECHOCARDIOGRAPHIC MEASUREMENTS cm mean(SEM)

	CONTROL	AEROBIC	POWER
RVIDD1	3.8 (0.1)	3.9 (0.1)	3.9 (0.1)
RVIDD2	3.9 (0.1)	3.8 (0.1)	4.0 (0.1)
AO1	3.8 (0.1)	3.7 (0.1)	4.8 (1.0)
AO2	3.9 (0.1)	3.7 (0.1)	3.7 (0.1)
LA1	3.1 (0.1)	3.4 (0.1)	3.3 (0.2)
LA2	3.3 (0.1)	3.3 (0.1)	3.2 (0.2)
LVIDD1	5.8 (0.2)	6.2 (0.2)	5.9 (0.3)
LVIDD2	6.1 (0.2)	6.1 (0.2)	5.9 (0.2)
LVIDS1	4.7 (0.2)	4.9 (0.2)	4.8 (0.2)
LVIDS2	4.6 (0.2)	4.7 (0.2)	4.5 (0.2)
IVS1	1.3 (0.05)	1.3 (0.04)	1.3 (0.07)
IVS2	1.4 (0.05)	1.3 (0.05)	1.2 (0.06)
LVPW1	1.2 (0.04)	1.2 (0.05)	1.1 (0.08)
LVPW2	1.3 (0.04)	1.2 (0.03)	1.1 (0.04)
FS1 %	0.19 (0.01)	0.22 (0.02)	0.52 (0.3)
FS2 %	0.25 (0.02)	0.22 (0.01)	0.24 (0.02)

TABLE 70

LEFT VENTRICULAR MASS, BASELINE, SIX MONTHS AND INTERVAL CHANGE (g) mean (SEM)

	CONTROL	AEROBIC	POWER	ANOVA
LVM1	374.2 (29.2)	437.5 (25.4)	408.2 (38.9)	0.3
LWM2	440.5 (32.0)	399.2 (25.2)	344.8 (20.4)	0.06
INTLVM	60.9 (25.6)	-35.6 (25.6)	-56.3 (39.4)	0.02

LVM1 baseline LVM; LVM2 six month LVM; INTLVM interval change

TABLE 71

SEPTAL MOTION AT BASELINE

	CONTROL	AEROBIC	POWER
NORMAL	1	3	2
HYPOKINETIC	11	13	9
PARADOXICAL	11	8	6

TABLE 72

SEPTAL MOTION AT SIX MONTHS

	CONTROL	AEROBIC	POWER
NORMAL	1	3	2
HYPOKINETIC	11	15	10
PARADOXICAL	11	6	5

TABLE 73

MEAN RIGHT VENTRICULAR END DIASTOLIC DIMENSION AT BASELINE cm

	CONTROL	AEROBIC	POWER
NORMAL	3.23	3.8	3.74
HYPOKINETIC	3.83	3.87	3.89
PARADOXICAL	3.73	3.89	3.86

SECTION XV

GENERAL DISCUSSION

The work of this thesis shows that power (strength) exercise training can be carried out safely in post-CAS patients with an improvement in exercise performance. It confirms that aerobic exercise training confers early benefit in exercise performance. A favourable haemostatic profile results from exercise training with a reduction in fibrinogen levels in the aerobic-trained group and a slight fall in factor VII levels in the power-trained group. In these patients, neither mode of exercise training caused clinically important changes in lipid levels, or myocardial function in terms of ischaemia, ventricular arrhythmias, perfusion, contraction or mass. The improvement in exercise performance would translate into a better ability to cope with daily physical activities. The reduction in fibrinogen levels would reduce subsequent cardiac events and improve the patients' prognosis. Power exercise training should be a useful addition to the traditional aerobic programmes used in cardiac rehabilitation. In post-sternotomy patients it may be wise to defer exercise training until wound healing is complete.

There is a small risk of cardiac events during physical activity (Winslow 1987; Thompson 1988). There were no deaths or cardiac arrests during the training sessions. No heart rate or other cardiovascular monitoring was done. The patients symptoms were used as a guide for their rate of training. A training effect was achieved with a lower minimum and mean heart rate with increased exercise ability after training. The routine performance of cardiovascular monitoring in exercise classes is doubtful.

The patients assigned to exercise training attended most of the sessions, though as in any study, compliance was not absolute (Radtke 1989). The use of specialised gymnasium equipment for power training would increase the financial cost of the programme should it be recommended for every cardiac rehabilitation centre. Conversely, no such cost would be incurred for the aerobic exercises which could be home-based. Similar benefit has been found in supervised and unsupervised exercise programmes (Stevens & Hanson 1984; Bethell & Mullee 1991), and in low and high intensity exercise (Goble et al 1991; Worcester et al 1993).

The inclusion of patients with history of previous MI made the study sample representative of post-CAS patients seen in clinical practice. Many candidates for CAS come from the post-MI population, and this is likely to increase in the era of thrombolysis. It may be suggested that these post-MI patients make the group less homogeneous in terms of viable cardiac muscle susceptible to influence by exercise training. It is known though that even infarcted myocardium has some residual viability (Liu et al 1985; Schelbert 1988). In that regard, the investigations to use in future studies may be more sophisticated tests of myocardial perfusion and function such as thallium re-injection studies (Dilsizian et al 1990; Rocco et al 1991; Dilsizian et al 1991), quantitative thallium single photon emission computed tomography (SPECT) (Strauss & Boucher 1986; Kiat et al 1988; Maddahi et al 1989; Mahmarian et al 1990), positron emission tomography (Bonow et al 1991), exercise and dobutamine echocardiography (Crouse et al 1992).

Improved myocardial perfusion is less likely to be observed after exercise training post-CAS than it is after MI (Foster 1986). Coronary angiography and graft studies would have provided the anatomical detail on coronary perfusion. It is pertinent to the question of graft occlusion and the effects that exercise training might have on its occurrence. Of particular relevance to this study is the possible effect on graft patency of the lowering of fibrinogen levels after aerobic exercise training. Future studies could be directed at that aspect. There was no clear effect on myocardial perfusion using thallium scanning, except in a small subgroup with previous anterior infarction. Anatomical information might have been of interest in this subgroup.

Cardiopulmonary exercise testing would have increased the objectivity of the treadmill exercise tests. It is useful to measure the anaerobic threshold directly (Coplan et al 1986; Ades & Grunvald 1990; Blumenthal et al 1991). However the inclusion of a control group does compensate to a large extent because it enables us to exclude habituation as a factor in the marked increase in treadmill time achieved by the trained groups. Motivation is a confounding factor which is difficult to control for and indeed to measure. It is however common to all studies which involve active cooperation from the subjects.

This study was about effects, not mechanisms. Future studies could try to discover the mechanisms underlying the effects of strength as well as aerobic exercise training. So far, such studies have been in aerobic exercise training. They have yielded varying results as to whether these effects are of peripheral origin, confined to changes in skeletal muscle and arteriovenous oxygen

difference, or of central origin with improvements in cardiac performance (Froelicher 1987a).

The widespread use of the internal mammary artery graft has added survival benefits for the post-CAS patient. To show an increase in this good prognosis due to exercise training would take very large numbers of patients and prolonged follow-up. A study of that nature is unlikely to be done. In post-MI patients the prognosis has improved steadily and especially with thrombolysis. Those who survive to undergo exercise rehabilitation are likely to do well. I believe that the question about the prognostic benefit of exercise rehabilitation is not likely to be taken any further. We are left with pooled results from various studies of post-MI exercise training from which to draw conclusions - in that situation, prognosis is improved with 20% reduction in all-cause mortality operating over three years and 25% reduction in reinfarction rate (O'Connor et al 1989).

It may have been useful to include psychosocial measurements in the assessment of these patients. Factors such as mental state, general well-being, quality of life, and work status were not included because I think that these factors are susceptible to influences such as socioeconomic climate, that can not be controlled.

From other observations that I made during the study, it was clear to me that exercise rehabilitation need not be universally applied. In simple terms, the majority enjoyed the workout, camaraderie and contact with staff, but two patients were vaguely uncomfortable with it and may not have derived as much general benefit from the programme as was possible.

Prediction of outcome in exercise rehabilitation is another vexed question (Myers & Froelicher 1990). Studies by van Dixhoorn et al (1989, 1990) suggest that psychosocial factors can influence the outcome of cardiac rehabilitation. The present study did not examine any such factors. It may be particularly interesting to assess psychological changes after CAS and the effects that exercise training could have on them.

Linear regression analysis showed a negative correlation between baseline exercise performance and interval change in treadmill time in the exercise trained groups (figures 20 to 22). For the aerobic group, $r = -0.42$, $p = 0.03$; for the power group, $r = -0.39$, $p = 0.05$; there was no correlation between the two variables in the control group. This suggests that those with low baseline exercise performance tend to derive more benefit from exercise training than those with high baseline exercise performance. There was a positive correlation between baseline treadmill time (MTT1) and six month treadmill time (MTT3) in all the groups (figures 23 to 25). This correlation was strongest in the control group in whom there was no correlation between baseline treadmill time and interval change in treadmill time ($r = 0.87$, $p < 0.00001$). In the aerobic group, $r = 0.65$, $p = 0.0003$; in the power group, $r = 0.77$, $p < 0.00001$. After exercise training, those with a low baseline exercise performance improved more than those with high baseline performance. In this group, the degree of benefit could be predicted from the intercept and slope of the appropriate graph. The results could perhaps be extrapolated to similar patients using the same training programmes.

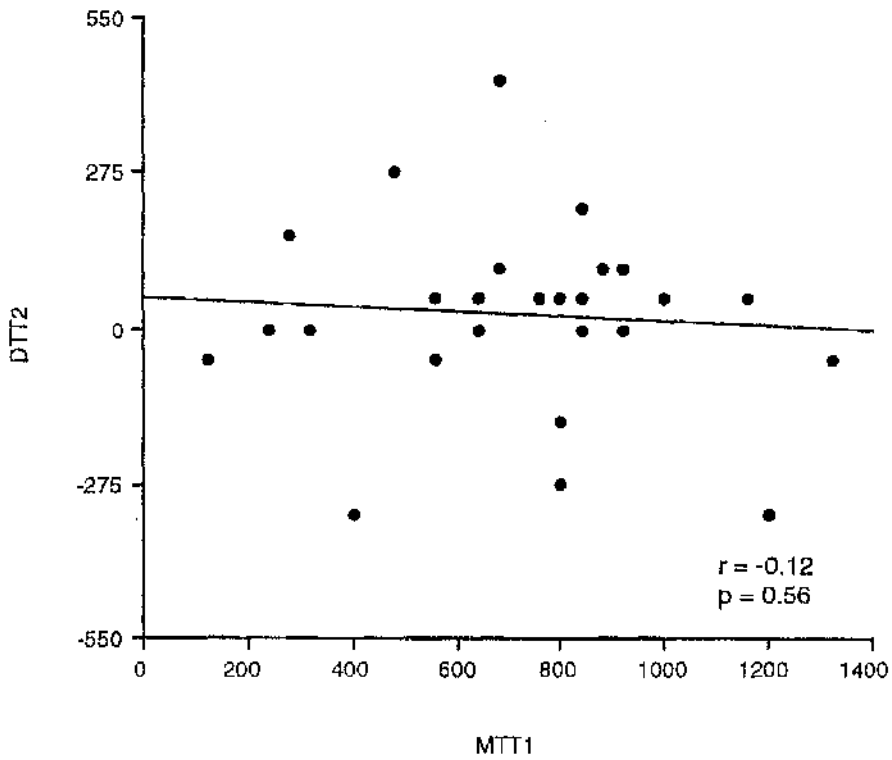


Figure 20

Correlation between baseline treadmill performance and interval change in treadmill performance in Control group

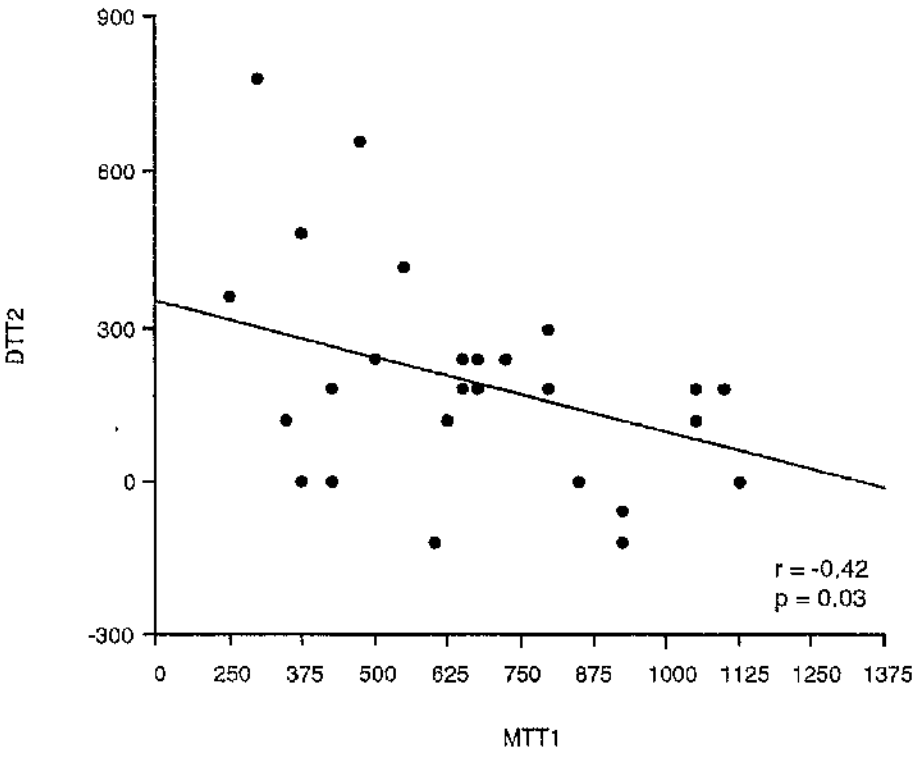


Figure 21

Correlation between baseline treadmill performance and interval change in treadmill performance in Aerobic group

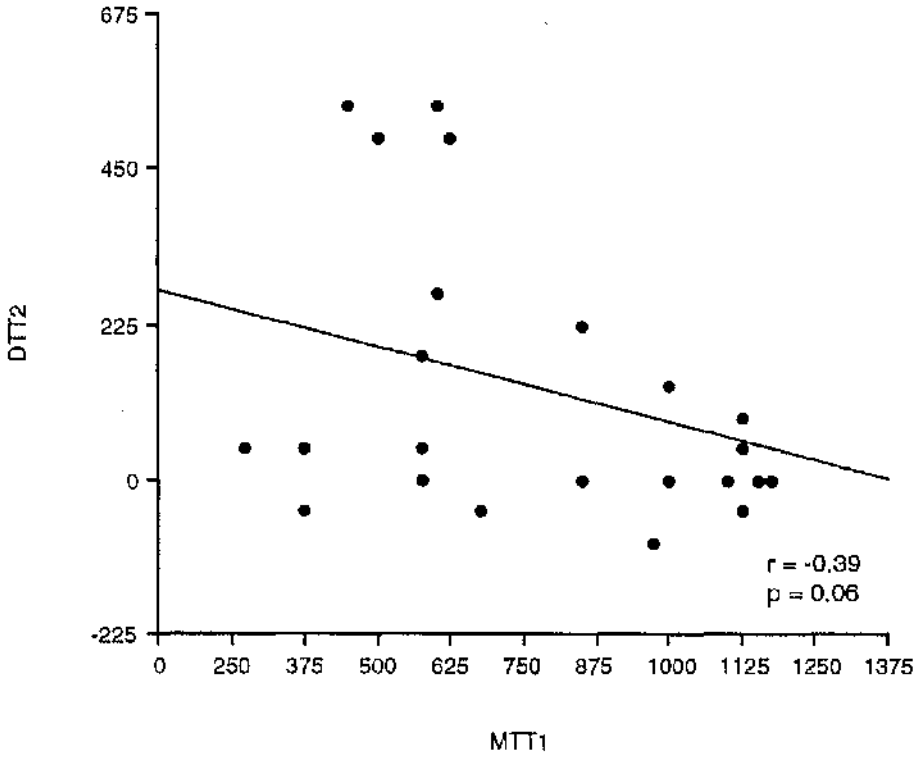


Figure 22

Correlation between baseline treadmill performance and interval change in treadmill performance in Power group

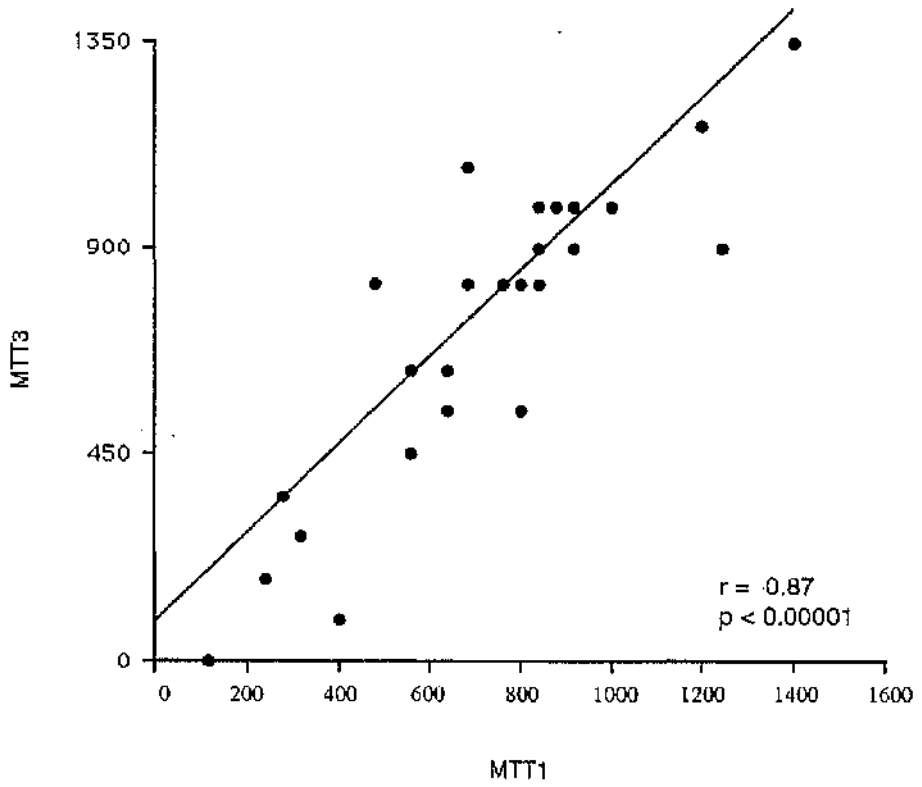


Figure 23

Correlation between baseline treadmill performance and six-month treadmill performance in Control group

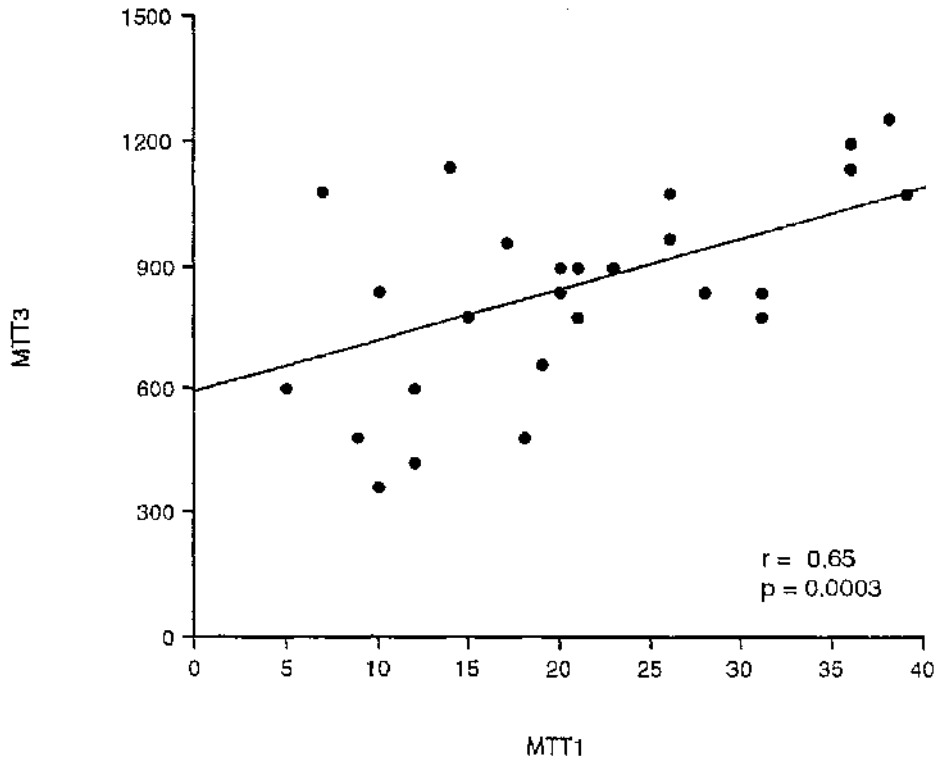


Figure 24

Correlation between baseline treadmill performance and six-month treadmill performance in Aerobic group

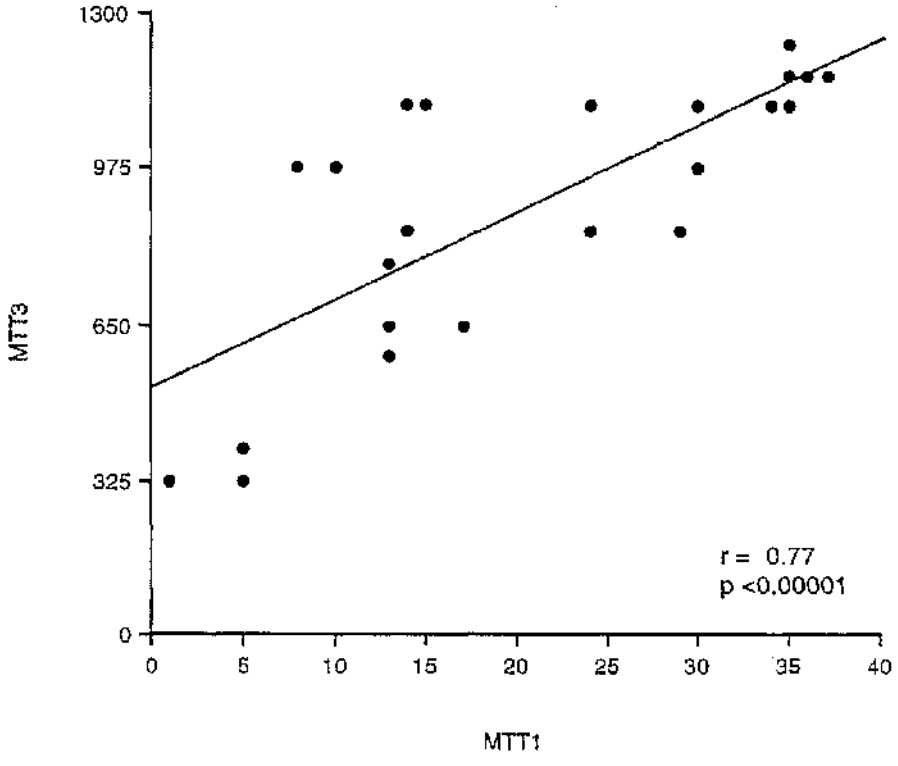


Figure 25

Correlation between baseline treadmill performance and six-month treadmill performance in Power group

Treadmill exercise may not be a fair means of testing the effects of power training. The delay in the appearance of significant improvement in treadmill time could be a reflection of this. Future studies could examine the patients by standardised power exercise tests such as the one repetition maximum test using arm and leg muscles. This would assess any changes in muscle strength and may be done in addition to the treadmill test to determine if there is any difference in the two methods of testing in assessing the effects of aerobic and power exercise training. A further refinement could be the determination of the effects of such training on peripheral muscle structure and function involving blood flow patterns, muscle metabolism and biopsy. To date such studies have been done in small groups of patients with heart failure and after aerobic training (Sullivan et al 1988).

So far, investigators have concentrated on the effects of different strategies on systolic dysfunction in CAD. There is increasing evidence for the importance of diastolic dysfunction in CAD. Diastolic function can be assessed noninvasively by Doppler echocardiography (Channer et al 1986). It would be interesting to assess whether exercise training affects diastolic function, by Doppler studies of mitral inflow. The ratio of peak early diastolic velocity (E) to peak late diastolic velocity (A) or E/A ratio provides information about left ventricular relaxation. This could readily be followed up in a controlled study on exercise rehabilitation. At the time of this study, the necessary tools for investigating diastolic function were not available to the author.

Cardiac rehabilitation is being expanded now to include patients with the whole spectrum of cardiac disease i.e. angina, post-MI, post-CAS and other cardiac surgery, post-PTCA and heart failure (Conn et al 1982; Coats et al 1990; P.RE.COR group 1991; Todd et al 1992; Pashkow 1993), and the elderly (Elkowitz & Elkowitz 1986; Ades & Grunvald 1990; Blumenthal et al 1991). There should be no doubt about its usefulness which has been questioned by some authors (Gleichmann 1987; Tunstall Pedoe 1990; Lipkin 1991; Chua & Lipkin 1993), and its role should be expanding.

Cardiac rehabilitation can be recommended strongly after coronary artery surgery. It would confer added clinical benefits, allow the patients to improve their functional capacity and favourably influence aspects of their cardiovascular risk factor profile.

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LIST OF ABBREVIATIONS

ACE:	angiotensin converting enzyme
ANOVA:	analysis of variance
CABG:	coronary artery bypass grafting
CAD:	coronary artery disease
CAS:	coronary artery surgery
CASS:	Coronary Artery Surgery Study
CV:	cardiovascular
ECG:	electrocardiograph
HDL:	high density lipoprotein
IMA:	internal mammary artery
LAD:	left anterior descending
LAO:	left anterior oblique
LDL:	low density lipoprotein
LV:	left ventricle
MI:	myocardial infarction
VLDL:	very low density lipoprotein

APPENDIX

CERTIFICATE

FOR THE

ADMINISTRATION OF RADIOACTIVE MEDICINAL PRODUCTS

Certificate Reference Number RPC 232- 2 (8)

The Health Ministers within the meaning of the Medicines Act 1968 hereby certify that for the purposes of section 60 of that Act and of regulation 2 of the Medicines (Administration of Radioactive Substances) Regulations 1978

Norman Mackay
Victoria Infirmary
Glasgow
G42 9TY

may administer for 2 years from the date of this certificate or for the duration of the project,whichever is the shorter, the radioactive medicinal products specified in the Schedule to this certificate for the purpose(s) there specified.

Signed by authority of the Health Ministers

.....

Date 20/01/89

Health Services Division
Department of Health

Dr N Mackay
Victoria Infirmary
Glasgow
G42 9TY

Date of Certificate 20/01/89

SCHEDULE TO CERTIFICATE NUMBER RPC 232- 2 (8) Sheet 1

* Serial	Nuc-lide	Chemical form	Treatment or Investigation	Purpose
43.a. 1.vi	99mTc	TcO4-	Objective as stated in application dated 14/11/88	Research
81.a. 1	201Tl	Tl+		Research

* as listed in Appendix I of the Notes for Guidance
Unlisted Serial numbers are included for ease of identification by the ARSAC Secretariat

Department of Health and Social Security
Alexander Fleming House Elephant and Castle London SE1 6BY

Telex 883669 Telephone 01-407 5522 ext 6443.

Dr N Mackay
Division of Medicine
The Victoria Infirmary
Glasgow
G42 9TY

Your reference

Our reference

Date
24 January 1989

Dear Dr Mackay

THE MEDICINES (ADMINISTRATION OF RADIOACTIVE SUBSTANCES) REGULATIONS 1978
CERTIFICATE TO ADMINISTER RADIOACTIVE MEDICINAL PRODUCTS

With reference to your application dated 14 November 1988 I am also writing on behalf of Health Ministers to enclose certificate number RPC
Which authorises you to administer the radioactive medicinal products listed in the Schedule to the certificate for the purposes there specified. The normal place(s) of administration of the radioactive medicinal products and the usual level of administered activity for the purpose of the certificate are understood to be those set out in your certificate application which forms the basis of this authorisation.

Authorisations for administration of diagnostic and therapeutic purposes are valid for 5 years. Those for research purposes are valid for 2 years or for the duration of the research project if this is less than 2 years.

Every clinical research investigation involving the use of radioactive medicinal products should be checked and approved by an ethical committee as recommended in the report issued by the Royal College of Physicians. In all instances, ultimate approval for the project as a whole will lie with the ethical committee which should ensure that the applicant holds the necessary authorisation and takes note of any comments made by the ARSAC.

If you wish to seek variation or renewal of your certificate you should do so by making application in good time to the above address.

Yours sincerely

R J MOORE

Enc

APPLICATION FOR CERTIFICATE TO ADMINISTER MEDICINAL PRODUCTS
(Made under "The Medicines (Administration of Radioactive Substances) Regulations 1978" (SI) 1978 No 1006

i. Before completing this form please read carefully the Notes for Guidance (reference number 1984) particularly Parts II and III

ii. Please complete in typescript or black ink and submit as soon as possible to the Department of Health and Social Security, Division HS1A, Room A419 Alexander Fleming House Elephant and Castle, London SE1 6BY

PART A APPLICANT (being the fully registered practitioner clinically responsible for administration of radioactive medicinal products)

1.1 Surname ...MacKay..... 1.2 Forenames ...Norman.....

1.3 Post Position ...Consultant Physician.....

1.4 Date of appointment ....April 1973.....

1.5 Specialty ..General medicine/Nuclear medicine.....

1.6 Address for correspondence

Division of Medicine,
The Victoria Infirmary,
Glasgow G42 9TY.

1.7 Name and address of employing authority/organisation

Greater Glasgow Health Board,
Bath Street,
GLASGOW G1.

1.8 Medical/Dental qualifications and dates

MB.ChB	1959
MRCP Glas	1962
MRCP Edin	1963
MD	1973
FRCP Glas	1974
FRCP Edin	1975

1.9 Other qualifications relevant to administration of radioactive substances, with dates.

1.10 Previous experience and training relevant to administration of radioactive medicinal products. (Please give details including dates, names of institutions and nature of work and products with which the applicant is familiar).

Stobhill General Hospital 1967 - 1972 - Ted cell and platelet kinetics using chromium. Platelet studies suing Selenomethionine.

The Victoria Infirmary 1979 -
Procedures covered in current certificate.

1.11 Certificates to administer radioactive medicinal products currently or previously held (if any)

Date	Certificate reference number
12.3.87	

I hereby apply for a certificate to administer the radioactive medicinal products listed in Part B of this form for the purposes there specified. I have available to me for such administration the supporting services indicated in Part C of the form.

Signature ..... Date 14.11.88

PART B continued

3. RESEARCH (see paras 26 and 27 of Notes for Guidance)

3.1 In respect of each proposed study please specify:-

3.1.1 The name and address of the premises where the study is to be undertaken

The Victoria Infirmary

Langside,

Glasgow G42 9TY.

3.1.2 The names and qualifications of other participating practitioners (if any)

Dr. N. MacKay MD FRCP
Dr. D. Ballantyne MD FRCP
Dr. D. Wosornu MB MRCP

3.1.3 The objects of the study (as in the submission to the Ethical Committee). A copy of this submission may be attached.

See attached sheet
Ethical Committee approval granted 9.11.88

3.1.4 Details of radionuclide(s) to be administered*

Radio-nuclide	Chemical form	Route of administration	Proposed activity	Number and frequency of administrations	Brief details of other nuclides to be administered simultaneously or sequentially
Tl201	Thallous Chloride	IV	80 MBq	2 separated by 6 months	None
Tc99m	Pertechnetate (pre injection of Amerscan)	IV	800 MBq	2 separated by 6 months	
				None - On each occasion administration of 99mTc will be at least 2 weeks after administration of 201 Tl	

*In the case of research involving neutron activation analysis appropriate details should be entered under Section 1.4 of Part B and a reference made under 3.1.4

PART B continued

3.1.5 Details of patients to be studied

Number	Age range	Sex	Clinical Condition	Estimate of effective dose equivalent per administration*
Sixty	35-70 years	male	After coronary artery bypass grafting	7mSv per administration for 99m-Tc labelled red cells 25mSv per administration for 201-Tc

*in mSv.calculated as in paragraph 48 of the Notes for Guidance

3.1.6 Details of any normal control subjects to be studied none

Number	Age range	Sex	Any other relevant information	Estimate of effective dose equivalent per administration*

*in mSv.calculated as in paragraph 48 of the Notes for Guidance

3.1.7 If pregnant women or nursing mothers are to be studied give reasons and details of special radiation protection measures to be taken.

Not applicable

PART B continued

3.1.8 If it is proposed to administer rare or unusual substances the following information is requested.

a. The formula of the radiopharmaceutical and the site of its label.

b. A summary of the animal experiments.

c. A description of the method used to estimate the human radiation absorbed dose from the animal data.

d. A table showing the animal data for each organ.

Not applicable

3.1.9 If it is proposed to expose patients or normal subjects to any machine-produced radiation, the following information is requested:

a. The nature of the machine-produced ionising radiation;

b. The purpose of the exposure;

c. The number of exposures, or the length of exposure, as relevant;

d. An estimation of the total effective dose equivalent.

Not applicable

PART C. EQUIPMENT, STAFF AND FACILITIES AVAILABLE TO THE APPLICANT

1. In respect of the premises* specified in Part B of this form as the place where tests, therapy or research are normally to be carried out please give:-

1.1 The name of the premises

The Victoria Infirmary,
Glasgow G42 9TY

1.2 Details of available scientific support services including as appropriate:-

The name, post and qualifications of the senior scientist responsible for scientific services

Mr. M. B. D. Cooke BA, CPhys, M Inst P.
Principal Physicist

The post and qualifications of other scientific staff Physics

The Victoria Infirmary - Principal physicist, two medical technicians, MPT2 and MPT3.

Regional Radionuclide Dispensary, Western Infirmary, Glasgow - Top grade physicist and other physicists, principal pharmacist, five medical physics and pharmacy technicians.

The facilities available for dosimetry, storage and stock control, dispensing, patient monitoring and equipment calibration.

Victoria - Radiopharmaceuticals are received daily in single dose vials from the regional radionuclide dispensary (see below), therapeutic doses are not stored on the premises overnight. Radioisotope laboratory with clean bench area reserved for preparation of injections and blood labelling, shielded fume cupboard, lockable refrigeration. Contamination monitor, dose calibrator.
Western - Clean laboratory with two contained work stations. Radioisotope laboratory with approved store. Radioisotope calibrators (4) and calibration sources, contamination monitors (4). Well counter and radiochromatogram scanner. Packaging equipment. Remote store for radiocative waste. Procedures and record keeping approved by Radiological Protection Adviser and Medicines Inspector.

*Where more than one premises is involved please give the information in respect of each, using additional sheets as necessary.

PART C continued

1.3 The major items of equipment available (and their dates of manufacture) for carrying out the procedures listed in the application

One Technicare Sigma 410 Gamma Camera, April 1978
ADAC/CGR 7310 Computer March 1981
One LKB 1280 "Ultragamma" automatic counter with printer, October 1976

1.4 The name and official address of the Radiation Protection Adviser

Mr. J. Kennedy
West of Scotland Health Boards
Department of Clinical Physics and BioEngineering
11 West Graham Street,
Glasgow G4 9LF

1.5 The Radiation Protection Adviser should sign below to indicate that he is satisfied with your arrangements for dealing with contamination accidents.

Signature ..... Date 17 Nov 88

1.6 The name, position and official address of the person completing Part C (This should be the person with overall responsibility for the scientific aspects of the work (which may or may not be the applicant)).

Mr. M. B. D. Cooke
Principal Physicist
Department of Clinical Physics and Bio-Engineering
Victoria Infirmary
Glasgow G42 9TY

Signature ..... Date 17 Nov 88