A STUDY OF THE MECHANISMS UNDERLYING THE CARDIAC EFFECTS OF EXERCISE TRAINING IN ANGINA PECTORIS

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It has taken five years to complete this thesis since the development of the original idea. Progress has been delayed by recruitment difficulties, problems with study techniques and the need to modify methods of analysis. With each successive hurdle have come doubts about whether the study would ever reach fruition. That it has done so is to me a source both of great relief and some pride. It is clear to me however that it would not have been possible without the help of a great many people and I acknowledge my debt of gratitude to them. I would in particular like to extend my thanks to Miss Margaret Smith, Senior PMT, who has selflessly given both of her time and expertise over the years. She has personally carried out all exercise tests and 24 hour ambulatory ECG's and the high technical quality of her work has contributed greatly to the success of this study. She has in addition made as great a contribution in other ways by her regular attendance at the exercise classes and by her words of encouragement to the patients and, on more than one occasion, to the author.

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I hereby declare that this thesis was composed by me and that, save for the contributions acknowledged above, the work described herein was carried out entirely by the author.

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CONTENTS

ABSTRACT OF THESIS

This thesis investigates the use of exercise training as a therapy in the management of angina pectoris. The hypothesis underlying this work is that in the presence of ischaemia the myocardium will, if possible, respond in such a way as to minimise the effects of ischaemia. Improved collateral function was felt to be the most likely mechanism.

A series of non-invasive investigations was developed in such a way as to make them useful for the detection of any possible improvement in myocardial ischaemia. These investigations included treadmill exercise tolerance testing, Thallium scintigraphy, Technetium ventriculography, exercise echocardiography and 24 hour ambulatory ECG monitoring. These techniques were refined for use in this study by the development of computerised analysis where appropriate.

Forty male patients under 60 years of age with angina pectoris and no prior myocardial damage were recruited and randomised into exercise and control groups. Both groups were followed up over a one year period, the exercise group carrying out a brief daily home-based exercise programme, using the Canadian Airforce PBX Program for Physical Fitness.

The techniques developed proved to be effective follow up tools in this group. Using them significant improvements in treadmill performance were demonstrated in the exercise group. These improvements were found to be partly due to changes in the peripheral control of exercise induced heart rate increases but

also due to myocardial improvements. The peripheral effects were compared to and contrasted with betablockade. Within the myocardium significant reductions in ischaemic area were demonstrated, particularly in the territory of the left anterior descending coronary artery. These improvements in perfusion were accompanied by improvements in left ventricular function and regional wall motion. The improvements demonstrated in the laboratory were also evident during ambulatory ECG monitoring.

The results demonstrated support the hypothesis outlined that controlled myocardial ischaemia can induce improvements in myocardial perfusion, perhaps due to collateral enhancement, and furthermore support the use of these techniques in such follow up studies.Further studies would be justified and indeed necessary to convincingly prove the hypothesis. Such studies may need to be multicentre in order to recruit sufficient numbers and ideally should involve coronary angiography and coronary perfusion assessment.

SECTION I

INTRODUCTION

I.1

PLAN OF THESIS

This thesis contains five sections, each of which is further sub-divided into appropriate subsections. The first section is the introduction to the thesis, sections II and III contain the authors original studies, section IV comprises a general discussion and section V contains the appendices.

The introduction describes the rationale for undertaking these studies. It is brief and referenced only where necessary since most of the areas are covered in greater depth elsewhere.

Section II deals with the selection of appropriate patients, exercise programme and investigations. The design of the study is explained and the basic methods described. Some of these techniques required to be adapted specifically for this study and where this was necessary a description of the adaptations is included. Further modification of some techniques was necessary during data analysis and this is detailed in the appropriate sub sections of section III along with any necessary assessment of techniques.

Section III deals with the results of the study and is sub-divided such that each important aspect of the study is covered in detail in its own sub-section, e.g. the section on myocardial perfusion deals with the results of thallium studies, the modifications required during analysis of these studies and a

discussion of the results.

Section IV considers the study as a whole. It considers how the techniques agree or differ in their results and explains the author's conclusions with regard to the value of the techniques and of the training programme. Specific examples are used in this section to illustrate the points made. The section ends with the author's recommendations regarding exercise training in the light of these studies and highlights the further questions raised by these studies.

Following Section IV is a reference list, list of tables and figures and a list of commonly used abbreviations in the thesis.

I.2

AIMS OF THE STUDY

Ischaemic heart disease is one of the major epidemics of the 20th Century. Its two main manifestations of angina pectoris and myocardial infarction however remain poorly understood. Coronary atheroma is the pathological manifestation of the disease and acute occlusion causes myocardial infarction while progressive narrowing ultimately leads to exercise induced ischaemia and angina pectoris. It is probable that changes within atheromatous plaques and alterations in coronary artery tone may precipitate infarction or ischaemia. Consideration of these patho-physiological mechanisms has led to the development of drug treatment which is essentially palliative, particularly with respect to the management of angina pectoris. The use of beta-blockers, calcium antagonists and nitrates are all based on the concept of increasing myocardial oxygen supply or reducing myocardial oxygen demand with the emphasis on the latter. While this undoubtedly alleviates symptoms in the short term, the effect on the natural history of the disease of such an approach is unknown.

While treating symptoms of coronary heart disease we attempt to alter the natural history by identifying the aetiological agents and, where possible, removing these. Attention is paid therefore to dietary fats, cigarette smoking and hypertension.

Together with a family history of ischaemic heart disease these factors have been identified as associated with an increased risk of coronary atherosclerosis (1-3) and it seems reasonable to assume that control of these will at least slow down disease progression. To date, however, studies based on this approach have produced inconclusive results.(4,5) The likely explanation is that in most cases the disease presents at an advanced stage. By the time infarction or angina occurs there is either coronary artery occlusion or severe stenosis. In the majority of symptomatic cases there is more than single vessel disease. To reverse such disease simply by manipulating the factors mentioned is improbable and to date no drug has been identified which will reverse such advanced atheroma.

Can we remove the precipitants of myocardial infarction or sudden death? There is little to suggest that drugs for symptomatic relief afford protection against such events. Much has been made of the use of betablockers and secondary prevention but even recent "successful" studies (6,7) show limited value only. The smoking of cigarettes produces changes in vascular tone, blood coagulability and adrenergic hormone levels which might be expected to be associated with cardiac events and indeed there is evidence that this is so.(2) Cessation of smoking therefore may remove one important trigger. However most cardiac events appear random and are not clearly associated with a triggering event. In individuals with ischaemic heart disease they will occur despite the best efforts of patient and physician.

If we accept the above then an important question to be

addressed is "Can we modify the response of the heart to the disease in such a way as to lessen the effect of these major events?" There is one aspect of advanced coronary atheroma which opens up perhaps the most potentially useful area for disease modification in this respect. The coronary tree has the ability to produce collateral vessels to supply an ischaemic area by an alternative route. The effect of a proximal lesion may vary therefore according to the supply of collaterals to the area distal to the stenosis or occlusion. We know there is a relationship between the extent of disease and prognosis.(8) Although unproven it seems reasonable that the real link is in terms of area at risk. Reduction of that area, either naturally by collateralisation or artificially by coronary artery bypass grafting, would seem a logical step to improve prognosis. Studies have demonstrated that in certain groups of patients coronary grafting can be recommended on prognostic grounds.(8,9) Is there any evidence to suggest that collateralisation can afford similar protection?

There has over the years been continuing debate about the effectiveness of collateral circulation. Investigators agree that collaterals are larger in patients with coronary disease and particularly in those with severe stenosis or occlusions.(10-13) Arguments continue over whether these collaterals are functionally useful or simply disease markers. Some authors suggest that they develop in response to ischaemia and cannot therefore anticipate it and hence will never be effective.(14-16) There are however studies which have shown that infarct size is reduced in the

presence of collaterals,(17) that left ventricular function after infarction is better in those individuals with effective collaterals, (18,19) and that there is a reduced incidence of major complications of infarction such as cardiac rupture (20) or cardiogenic shock (21) in the presence of collaterals. There are many reports of complete coronary occlusions without infarction in collateralised individuals.(12,13,17) They do seem therefore to be prognostically important and have major impact on the natural history of the disease. In this respect they mirror the effect of coronary artery surgery. To accept this view does not necessarily disagree with those who state that collaterals cannot logically remove ischaemia altogether. They may reduce the area at risk or indeed the size of ischaemic area in angina pectoris without abolishing that area. The argument between the protagonists and the antagonists in this debate may simply be one of degree.

In the light of the above it seems logical to attempt to identify ways of encouraging collateral development. On logical grounds that means encouraging ischaemia rather than removing it. You have then something of a paradox. If we wish to reduce area at risk or ischaemic area then we may have to abandon or modify our traditional approach of palliative therapy. This belief is supported by studies which demonstrate a direct relationship between duration of angina and presence of angiographic collaterals.(22,23) The next step from reduction of anti anginal therapy is to actually provoke ischaemia. The most reliable way of doing this is to increase myocardial work by

exercising. Such exercise should be of sufficient intensity and frequency to provoke ischaemia on a regular basis. The key to such an approach however is to design a blend of exercise and drug therapy which produces the required amount of ischaemia while allowing sufficient symptomatic relief to allow patients to carry on a near normal lifestyle and to carry out their exercises. In this respect we are aided by the fact that exercise training, by its effect on peripheral receptors, has been shown to improve exercise tolerance in ischaemic heart disease.(24) In trained individuals at any given level of sub maximal exercise there is a reduction in heart rate and blood pressure and hence myocardial work. This reduction in heart rate stems from the reduced level of reflex stimulation of the cardiovascular control area in the mid brain by receptors in trained muscles. Exercise training can therefore exert its own anti anginal effect minimising the need for drug treatment. It may be possible therefore to use exercise training of high intensity to provoke ischaemia and induce collateralisation while at the same time improving symptoms.

It was the intention therefore of these studies to develop an exercise programme capable of achieving the above aims and to use that programme to treat individuals with ischaemic heart disease. To do this it was necessary to identify a suitable group for study and to choose which techniques were most appropriate with which to study them. How this was achieved is described in detail in section II of this thesis.

SECTION II

SUBJECTS AND METHODS

II.1

PATIENT SELECTION AND RANDOMISATION

From analysis of previous studies involving exercise training it is evident that the majority suffered from the same basic design fault. The groups chosen covered a wide range of clinical situations within the blanket heading of ischaemic heart disease from individuals with asymptomatic coronary disease to patients with post myocardial infarction angina. This results in two problems, firstly a wide range of baseline measurements from which to measure any change making it difficult to achieve statistically significant results and secondly a group whose response to exercise is inevitably going to vary considerably. Clearly it is necessary to choose a more homogeneous group of patients. It is equally important, however, to recruit sufficient numbers within a suitable time period.

From the discussion in the introduction it is clear that exercise induced ischaemia would be a prerequisite for this study. Furthermore it was important that patients chosen should have the greatest potential to collateralise and to reverse ischaemic areas. Patients with previous myocardial infarction were therefore excluded. Such patients would have had several disadvantages. Firstly they would have occluded vessels with little potential to supply collaterals. Secondly, they would have scar tissue with no potential for revascularisation and a "dilutional" effect on the results of reperfusion studies.

Thirdly, if reversible ischaemia was present this would imply probable multiple vessel disease and less likelihood of producing effective collaterals. Finally to choose patients with infarcts of less than six months duration introduces bias because of changes in fitness and cardiac status which occur during the recovery period. The study was confined to male patients because of ease of investigation (see chapter II.3) and an upper age limit of 60 years was set because the exercises carried out were of high intensity and it was felt that musculoskeletal problems might be a limiting factor in the older age group. The final study group therefore consisted of males up to 60 years of age with chronic stable angina of at least six months duration without prior myocardial infarction. These patients were recruited from the cardiology out patient clinics at the Victoria Infirmary between July 1984 and December 1986.

The required population size for a study of this nature is difficult to assess. The ideal number varies depending on which parameter one choses to study. A range of parameters was considered. Estimates of standard deviation for the paramaters were taken from published studies and approximate numbers required to produce significant results at the 5% level for a 20% improvement and 30% improvement calculated by the formula

$$N = \frac{(u + v)^2 \, (SD1^2 + SD2^2)}{(\text{mean } 1 - \text{mean } 2)^2}$$

(for statistical power = 90%, u = 1.28 and for significance level = 5%, v = 1.96)

This suggested that to have a statistical power of 90% a group size of 20 - 80 would be required depending on the parameter studied. It was hoped initially that patient recruitment would be completed within one year, with a further year to complete the study. It was estimated that 20 exercise patients and 20 controls could be recruited in that time. Since the study group was to be more homogeneous than that chosen by other authors, it was reasonable to expect that the standard deviations would be narrower than those used to calculate the estimated numbers and that 20 patients in each group might therefore be sufficient. Nonetheless it was clear that we would require to demonstrate an improvement of 30% in most parameters. This seemed clinically appropriate and furthermore a group size of 20 was ideal for supervision by one physician and an ideal size for the exercise class.

Prior to initial exercise testing informed consent was obtained for the study and any anti anginal medication was withdrawn. Betablockers in particular were stopped for seven days before testing and any patient who could not stop betablockers was excluded from the study. On initial exercise testing any patient who developed exercise induced ventricular dysrhythmias or whose exercise test was negative using conventional criteria was excluded. Exercise induced hypotension or severe dyspnoea were not considered suitable reasons for exclusion and concomitant disease such as hypertension or diabetes was also allowed. Following initial exercise testing therefore patients were randomised into exercise training and control groups

using a random number generator programme on a Texas Instruments T1-S2 calculator. During the recruitment period 40 suitable patients were identified and 20 were randomised into each group. The demographic data for the two groups are shown in Table 1 and in these respects randomisation was successful. The mean age for the exercise group was 53 (range 46-60) with a mean duration of angina of 20.0 months, while the mean age for the control group was 51 (range 37-60) with a mean duration of angina of 12.7 months. There was a low overall incidence of cigarette smoking (four in the exercise group and five in the control group) although many patients had been former smokers, most having stopped shortly after diagnosis. There were no diabetics and although blood lipids were not checked routinely there were no known patients with familial hyperlipidaemia.

Table 1a

Demographic Data: Exercise Group

Patient	Age	Duration of angina (mts)	Smoking habits	Height (ins)	Weight (lbs)
1	51	24	Ex smoker	74	220
2	55	8	Ex smoker	70	175
3	47	10	Non smoker	69	190
4	45	24	Ex pipe smoker	70	188
5	57	6	Ex smoker	68	165
6	55	12	Ex smoker	64	142
7	60	36	Ex smoker	68	136
8	51	6	Ex smoker	72	221
9	52	9	Smoker	64	159
10	55	60	Smoker	74	198
11	52	8	Smoker	74	215
12	60	24	Non smoker	70	188
13	48	6	Ex smoker	68	148
14	59	18	Non smoker	67	140
15	57	108	Non smoker	67	150
16	58	6	Non smoker	68	196
17	48	12	Smoker	68	198
18	46	12	Ex smoker	69	204
19	48	6	Non smoker	67	182
20	58	6	Ex smoker	72	220
Mean	53	20.0	NA	69	182
S.D.	-	24.6	NA	3	28

Table 1b

Demographic Data: Control Group

Patient	Age	Duration of angina (mts)	Smoking habits	Height (ins)	Weight (lbs)
21	57	8	Non smoker	62	127
22	60	96	Non smoker	73	191
23	54	10	Ex smoker	69	187
24	50	12	Smoker	70	175
25	55	6	Non smoker	67	166
26	48	15	Non smoker	68	181
27	53	10	Ex smoker	71	190
28	53	6	Ex smoker	73	225
29	56	6	Non smoker	68	170
30	48	6	Ex smoker	71	184
31	40	8	Ex smoker	70	214
32	53	12	Smoker	70	205
33	49	6	Smoker	66	159
34	60	9	Non smoker	68	170
35	37	6	Smoker	66	181
36	56	6	Ex smoker	68	165
37	50	12	Smoker	66	143
38	46	6	Ex smoker	68	171
39	45	8	Non smoker	70	216
40	50	6	Ex smoker	68	190
Mean	51	12.7	NA	69	181
S.D.	-	9.8	NA	3	24

II.2

THE EXERCISE PROGRAMME

Just as the choice of patients was vital to this study, so was the choice of exercise programme. Previous studies have often chosen low intensity exercise of between 50 - 70% of the patients maximal heart rate achieved on treadmill testing. This was based on the belief that exercise training should not exceed the threshold for ischaemia. It was integral to this study however that ischaemia should be precipitated to encourage collateralisation. An exercise programme was required which contained high intensity exercise. However since it was anticipated that fitness would be low initially but would improve with training thus raising the threshold for ischaemia, a graded exercise programme was necessary. Clearly it would also be desirable to have a programme which would be carried out daily rather than the more usual three times weekly.

The Canadian Airforce 5BX programme for physical fitness had all the above requirements.(25) It is a brief (11 minutes) daily exercise programme of five callisthenic type exercises which was developed initially to train Canadian Airforce flying crew. It is graded in increasing increments to achieve a progressive increase in fitness and contains target levels according to age. Individuals should advance from the bottom to the top of a chart at suitable intervals and advance from chart to chart. For the

purposes of this study charts 1 - 3 were deemed to cover all age groups taking part (Figs. 1 - 3).

The initial exercise level for example (D - on chart 1) consists of touching the floor twice with the feet apart, three partial sit-ups, four extensions lying face down and two press-ups keeping the knees on the floor. The patient then jogs on the spot for 75 double steps (left and right) and carries out 10 scissor jumps before completing the final 25 jogs. This brief set of exercises is easily completed within the 11 minute time span allotted.

With satisfactory progress the patient may within 12 weeks be at level A + on chart 1 where the allotted 11 minutes is more challenging since he has to complete 20 toe touches, 18 partial sit-ups, 22 extensions, 13 modified press-ups and four sets of 75 jogs interspersed with four sets of 10 scissor jumps before a final 50 jogs (to a total 400 jogs).

On charts 2 and 3 the types of exercise become progressively more difficult e.g. the toe touching exercises become more complex, the sit-ups complete and the press-ups full press-ups then complex press-ups and as for chart 1 the number of each exercise done becomes greater as the individual progresses up the chart. Throughout however the 11 minute time schedule remains constant.

Level A + on chart 3 represents the maximum level of exercise in this study. The patient stretches up and back then touches the ground on the left of his feet, between his feet and to the right. This exercise is carried out 30 times. He then performs

Figure 1

Chart 1 Physical capacity rating scale

Age groups

6 yrs maintains B

7 yrs maintains A

Level	Exercise				
	1	2	3	4	5
A+	20	18	22	13	400
A	18	17	20	12	375
A–	16	15	18	11	335
B+	14	13	16	9	320
B	12	12	14	8	305
B–	10	11	12	7	280
C+	8	9	10	6	260
C	7	8	9	5	235
C–	6	7	8	4	205
D+	4	5	6	3	175
D	3	4	5	3	145
D–	2	3	4	2	100

1. Feet astride, arms upward. Forward bend to floor touching then stretch upward and backward bend. Do not strain to keep knees straight.
2. Back lying, feet 6" apart, arms at sides. Sit up just far enough to see your heels. Keep legs straight, head and shoulders must clear the floor.
3. Front lying, palms placed under the thighs. Raise head and one leg, repeat using legs alternately. Keep leg straight at the knee, thighs must clear the palms. (Count one each time second leg touches the floor.
4. Front lying, hands under the shoulders, palms flat on the floor. Straighten arms lifting upper body, keeping the knees on the floor. Bend arms to lower body. Keep body straight from the knees, arms must be fully extended, chest must touch floor to complete one movement.
5. Stationary run. (Count a step each time left foot touches floor.) Lift feet approximately 4" off floor. Every 75 steps do 10 'scissor jumps'. Repeat this sequence until required number of steps completed. Scissor jumps. Stand with right leg and left arm extended forward and left leg and right arm extended backward. Jump up - change position of arms and legs before landing. Repeat (arms shoulder high).

Figure 2

Chart 2 Physical capacity rating scale

Age groups

8 yrs maintains D-
9 yrs maintains C-
10 yrs maintains B-
11 yrs maintains A-
45-9 yrs maintains A+
50-60 yrs maintains C+

Level	Exercise				
	1	2	3	4	5
A+	30	23	33	20	500
A	29	21	31	19	485
A-	28	20	29	18	470
B+	26	18	27	17	455
B	24	17	25	16	445
B-	22	16	23	15	440
C+	20	15	21	14	425
C	19	14	19	13	410
C-	18	13	17	12	395
D+	16	12	15	11	380
D	15	11	14	10	360
D-	14	10	13	9	335

1. Feet astride, arms upward. Touch floor and press (bounce) once then stretch upward and backward bend.
2. Back lying, feet 6" apart, arms at sides. 'Sit up' to vertical position, keep feet on floor even if it is necessary to hook them under a chair.
3. Front lying, palms placed under thighs. Raise head, shoulders and both legs. Keep legs straight, both thighs must clear the palms.
4. Front lying, hands under the shoulders, palms flat on floor. Straighten arms to lift body with only palms and toes on the floor. Back straight. Chest must touch floor for each completed movement after arms have been fully extended.
5. Stationary run. (Count a step each time left foot touches floor). Lift feet approximately 4" off floor. After every 75 steps, do 10 'astride jumps'. Repeat this sequence until required number of steps is completed.

Astride jumps. Feet together, arms at side. Jump and land with feet astride and arms raised sideways to slightly above shoulder height. Return with a jump to the starting position for count of one. Keep arms straight.

Figure 3

Chart 3

Physical capacity rating scale

Age group

12 yrs maintains D+
13 yrs maintains C+
14 yrs maintains B+
35–39 yrs maintains B
40–44 yrs maintains C

Level	Exercise				
	1	2	3	4	5
A+	30	32	47	24	550
A	30	31	45	22	540
A–	30	30	43	21	525
B+	28	28	41	20	510
B	28	27	39	19	500
B–	28	26	37	18	490
C+	26	25	35	17	480
C	26	24	34	17	465
C–	26	23	33	16	450
D+	24	22	31	15	430
D	24	21	30	15	415
D–	24	20	29	15	400

1. Feet astride, arms upward. Touch floor 6" outside left foot, again between feet and press once then 6" outside right foot, bend backward as far as possible, repeat, reverse direction after half the number of counts.
2. Back lying, feet 6" apart arms clasped behind head. Sit up to vertical position, keep feet on floor, hook feet under chair etc. only if necessary.
3. Front lying, hands interlocked behind the back. Lift head, shoulder, chest and both legs as high as possible. Keep legs straight and raise chest and both thighs completely off floor.
4. Front lying, hands under the shoulders, palms flat on floor. Touch chin to floor in front of hands - touch forehead to floor behind hands before returning to up position. There are three definite movements, chin, forehead, arms straightened. Do not do in one continuous movement.
5. Stationary run. (Count a step each time left foot touches floor). Lift feet approximately 4" off floor. After every 75 steps do 10 'half knee bends'. Repeat this sequence until required number of steps completed.

Half knee bends. Feet together, hands on hips, knees bent to form an angle of about 110 degrees; do not bend knees past a right angle.
Straighten to upright position, raising heels off floor, return to starting position each time. Keep feet in contact with floor - the back upright and straight at all times.

32 sit-ups with his hands clasped behind his head followed by 47 hyperextensions while lying face down. Twenty four press-ups are then performed where the chin is touched to the floor in front of his hands followed by the forehead behind the hands before pushing up. Finally seven sets of 75 jogs with seven sets of 10 knee bends is carried out with a final 25 jogs. Clearly at this level the exercises have to be carried out rapidly with few rests to be completed within 11 minutes.

From the above descriptions it is clear that the Canadian Airforce PBX Program differs in other respects from the more usual programmes used by cardiac exercise groups. Apart from being a daily programme it is also much shorter than the usual 30 - 40 minute programmes. The choice of exercises is also somewhat atypical. While retaining a large aerobic component, it also contains some power exercise. There are no purely isometric exercises but the press-ups, sit-ups and trunk curls do involve significant power components. While high level isometric exercise is generally not recommended for cardiac patients, most young patients with angina carry out some degree of exercise with a power component during their daily lives and therefore it was felt that a programme which covered most muscle groups and which contained a mixture of aerobic and power exercise would be useful to improve overall fitness for daily living.

Several modifications were made to the standard programme. The age levels were used only as a rough guide to expectations and patients were neither expected to achieve their goal nor to stop at that level. Each exercise level was to be carried out for a

minimum of one week. Provided a patient could carry out that level within the 11 minute time limit and without excessive angina or dyspnoea (mild to moderate discomfort at the end of exercise was allowable) he could progress to the next level.

The use of a daily programme such as this in a relatively young group meant that it was not practical to supervise all exercise sessions. It was furthermore felt undesirable to do so. It was intended that this exercise programme would be the cornerstone of the patient's rehabilitation and that allowing the patient to carry out exercise of this intensity at home would provide them with the confidence to increase their general level of activity and in so doing produce further cardiac stimulation. A supervised session was therefore held once weekly lasting one hour. Patients were introduced to the programme at this session and were encouraged at least in the early stages to attend each week to advance to the next level of exercise under supervision. Attendance was not however essential throughout the study but the session was used also as an opportunity for the patients to discuss any problems with staff and with other patients. An understanding of their disease was encouraged because this study was not based on achieving early symptomatic relief and indeed in some cases withdrawal of previous anti anginal agents meant that symptoms were initially worse. It was hoped however that patient education would produce the understanding required to achieve the necessary stimulus to collateralisation. These weekly sessions were attended by physiotherapists to advise on the technique of the exercises and to supervise progress. The supervising

physician was also present (the author) to answer patient questions.

The Canadian Airforce programme has been used previously in studies and has been shown to increase fitness in normal volunteers (26) and in patients with ischaemic heart disease.(27) It has also been used previously in work from this hospital.(28) For the purposes of this study a duration of one year on the programme was considered optimal.

As discussed in the introduction it was intended that anti anginal medication would be kept to a minimum and that where possible it would be tailored to the daily needs of the patient. This process involved further patient education. It was desirable that the control group would also receive similar advice to minimise the effect of drug therapy on the study. Nifedipine and GTN were chosen as the most useful agents. All patients were advised to use GTN for angina which was not relieved quickly by rest. Nifedipine was used prophylactically in a dose of 10-20 mg t.d.s. As symptoms improved during the study the dose was reduced or stopped and in addition patients were advised that it was not essential to stick rigidly to the dose schedule. Thus doses could be missed on 'sedentary' days or increased on 'active' days. If further anti anginal therapy was required Isosorbide Dinitrate could be used, although in practice this was required only by one exercise and one control patient. Any patient who required a betablocker was withdrawn from the study, firstly since the interaction between betablockade and training is unclear and secondly since part of this interaction was under study.

The control group in this study were receiving less than maximal anti anginal therapy for the duration of the study and were therefore kept under closer supervision than would otherwise have been the case. During the initial investigation phase the opportunity was taken to discuss their disease and the use of drug therapy. They were given general advice but were not told that exercise was being used on another group. Where the topic was raised by patients they were given general advice that exercise might be beneficial and advice on the appropriateness of various forms of exercise. They were further advised that a formal programme may be available to them at a later date. These patients were reviewed at three monthly intervals during the study and were advised to contact the author directly in the event of a change in symptoms or if they had any questions about their condition. While some patients in each group did deteriorate during the study, no patient received inappropriate treatment or had treatment withheld because of participation in the study.

Dietary advice was given to those patients who sought such advice or to those who were considered overweight. In these circumstances referral to the hospital dietician was undertaken. While this may introduce a further significant variable influencing cardiac performance it was considered that any dietary difference between the groups arising from participation in the study was attributable to participation in the exercise programme. The same view was taken with regard to participation in additional exercise such as swimming. Likewise, while the incidence of smoking was low in both groups, no attempt was made to monitor

this by measurement of carboxyhaemoglobin levels, since any intergroup difference during the study would again reasonble be attributed to participation in the study.

In adopting the above approach one must accept that it is impossible to study the pure effect of an exercise programme on myocardial perfusion in a clinical setting. Once can only assess the effects of participation in such a programme and recognise that such participation may include the modificiation, inadvertently or otherwise, of the patients' lifestyle.

II.3

THE INVESTIGATIONS

While coronary angiography is often regarded as the gold standard for the investigation of ischaemic heart disease there are a number of reasons why it should not be regarded as such in a study of this nature. It would provide anatomical data regarding the extent and distribution of coronary artery disease and regarding the presence of collaterals but would give no information on the effectiveness of such a supply and may give misleading anatomical information. Post mortem angiographic studies have demonstrated the existence of small collaterals which cannot be seen by coronary angiography and it is accepted that a minimum diameter of 160u is required before angiographic visualisation.(29,30) Furthermore the visualisation of collaterals is dependent on the pressure at which dye is injected.(31) Variation in operator technique or indeed radiographic technique may lead to the erroneous conclusion that collaterals have appeared or disappeared between two studies. When one adds to this the effect of stenoses in the donor and recipient vessels on opacification of collaterals then it is clear that angiography cannot supply reliable information with respect to collaterals. It is worth noting that those studies which have

shown a positive correlation between the presence of collaterals and improved myocardial function have been the ones which have attempted to categorise the collaterals according to degree of opacification and hence effectiveness.(19,32,33) To attempt a longitudinal study with serial angiography on such a basis would not be possible for the reasons mentioned.

The value of coronary angiography in this study would have been to allow categorisation of patients on the basis of initial extent of disease to assess whether a particular subgroup of patients obtain the best result from exercise training. However with the number of patients involved in this study, meaningful statistical information would not be possible. It was decided therefore that serial coronary angiography before and after training may produce misleading results and that single angiography would produce results worthy of comment only but without statistical significance. Under these circumstances an invasive investigation of this sort was inappropriate and coronary angiography was carried out only where clinically indicated during the study.

Non-invasive investigations are a more appropriate way of monitoring the changes brought about by exercise training for they have the ability to supply functional information which cannot readily be obtained by invasive means. Whether a collateral can or cannot be seen angiographically is of little relevance. Whether it produces improvements in myocardial function and perfusion is the key question. Furthermore this question must be asked at the appropriate time. A collateral which functions at

rest is of some value but one which functions under stress when hypoxia is present is of much more use. It is conceivable that collateral function may deteriorate with exercise, particularly where the donor vessel itself is diseased, leading to a fall in perfusion pressure on exercise. However mature collaterals have been shown to possess a muscular media which suggests they may respond to changes in vasomotor tone.(34) It is possible therefore that exercise induced hypoxia may lead to dilatation of collaterals with improved function on exercise to relieve that hypoxia. The basis of any study into the development of collaterals must therefore be the stress test.

Treadmill exercise tolerance testing was used where possible in this study. It provides a form of stress which is more acceptable to patients than bicycle exercise. It was used to provide data on patient fitness and threshold for myocardial ischaemia and as a stimulus for ischaemia in perfusion studies. A wide range of treadmill protocols is available and the protocol chosen and the reasons for that choice are detailed below. The exercise tolerance results obtained form the first subsection of section III.

In the light of the above discussions myocardial perfusion imaging during stress would be central to a study into the potential benefits of exercise training. The ideal isotope for such studies would have a high affinity for myocardium providing a high target to background count ratio and would emit a high abundance of gamma energy in the 100 - 300 KeV energy range, the ideal range to combine acceptable resolution with good sensitivity

for single crystal gamma cameras. In addition, one would wish the uptake of isotope to bear an inverse linear relationship to the degree of myocardial ischaemia and for subsequent redistribution of isotope to be delayed after cessation of exercise for sufficient time to allow image acquisition.

The most widely used isotope for perfusion imaging is Thallium 201. It is however far from being ideally suited to the purpose. After intravenous injection Thallium 201 is distributed to the tissues in proportion to their percentage of cardiac output. As a result only some 5% is delivered to the myocardium resulting in a poor target to background ratio of 2 or 3 to 1. This makes recognition of perfusion abnormalities rather difficult. Furthermore Thallium 201 decays by electron capture emitting mainly mercury K x-rays with energies ranging from 69 to 83 KeV. This provides acceptable but less than ideal internal resolution. In its favour however, there is a high extraction of Thallium from the blood by the tissues during first pass and a linear relationship exists between myocardial Thallium concentration and coronary blood flow.(35) Some two minutes after injection of Thallium, the concentration of Thallium in the blood is only 10% of the initial concentration. Unfortunately this low blood concentration of Thallium results in an electro potential gradient favouring egress of Thallium 201 from the myocardial cells back into the intravascular compartment. This process of Thallium washout depends on relative myocardial and blood concentrations. This therefore favours clearance of Thallium from normal myocardium where the concentration is high

but reduced washout and on occasions wash-in in ischaemic zones where initial concentration is low. This process has the effect of reversing the ischaemic defect and effectively limits the time of acquisition of scans to 20 - 30 minutes.

In view of the above deficiencies it is perhaps surprising that Thallium 201 scintigraphy has remained the accepted technique for non invasive perfusion imaging for many years and that it has not been surpassed by newer isotopes. Perhaps however there is some merit in this in that it has been widely studied by many authors and subjected to various computer processing procedures in an attempt to enhance its ability to detect areas of myocardial ischaemia. While reservations remain about the techniques of Thallium scintigraphy, they have developed to the stage where it is at least feasible to use them for a follow up study of this nature. The exact choice of technique therefore depended partly on the availability of equipment within the Victoria Infirmary and partly on published work by other authors who have developed techniques considered by the author to be suitable for this study. Exact details of these techniques are given later in this section with a description of further modifications in the appropriate subsection of section III.

Another important area to asses in this study is myocardial function. Again a number of options were available. Had coronary angiography been undertaken, then single or preferably biplane contrast ventriculography would be an obvious choice. The area of the left ventricle can be outlined and calculated and by the application of one of the available formulae an

approximate value for left ventricular volume can be obtained. By calculating end diastolic and end systolic volumes, ejection fraction may be calculated. Hammermeister and colleagues in 1974 (36) demonstrated that in addition provided high frame rate cineangiography was used volumes could be plotted throughout the cardiac cycle allowing the production of diastolic and systolic left ventricular function curves. There are however a number of disadvantages in this technique. Firstly cineangiography is a 2-dimensional technique from which 3-dimensional calculations are being made. This may introduce inaccuracies particularly in assessment of changes in regional function. Secondly it contains information about a limited number of cardiac cycles which in themselves may be atypical since they follow the injection of a volume of contrast material. Thirdly the technique can really only be applied at rest. Gated Technetium blood pool angiography can overcome these limitations. It is based on isotope count density and as such is 3-dimensional, it averages information over a large number of cycles, and it can be used in association with stress testing. Its analysis however requires the use of computer programmes to smooth the images and to detect the edge of the left ventricle, as well as to calculate the parameters required. Each programme inevitably corrupts the raw data to some degree, raising doubts over the validity of results obtained by this technique. Nonetheless it has gained widespread usage particularly for the assessment of global and regional ejection fractions. For this study these measurements were particularly applicable since exercise training might exert a general effect on

left ventricular function apart from any local effect related to myocardial perfusion. While Technetium 99 is a more suitable radioisotope for use with the gamma camera than Thallium since it produces pure gamma ray emissions in the optimal energy range, the limitations of the imaging system available in the Victoria Infirmary lessen its value. The gamma camera used has a low count rate capability. The relatively low number of counts obtained during imaging introduces a greater degree of statistical variability. In addition the camera is also bulky and not mobile and could not therefore be used in conjunction with exercise stress. It was necessary therefore to use cold pressor stress as the stress test. This however does have the advantage of allowing acquisition of stress data with the patient lying still. This is important for assessing regional left ventricular function accurately enough to make a sequential study meaningful. Despite these limitations it was hoped that this technique might provide useful supportive information in the assessment of possible changes in myocardial perfusion.

Two-dimensional echocardiography may be used to assess regional and global left ventricular function and has also been combined with stress testing. Semiquantitative and quantitative techniques have been used to analyse these studies though stress studies have to date only been used for global quantitative analysis. In this work 2-dimensional echocardiography was used in conjunction with treadmill testing in an attempt to assess whether it added to the information obtained by the methods used with gated Tc angiography. This technique required more

assessment with respect to its value and this is detailed in section III.

Finally, the above techniques provide extensive information about changes which can be observed in the laboratory situation. This work would not be complete however without an assessment of the practical value during normal daily activities. All patients were further assessed therefore by 24 hour ambulatory ECG monitoring both of heart rate and ST segment shifts.

All investigations were repeated after one year.

Exercise Tolerance Testing

Treadmill exercise tolerance was assessed before and after training using a Marquette Case II system. This is a computerised 12 lead ECG monitoring system linked to a motor driven treadmill. It provides continuous monitoring of a standard 12 lead ECG throughout the test, displaying 12 leads updated at 15 sec. intervals. In addition there is a continuous display of leads II, V1 and V5 and a display of the lead showing maximum ST depression. The duration of test, duration of stage, heart rate, minimum ST level and total number of PVC's are also displayed. The system was programmed to print out a 12 lead ECG at one minute intervals throughout the test and at one, three and five minutes into recovery. In addition resting ECG's were recorded sitting and standing and an ECG prior to stopping was also recorded. Blood pressure was measured at rest and between 2 and $2\frac{1}{2}$ minutes of each stage as well as immediately prior to stopping and twice during recovery. The usual end points of chest

pain, dyspnoea, fatigue, dysrhythmia or 3 mm ST depression were chosen.

The choice of treadmill protocol was made with a number of points in mind. Firstly all patients in this study were relatively young males. From experience it was found that 3 MPH was an ideal walking pace for such a group. A protocol commencing at lower speeds is technically difficult and higher speeds cause some patients to jog. It was desirable to have a smooth transition from stage to stage with a slow but linear increase in workload and hence a steady rise in heart rate to find an accurate end point. The Naughton protocol (37) consists of a constant 3 MPH beginning with no gradient. The slope is increased in increments of 2.5% at two minute intervals. This has been estimated to be equivalent to a VO2 of 10.5 ml 02/Kg/min (3 METS) initially with an increment of VO2 of 3.5 ml 02/Kg/min (1 MET) for each stage. It thus produces the modest but steady increase in workload necessary for accurate determination of end point. Naughton's protocol allowed two minutes for each stage. For the purposes of this study this was extended to three minutes to ensure plateauing of the heart rate and to allow time to accurately measure blood pressure. The maximum gradient was 25%. Thereafter a final stage was added where necessary at 4 MPH and 25% gradient giving a total maximum treadmill time of 36 minutes. This was longer than is ideal since muscle fatigue and lactic acidosis can effect lengthy tests of this sort. In practice however, such a long tests was rarely required. This modified Naughton protocol was used for all exercise tests including

initial diagnostic testing.

In the timetable of investigations (Figure 4) there were two opportunities to measure treadmill performance since the same technique was used for Thallium scinitigraphy and exercise echocardiography. Exercise echocardiography was carried out in the afternoon and was the initial investigation. Thallium scinitigraphy took place one week later in the morning after an overnight fast and it was these data which were used for analysis in the first subsection of section III. This therefore allowed the initial test to be used to familiarise the patient with the procedure minimising the learning effect of subsequent testing and, in addition, meant the data were obtained in the early morning and fasting, in order to minimise variability due to diurnal variation and ingestion of food.(38)

The Marquette system automatically records the heart rate on each ECG and the degree of ST segment shift for each lead 80 msec after the J point. All data were checked manually during the recording of results with particular reference to the points chosen for determination of ST shift. If these were accurate then the figure given was accepted to 0.1 mm. The only significant error in ST measurement occurred at high heart rates and in such cases a manual measurement was taken.

Thallium 201 Scintigraphy

Thallium 201 scinitgraphy was carried out in conjunction with the patient's second treadmill exercise test. An intravenous cannula was inserted into the left antecubital vein prior to

Figure 4

Timetable of investigations

Week No.	Investigation
1	Exercise echocardiography/treadmill ETT
2	Thallium 201 scintigraphy/treadmill ETT
2-3	Initiation of beta blockade
3	ETT on Atenolol
3-4	Withdrawal of beta blockade
4	Commencement of exercise training
5	Gated Technetium bloodpool angiography
5	24 hour ambulatory ECG monitoring
	One year's exercise training programme
52	Repeat exercise echocardiography/treadmill ETT
53	Repeat Thallium 201 scintigraphy/treadmill ETT
53-54	Initiation of beta blockade
54	ETT on Atenolol
54-55	Withdrawal of beta blockade
55	Gated Technetium bloodpool angiography
	24 hour ambulatory ECG monitoring

exercise, the patient having fasted for 12 hours and taken no medication for 24 hours (nifedipine or nitrate). Exercise was commenced and the patient was advised to tell the physician when he developed chest pain and when he could continue for only one minute longer. At that time 80 MBq of Thallous 201 chloride was injected through the cannula and flushed with 20 mls of 0.9% sodium chloride. After one minute exercise was stopped and the patient transferred by wheel chair to the scanning room for immediate scanning.

The Gamma camera used for this study was a Technicare Sigma 401 with a large field of view crystal and a general purpose low energy (140 KeV) parallel hole collimator. Date were acquired and stored in a 128 x 128 x 8 bit matrix on an ADAC CGR 7310 computer for subsequent processing. Images were obtained in the anterior, 45° left anterior oblique (LAO) and 65° LAO projections. The system was set to acquire a fixed number of counts for each view (350,000) and the time taken to do so was recorded. The camera was set to measure energy in the 68 -82 KeV range with an autopeak facility to track any drift in the Thallium peak and a window setting of 30%, as the best compromise between too few counts and too much scatter. During acquisition the spleen was masked with a lead shield. The patient was then free to go home and advised to have a light meal before returning three hours later for repeat scanning with a preset time, the time chosen being that which was required to acquire the morning counts. Thus a set of three stress images and three redistribution images was obtained. In the majority of cases initial acquisition was

complete within 20 minutes of injection of Thallium with an outside time limit of 30 minutes.

The images obtained as above were further processed to obtain circumferential profiles. Firstly the images were corrected for non cardiac background activity by interpolative background subtraction. This involves creation of an area of interest enclosing only the myocardium using a light pen. The programme then generates a horizontal plane comprising a three channel profile across the centre of the area of interest. A new set of values is assigned to the pixels within the reference plane. These values are interpolated values generated by the method first described by Goris (39) but modified according to a constant derived by Beck.(40) A background computed image is then determined as a fraction of the radioactivity in the myocardial region relative to the reference plane. Finally a background corrected image is created by subtracting the computed background image from the original unprocessed image.

The background corrected images are further processed using a programme which quantitates the spatial distribution of Thallium in the myocardium on each pair of immediate stress and redistribution images. The operator identifies the centre and apex of the left ventricle on each of the imaging pairs. The programme then generates 60 radii at 6° intervals from the centre of the ventricle commencing with the first radius (0°) at 90° counter clockwise from the marked apex and subsequent radii at 6° intervals clockwise from the 0° radius. It then searches each radius in turn for the hottest pixel. Having identified the

hottest pixel on each radius within the myocardial boundaries it displays the image on the screen with the inner and outer myocardial boundaries marked and each identified pixel highlighted. If this is accepted by the operator then each pixel is averaged with the two adjacent pixels on that radius. Once this process has been carried out on the stress and redistribution scans then both images are displayed on the screen. The operator can then choose to plot the count profiles calculated. The computer will identify the highest count value on either image and assign it a value of 100%. All other pixels are assigned a percentage value in proportion to this.

Profiles generated in this way contain information on the relative distribution of the Thallium around the circumference of the heart. The stress profile will identify ischaemia as an area with a relatively low initial uptake of Thallium. During the three hour delay before repeat scanning, redistribution of Thallium will take place and the defect will tend to normalise. In a normal scan the redistribution curve should be below the immediate post exercise curve and parallel to it. Where a reversible ischaemic defect is identified, the two curves will converge and may cross so that the three hour level in the ischaemic area exceeds the post exercise level.

In individuals with balanced triple vessel coronary artery disease the uptake of Thallium may be uniformly low in all areas. Such a profile may therefore show no defect since counts are spatially relative and plotted not as absolute values but as a percentage of maximum. Thallium clears from ischaemic myocardium

slowly however and therefore relatively high three hour profiles will result. To assess this the computer plots a "washout" profile by subtracting the three hour count levels from the post exercise count levels and expressing this as a percentage of the post exercise count levels. This temporally relative curve is also displayed on the screen which therefore displays the background subtracted stress and redistribution images, a graph of stress and redistribution profiles and a graph of washout. (Figure 5)

Although in theory one could compare two scans on the same individual by direct comparison of the curves, in practice matching curves would prove technically difficult. The above programme could be improved however by the addition of normal values to the curve. Maddahi has used a similar programme to that described above in normal individuals and in patients with ischaemic heart disease.(41) He has published normal values for stress and washout curves. These normal values identify lower limits of normality equivalent to two standard deviations below the mean for the group of normal individuals. Abnormal curves can be compared with these values to identify which areas fall below the normal range. This technique was found to have a sensitivity and specificity for the detection of coronary artery disease of 93% and 91% respectively. Using this method Maddahi and Abdulla were able to identify disease of the left anterior descending (LAD) territory with 82% sensitivity, disease of the circumflex territory with 61% sensitivity and right coronary artery disease with 90% sensitivity. The overall specificity for

Figure 5 'ADAC' derived Thallium circumferential profiles

identification of site of lesion usingboth profiles was 75%.(42) While sensitivity and specificity are not applicable to this study where all patients were known to have coronary disease these figures are nonetheless reassuring since they suggest that abnormalities detected by the somewhat complex programme are genuine. For this study therefore a computer programme was developed on a BBC Master computer to superimpose normal data from Maddahi's study onto the profiles generated by the above programme. In order to do this however, a further smoothing of the profiles was necessary. The programme produced therefore takes the profiles produced by the ADAC computer and carries out a three point circumferential smoothing. In addition the operator is given the opportunity to realign the stress and redistribution curves before calculating the washout values. This step was included since the original programme required the operator to identify the apex on both stress and redistribution scans separately and it was possible therefore to misalign them. Once aligned the stress, redistribution and washout profiles were plotted with Maddahi's normal range shown (see examples: Figures 6, 7 and 8).

While the normal range produced by other authors may not be entirely applicable in our laboratory in absolute terms it does provide a bench mark of normality against which all scans can be compared. This allows one to measure the extent of abnormality on two separate occasions and compare the results. Further analysis of the scans was carried out at the end of the study to assess the best method of comparison. This analysis is dealt

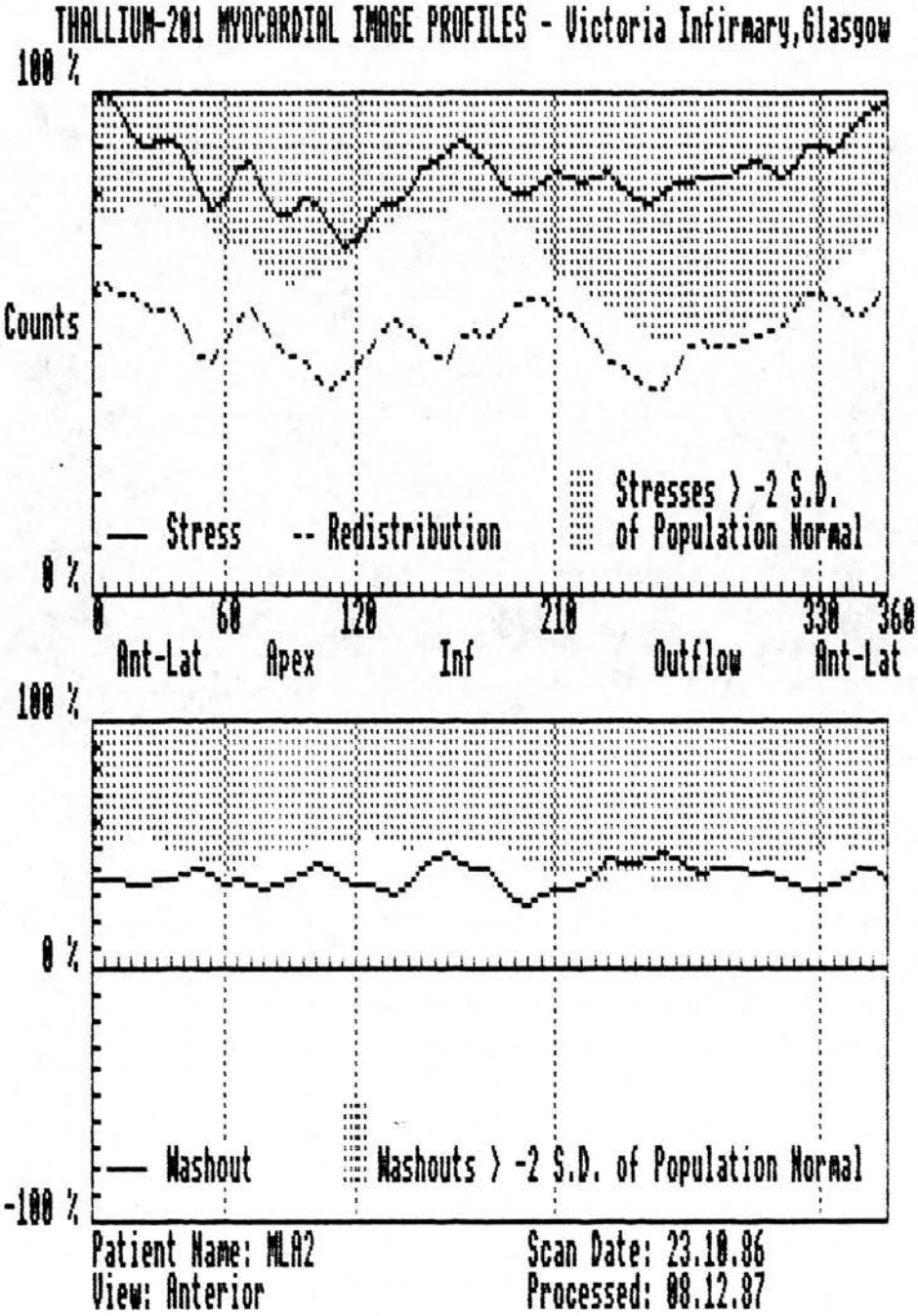


Figure 6 'BBC' smoothed Thallium circumferential profiles

Anterior view

Top graph - Stress (solid) and redistribution (broken) curves. Apex is assigned 90° and all other points are relative to this. Hottest pixel is assigned 100% counts with all stress and distribution values calculated as a % of this. The hatched 'normal' range applies only to the stress curve.

Bottom graph - Washout curve % = stress - redistribution ÷ stress x 100.

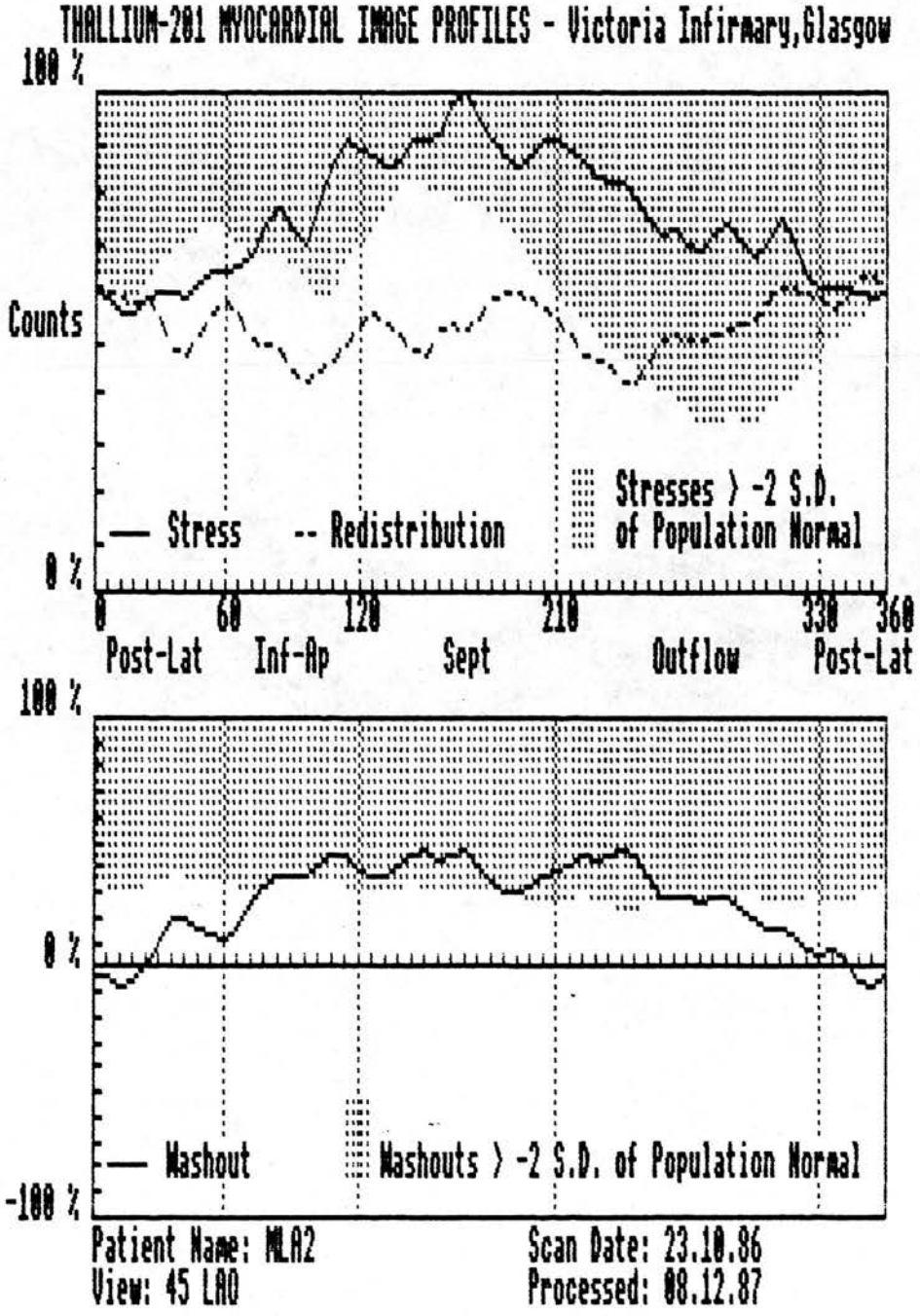


Figure 7 'BBC' smoothed Thallium circumferential profiles 45^{o} LAO view. See Figure 6 for details. Posterolateral stress defect and associated reduction in washout.

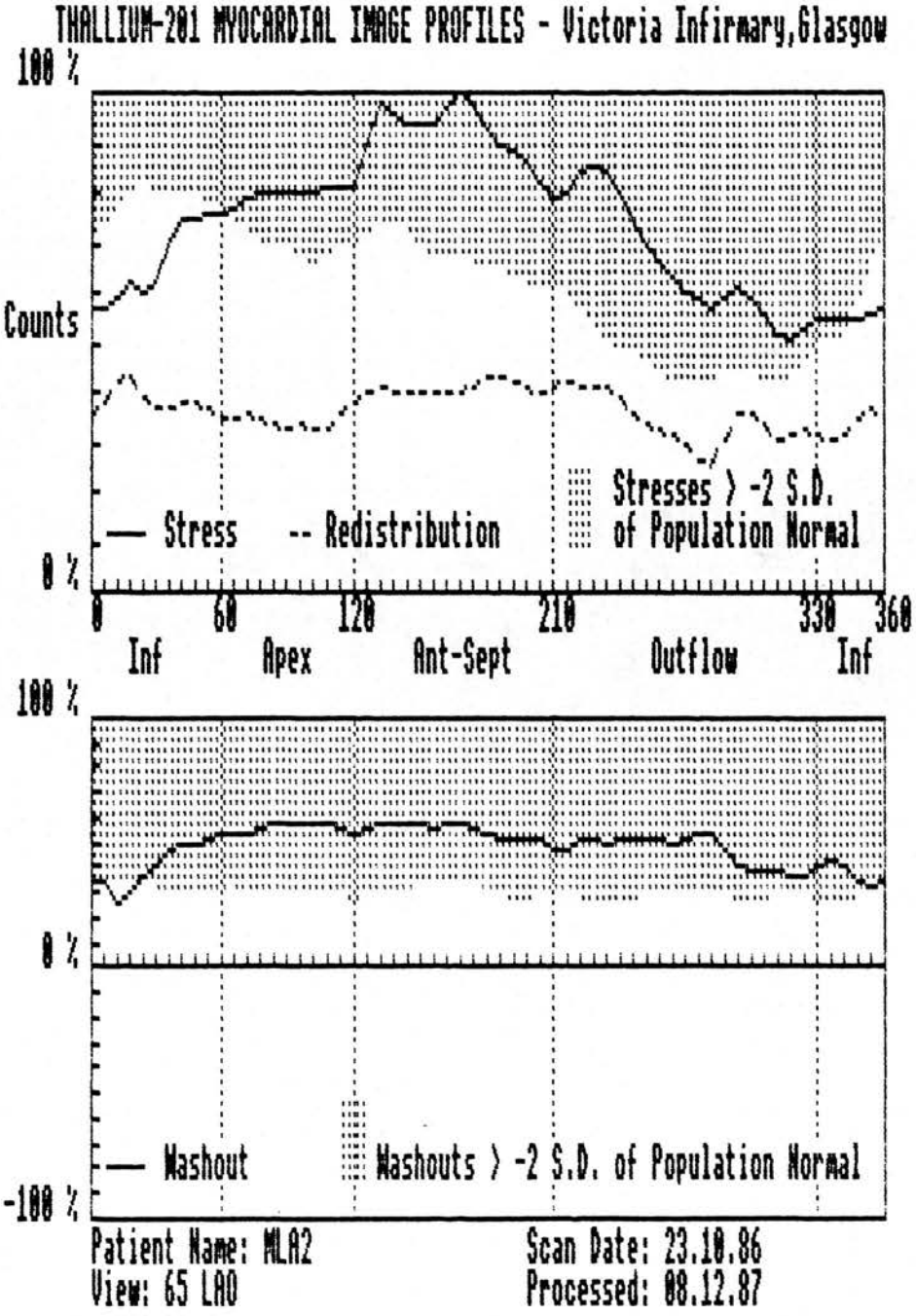


Figure 8 'BBC' smoothed Thallium circumferential profiles 65^{o} LAO view. See Figure 6 for details. Inferior stress defect.

with in the appropriate subsection of section III.

While other analysis programmes were available and were considered this programme was chosen since it fulfilled the criteria necessary to demonstrate and quantify a defect and required the minimum of operator interaction minimising inter and intra observer error and operator bias. All scans were however analysed by the same operator, who in addition examined each planar Thallium image in its unprocessed and background subtracted states to identify the area of ischaemia and compare this with the computer detected area to ensure that the defect was genuine. Since this was an automatic programme blinding was deemed unnecessary prior to analysis.

Gated Technetium Equilibrium Blood Pool Angiography

Gated Technetium blood pool angiography is a well established validated technique in the Victoria Infirmary and has been found to be reproducible with respect to measurement of global left ventricular function both at rest and during stress. The equipment used is that described under Thallium 201 Scintigraphy. The patient's red blood cells are labelled in vivo with Technetium 99m Pertechnetate by first giving an injection of 1 to 2 ug of stannous pyrophosphate which sensitises the red blood cells (RBC's) to subsequent injection of 740 MBq of Technetium 99m Pertechnetate some 20 minutes later. Using this technique RBC's are labelled with approximately 90% efficiency.(43)

Following red cell labelling a resting scan is acquired with the patient lying flat. A 30 - 45° LAO projection is used, the

exact projection being that which separates the right and left ventricles to a greater degree giving the best septal definition. A 10° caudal tilt is also used to minimise interference from the atria. During the procedure acquisition is gated to the patients ECG. The computer uses the R wave of the ECG as the gating device and divides the R-R cycle into equal portions. It is possible to divide the R-R cycle into either 16 or 32 portions. Chosing 32 portions produces a larger number of points on the LV function curve. Since this is a count based technique however it halves the number of counts avialable for each point and this introduces greater statistical variability for each individual point. In view of the limited count capability of the gamma camera and the constraints on acquisition time introduced by the cold pressor test it was considered that 16 portions was the most appropriate. Beats are acquired for six minutes and stored in frame mode in a 64 x 64 matrix to produce a summated representative cycle. The computer rejects any beat with an R-R interval outside a preset range ($\pm$ 20%) of the predetermined R-R interval, thus excluding ectopic beats from analysis.

After acquisition of the resting scan a stress scan is acquired using a similar technique. For this scan however, acquisition time is reduced to five minutes and the acceptable R-R interval range is constantly adjusted by the computer to take account of changing heart rate. Thus a beat outside the 20% window resets the R-R interval range. A stress scan is carried out during 5 minutes 30 seconds of cold pressor stress, acquisition of data commencing after 30 seconds. The patients

hand and forearm are immersed in a bath of crushed ice and water is continually passed through the ice to ensure adequate contact with the patient. Blood pressure and heart rate are recorded at rest and at one minute intervals throughout the stress test.

Image analysis was performed using the Standford automatic LV function analysis programme which constructs a time activity curve from which indices of left ventricular function can be calculated (Figure 9). The method is described in detail in the literature.(44,45) Briefly, 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 and the left ventricle is located by calculation of the XY co-ordinates 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 programme locates the left ventricle on the left part of the stroke volume image and identifies the edges of the ventricle on the diastolic image. A left ventricular area of interest is created and subsequently used for interpolative background subtraction. The area of interest is also used to create a 100 point volume curve and frequency components. From this curve the system calculates ejection fraction, dV/dT for systole and diastole, systolic time and length, fast emptying time and length and fast filling time and length. Ejection fraction

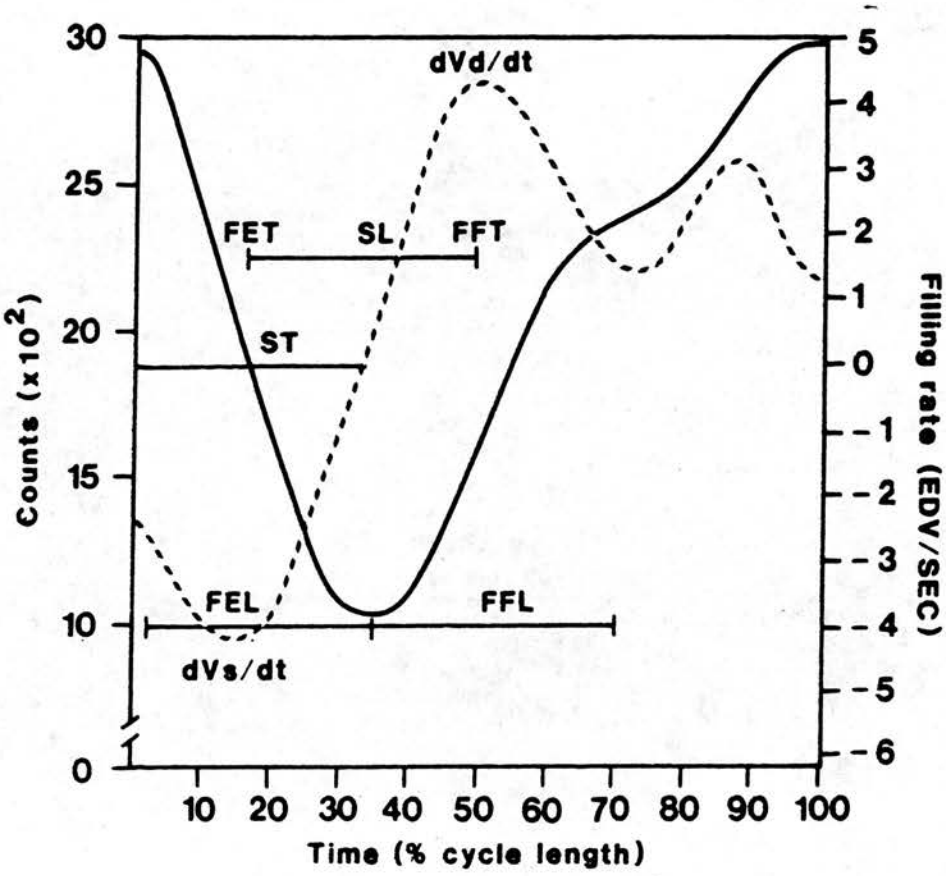


Figure 9 Left ventricular time activity curve and its first derivative (dotted line) with report parameters

FET	Fast ejection time. The point at which maximum rate of emptying occurs (5 total curve)
dVs/dt	Maximum rate of emptying (end diastolic volume/sec)
FEL	Fast ejection length: The duration of the fast ejection period (% total curve)
ST	Systolic time: The total systolic duration (% total curve)
SL	Systolic length: The duration of the period between maximum rate of emptying and maximum rate of filling (% total curve)
FFT	Fast filling time: The point at which maximum rate of filling occurs (% total curve)
dVd/dt	Maximum rate of filling (end diastolic volumes/sec)
FFL	Fast filling length. The duration of the fast filling period (% total curve)

is calculated as:

$$\frac{\text{end diastolic counts - end systolic counts}}{\text{end diastolic counts}} \times \frac{100}{1}$$

expressed as percentage. In addition regional ejection fraction is calculated by dividing the left ventricular area of interest into eight equal segments and using the above formula for each segment individually. Functional images of stroke volume, amplitude and phase are also produced but since the images are of limited value for follow up they were not used in this study.

The choice of technique in this study was to a large extent governed by necessity. Exercise radionuclide ventriculography is a well established technique of proven sensitivity and specificity for the detection of coronary artery disease. It produces a higher level of cardiac stimulation than isometric handgrip or cold pressor (46-48) and a predictable response in terms of ejection fraction. Thus it is well accepted that failure to increase ejection fraction by 5% during exercise is a good predictor of coronary artery disease. Furthermore Iskandrian and associates suggest that irrespective of resting ejection fraction an abnormal exercise response predicts reversible ischaemia.(49) The same cannot be said for isometric handgrip and cold pressor stress tests. While some authors have reported a fall in ejection fraction to be a sensitive indicator of coronary artery disease, (50,51) others have shown a fall in normal as well as abnormal individuals.(48,52) In previous work from the Victoria

Infirmary the use of change in ejection fraction with isometric handgrip or cold pressor failed to separate "normal" individuals from patients with ischaemic heart disease.(53) Both methods produced falls in ejection fraction in normals, though this was significant only for cold pressor (3.3% fall with isometric handgrip and 5.8% with cold pressor). The corresponding falls for a group of patients with coronary artery disease but normal resting ejection fractions were 5% and 8.6% respectively.

Though they are perhaps poor diagnostic techniques they have nonetheless value for follow up of patients with known coronary artery disease. Thus in this laboratory resting ejection fraction in normals was found to have a coefficient of variance of 5% and correlation coefficient of 85%. Using these figures a spontaneous variability for individuals in resting ejection fraction of 12% was calculated. The mean ejection fraction on two occasions differed by 1.2 $\pm$ 6.16%. In patients with coronary disease ejection fraction response to isometric handgrip and cold pressor was found to have acceptable reproducibility with no significant difference in mean response and coefficients of variance of 10% and 9% respectively.(53)

Perhaps the difficulty in using these techniques for follow up lies in the interpretation of the results. With regard to exercise radionuclide angiography where the normal response is a rise in ejection fraction, then a group of patients whose ejection fraction falls pre intervention and either rises or falls by less post intervention, can be said to have "improved" their ejection fraction response to exercise. This has been reported following

angioplasty, (54,55) coronary grafting (56-58) and indeed exercise training.(59-62) Where the response in normal individuals includes a fall in ejection fraction as it does for isometric handgrip and cold pressor, then it is less easy to interpret the results of intervention. The real fault lies perhaps in our understanding of the mechanism of action of isometric handgrip and cold pressor. These doubts not withstanding, resting ejection fraction was considered a clear choice for this study and it was hoped that the ejection fraction results from cold pressor might help in the final analysis of the mechanisms of changes in myocardial perfusion and function after training. Isometric handgrip was not used. While the assessment of other global parameters, particularly those concerning diastolic function, might be valuable since diastolic function, even at rest, has been shown to be impaired in the presence of coronary artery disease (63) and to improve after intervention, (64) there were doubts whether the parameters of left ventricular function measured would be useful in light of the limited count data available. Nonetheless taken as a whole the various parameters do describe the left ventricular function curve morphology. It might be useful to see whether there was any significant change in curve shape in association with global ejection fraction changes.

More important than the above measurements however is the assessment of regional myocardial function for it is here that one would hope to detect changes due to improved myocardial perfusion. In this respect the stress techniques chosen are particular relevant. The analysis of regional wall motion in

exercise radionuclide angiography adds little to the sensitivity and it is reported that only 50% of patients have exercise induced wall motion defects by this technique.(65) Reports of wall motion abnormalities for isometric handgrip and cold pressor are of similar proportions.(66) However computer assessment and measurement of regional ejection fraction can improve on these figures to the extent that Bodenheimer and his colleagues report 86% sensitivity for the detection of coronary artery disease when used with first pass studies.(67) Since first pass studies allow RAO and LAO views to be taken then the incidence of abnormality detected by gated studies may not be so high. However since they do acquire and average much larger numbers of beats then they are likely to be more reproducible. It is reasonable to expect therefore that gated technetium angiography in the LAO view in conjunction with cold pressor or isometric handgrip would provide the best technique for a study of this nature. Cold pressor has the further advantage of being independent of physical exercise and perhaps therefore divorced from the effect of training on the muscles. Although regional ejection fraction has been reported to be superior to regional wall motion, an analysis of wall motion by a semi-quantitative technique was also carried out in order that this might be compared to the results of exercise echocardiography by the technique now outlined below.

Exercise echocardiography

Compared with the nuclear techniques described above, exercise echocardiography remains experimental. It does however

have theoretical advantages over the nuclear techniques which suggested that it might be useful in this study. As previously mentioned the practicalities of our nuclear cardiology laboratory and gamma camera prevent the use of exercise stress with gated technetium bloodpool angiography. Our echocardiographs however are carried out using a Hewlett Packard 2-dimensional scanner which is portable and can be accommodated beside a motor driven treadmill. In those laboratories which can carry out exercise technetium bloodpool angiography one of the major limitations has been patient movement. The acquisition of a gated equilibrium scan requires that the heart remains in the same position relative to the camera throughout the period of acquisition. While this is easily accomplished at rest, it is extremely difficult on exercise. Devices have therefore been created which require the patient to hold handgrips on the camera or to be strapped to the table to minimise chest movement. Supine bicycle ergometry has been found to be better than treadmill exercise in this respect, but in both cases there is inevitable movement artefact which diminishes the reproducibility of exercise studies even with respect to global function. When one considers regional left ventricular function clearly the errors introduced by patient movement make the detection of regional abnormalities at best inaccurate. To use such a technique to monitor changes in these areas over time would be fraught with problems. Echocardiography uses single beat analysis and whether carried out visually or by computer uses landmarks within the left ventricle itself rather than externally fixed landmarks and in this respect is not

dependent on patient movement. Patient movement is however essentially as difficult a problem in other respects. Firstly it may be impossible to position the transducer during exercise to allow recording of an image of sufficient quality to analyse and secondly the view obtained may vary in position from that obtained pre exercise. Indeed the view obtained in some cases may vary from beat to beat or during beat. Again mechanical devices have been designed to fix the transducer to the patient's chest in an attempt to overcome these problems. Despite this, early 2-dimensional scanners produce scans suitable for analysis in about 70% of individuals only.(68-70)

Limacher in 1983 published details of his methods of post exercise echocardiography where scans were recorded pre and post treadmill exercise.(71) This removed the artefact associated with exercise leaving only the problems of tachypnoea and tachycardia with which to contend. He found that apical views could be obtained in 86% of patients after exercise and parasternal views in 83% He measured ejection fraction pre and post exercise and wall motion using a semi quantitative scoring system. The results of this technique for the detection of the range of severity of coronary artery disease compared favourably with that of change in ejection fraction on exercise by radionuclide ventriculography. He found that exercise induced abnormalities in wall motion were present in most cases for several minutes after exercise.

In order to use this technique as a follow up tool, the above method would be most appropriate in that it would allow the

patients to be positioned in a similar way for repeat scans. A couch was therefore positioned next to the treadmill and immediately exercise stopped the patient lay on the couch in a semi prone position lying on his left side with a 45° wedge cushion under the right side. His left arm was raised with the hand behind his head to "open up" the intercostal spaces. The apex beat was located and apical four chamber and apical two chamber or apical long axis views were recorded. The use of these views and identical positioning meant that the views were as reproducible one year apart as was practically possible. In most cases recognition of the apex beat was facilitated after exercise. In all cases scans were recorded within a time limit of five minutes after cessation of exercise.

Having acquired these scans it was important to identify which data were going to be most useful. In this respect there were two factors which most influenced the decision and indicated the complementary roles of exercise echocardiography and gated technetium bloodpool angiography. As previously mentioned, in this laboratory it has been found that ejection fraction analysis using cold pressor stress is a relatively insensitive technique for detection but a good tool for follow up of patients with coronary artery disease. Initial experience with exercise echocardiography demonstrated a number of factors which suggested that despite Limacher's success in identifying coronary artery disease using 2-dimensional echocardiography, and despite the advantages of using exercise rather than cold pressor stress, this technique could not be used with confidence in this study to

follow up changes in ejection fraction. Firstly, unlike technetium angiography, 2-dimensional echocardiography is by definition 2-dimensional. Since myocardial ischaemia is a local phenomenon the measured ejection fraction is very dependent on the view chosen. Minor changes in that view may therefore produce alterations in measured ejection fraction. Despite attempts to standardise the technique it was not possible to produce comparable results in individuals scanned on consecutive weeks, particularly in terms of absolute figures. The above problem is compounded by the fact that analysis of ejection fraction by 2-dimensional echocardiography is on the basis of a single beat. It is necessary to average the results of several beats to produce a figure. On doing so it is clear the problems related to the above exaggerate the normal beat to beat variability in ejection fraction. The final, and perhaps most important factor, is that the method used measures ejection fraction during a recovery period when it will inevitably be changing both as a result of change in physical activity and as a result of recovery of myocardial ischaemia. The former would be tending to reduce ejection fraction while the latter would increase it. The normal tendency for ejection fraction to rise on exercise is blunted in the patient with ischaemic heart disease by local myocardial dysfunction. During recovery the ejection fraction may rise if myocardial ischaemia reverses first, fall if myocardial ischaemic is prolonged after recovery from exercise, or remain unchanged if the two factors reverse at the same rate. Exercise training is associated with more rapid recovery in the post exercise period.

Heart rate and ejection fraction fall more rapidly. If exercise training were to produce an improvement in myocardial ischaemia and hence an improved ejection fraction response to exercise then this benefit may well be missed as a result of more rapid recovery of a resting state.

Adding the above deficiencies together with the difficulties in obtaining technically good "echos" in a population of middle aged overweight men with ischaemic heart disease, it was evident that for the purposes of this study ejection fraction analysis using exercise echocardiography would not be reproducible and would be of little value. It was therefore not assessed further.

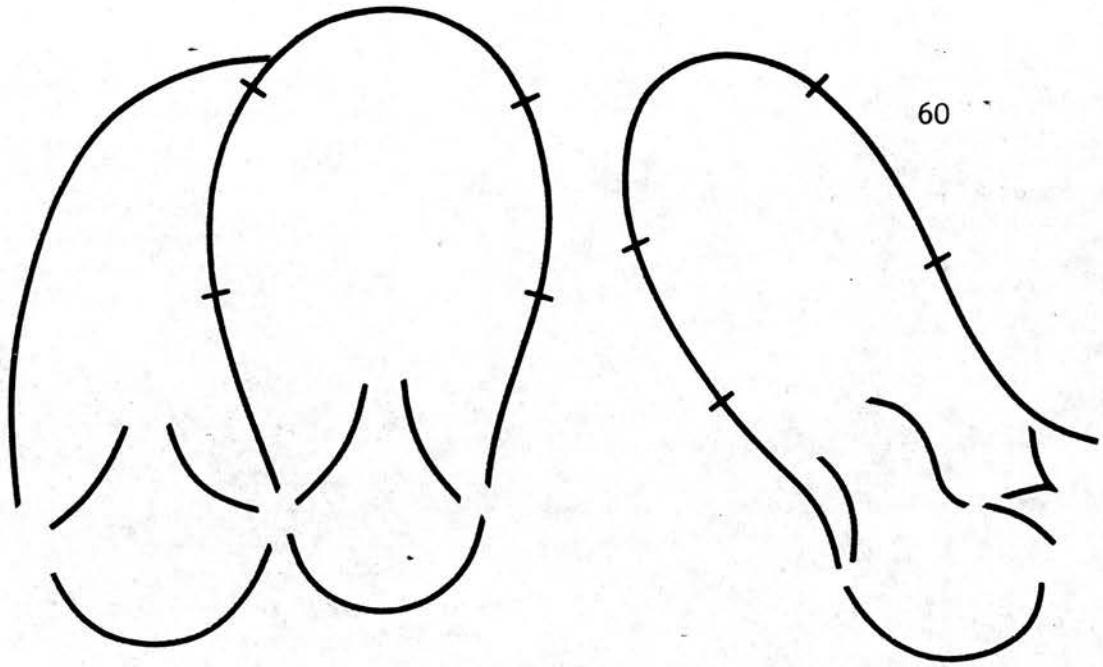
The disadvantages of echocardiography with respect to ejection fraction measurement are however advantages when one considers wall motion analysis. As described in the previous section, wall motion analysis was carried out on the LAO view using technetium angiography. Neither the edge detection method nor the regional ejection fraction method is however a true assessment of wall motion. Both imply wall motion by change in blood isotope activity. Echocardiography on the other hand demonstrates the left ventricular wall and since it is 2-dimensional can be angled to demonstrate different areas of the left ventricle. As shown in other studies wall motion defects produced on exercise persist for several minutes after recovery allowing time to demonstrate them.(71) It was therefore decided to use exercise echocardiography solely to measure resting and exercise induced abnormalities in the wall motion.

Abnormalities in wall motion may be measured quantitatively

or semi quantitatively. In the former method the images are frozen in end diastole and end systole, contours are drawn round the endocardium and a computer programme used to measure segmental change in internal radius. To be accurate it is important that the end diastolic and end systolic views are through the same plane. This is achieved best by asking the patient to stop breathing after a normal breath out. While this is relatively easy at rest, it is difficult to achieve immediately post exercise. Furthermore recognition of endocardium after exercise can be difficult. Attempts to analyse the scans using a commercially available software package demonstrated these difficulties and it was therefore decided that the semi quantitative method be used. The scans were recorded on video tape and played back with the aid of slow motion and frame by frame. The left ventricle was divided into five segments on each view and scored 0 - 4 as shown in Figure 10. The advantage of this technique is that it makes best use of the ability of 2-dimensional echocardiography to show continuous movement of the left ventricular walls throughout the cardiac cycle demonstrating areas of delayed wall motion not seen on methods employing end diastolic and end systolic frames only.

Of all the methods used in this study, this one potentially has the most significant observer error input. It was therefore necessary to assess inter and intra observer error during the study. The scans were analysed by two observers, one of whom was blinded to the identity of the patients and to which group they belonged. Pre and post intervention scans were processed in

Pre ex



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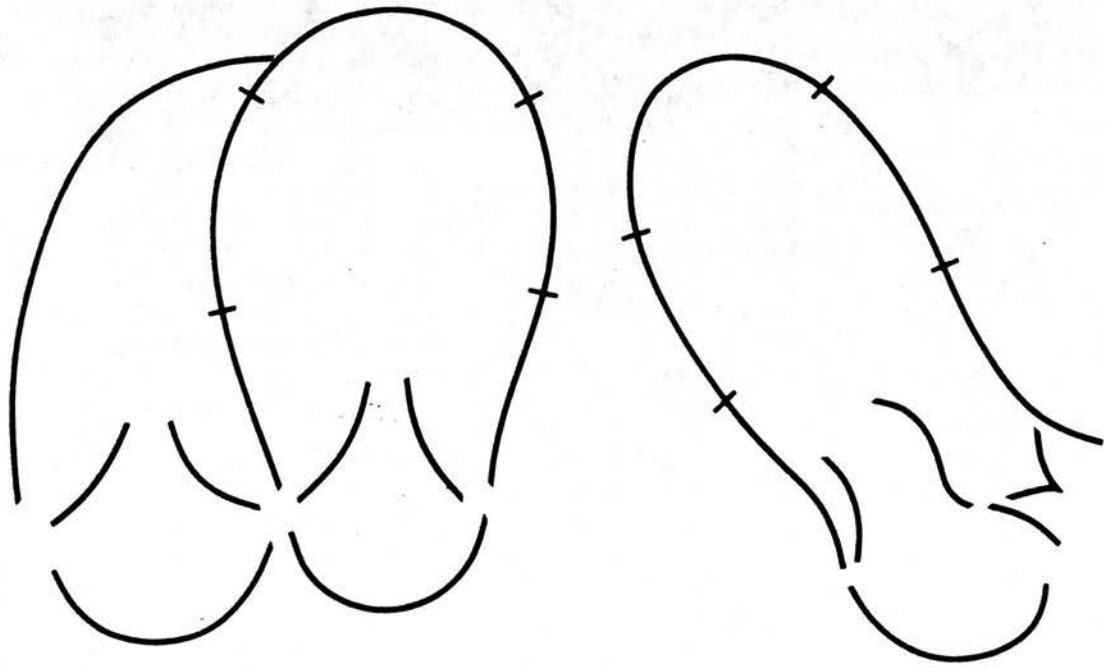


4 Normal

3 Hypokinetic

2 Severely hypokinetic

1 Akinetic

0 Dyskinetic

Figure 10 Exercise echocardiography scoring system

random order and in the first instance as individual scans. Pairs of scans were subsequently assessed in random order to directly assess any one year interval difference. Where the two observers differed in their assessment, scans were viewed by both observers together and if a consensus was not reached then a third observer was sought. Details of the assessment of intra and inter observer error are contained in the appropriate results section.

Ambulatory ECG Monitoring

The preceding investigative techniques provide a comprehensive study of myocardial perfusion and function in the laboratory setting. It is becoming increasingly apparent however that the assessment of ischaemic heart disease is incomplete without some measure of ischaemic activity outside the controlled environment of the exercise laboratory. The development of frequency modulated ambulatory ECG records now allows accurate monitoring of ST segment changes and has revealed information which makes such monitoring more vital, not only in the assessment of the disease, but also in the assessment of therapy.

Several authors have shown that angina pectoris accounts for only one quarter to one third of ischaemic episodes, the majority being unassociated with pain.(72-76) Such "silent" episodes may relate to alterations in the pain threshold or to other, as yet, unidentified factors. Whatever the aetiology they have the same characteristics as painful episodes and as such may well have the same clinical significance.(74,75) It has also been shown that the majority of episodes of ischaemia on Holter monitoring,

whether associated with angina or silent, are not secondary to increase in myocardial oxygen demand.(73-76) As such it is probable that they are secondary to alterations in myocardial oxygen supply. These facts raise therefore two important aspects of any therapy which ambulatory monitoring alone can address: the effect on silent ischaemia and the effect on ischaemia due to reduction in myocardial oxygen supply.

These areas have particular relevance to the question of the anti anginal efficacy of exercise training. As discussed in the introduction, the proven efficacy of exercise training relates to its effect on exercise induced increases in heart rate. This remains the only unequivocal effect of exercise training. If the majority of episodes of angina are not exercise induced then what effect can training have on these episodes? This question has not been addressed previously and will be covered in this study. Patients on training programmes report less angina and some become asymptomatic. Does this mean that they have fewer ischaemic episodes or have we merely changed then from painful to silent by raising their pain threshold for example by increasing endogenous opiate production? Answering these questions may reveal something not only of the effects of exercise but also of the nature of ischaemic episodes.

In this study Holter monitoring was carried out using the Oxford Medilog 4000 (MARS) ambulatory ECG recorder. This frequency modulated recorder has a frequency response of 0.05 - 40 hertz and a signal to noise ration of better than 30 decibels. The recorder processes each complex in real time and stores the

information on cassette tape. The information is later retrieved by playing the cassette through the Oxford Medilog MARS replay system. To ensure optimum quality, recorder heads were cleaned before each use and new batteries were used for each recording. Cassette tapes were demagnetised before use. Skin preparation is essential to the recording of accurate ST segment information. The chest was therefore shaved if necessary and the area of skin prepared by rubbing with an abrasive paste to remove the stratum corneum. Electrodes were then applied to the chest over bony sites as shown in Figure 11. This produced a recording of leads CM5 and a modified lead 2. An impedance meter was used to ensure the resistance between electrodes was less than 5 k ohms. The leads were then attached to the patient with surgical tape incorporating stress loops to reduce artefact due to lead movement. The whole electrode system was further fixed using an elastic vest and the recorder 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 commencing the recording. Two other channels on the recorder recorded a quartz time signal and a flutter compensation signal during the 24 hours.

The patients were instructed to wear the recorder during a "normal" day in mid week avoiding any period of activity which was outwith the usual routine. Those patients randomised to the exercise group were instructed to ensure that they carried out their exercises on one occasion at least during the 24 hours.

In addition to ST segment analysis, data were collected on

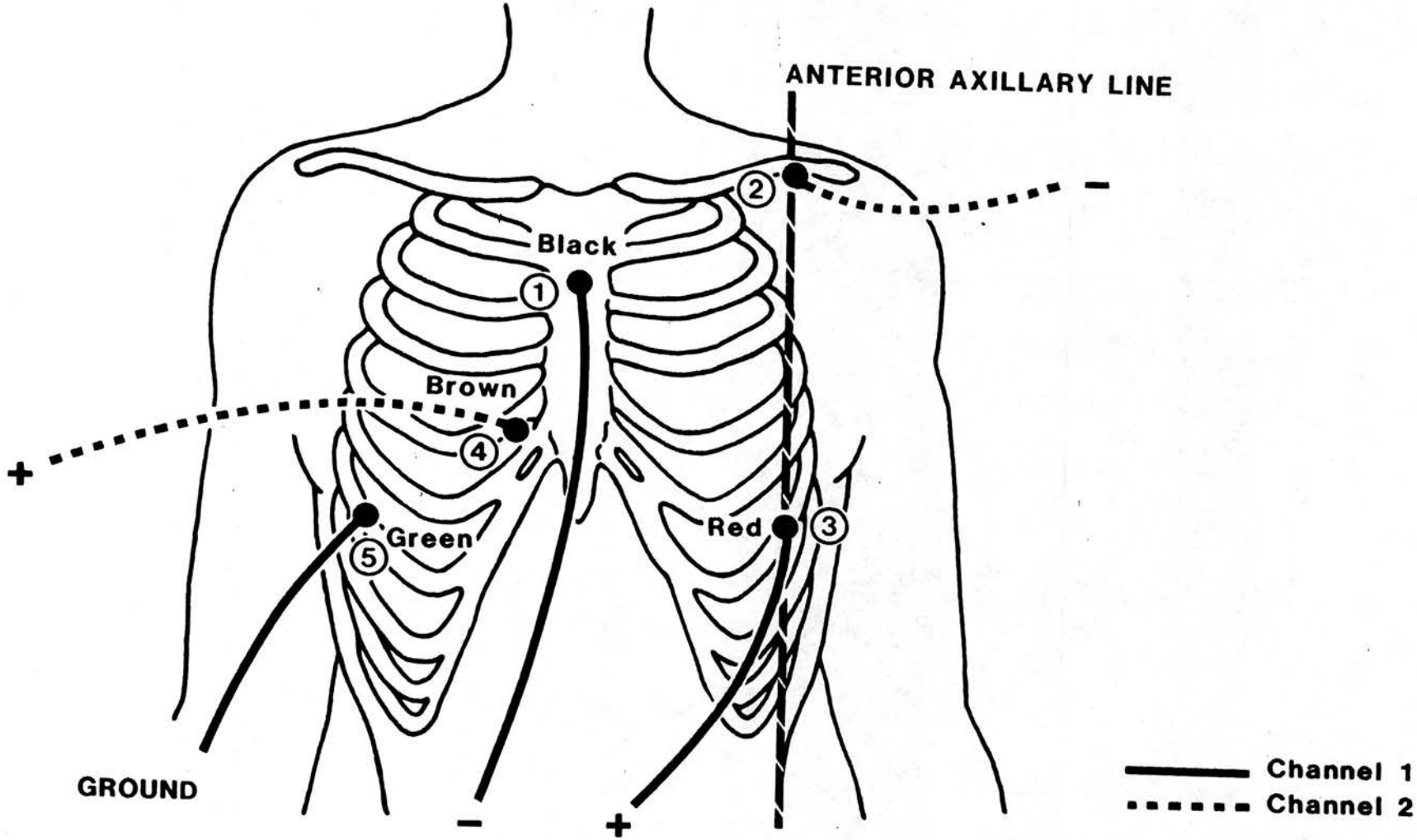


Figure 11 Lead positions for ambulatory electrocardiography
Electrodes 1 and 3 provide CM5 recording and electrodes 2 and 4 record lead I

minimum, mean and maximum heart rates and on arrhythmias. The definition of these and the details of tape analysis are contained in the results section.

11.4

STATISTICS

Statistical advice was obtained from a medical statistician at the outset of these studies. It was considered impractical and indeed unnecessary to attempt to correlate the results of one method of investigation with another. The authors view that each technique should be studied alone and then used to add to the overall consideration of the hypothesis was felt to be appropriate for a small study of this nature.

By chosing to carry out the tests on only two occasions, before and after intervention, the statistics were greatly simplified. Where data were found to be normally distributed, or could be made to fit a normal distribution by transformation, a Students 't' test was used. A paired 't' test was used for intragroup analysis and an unpaired 't' test for intergroup analysis. The corresponding tests for non-normal data were a Wilcoxan signed rank test and a Mann Whitney 'U' test.

There was considerable discussion over the need to use the Bonferroni correction for multiple comparisons. It was felt that in most instances the parameters were not randomly chosen but selected to study different effects of training and therefore Bonferroni was neither necessary nor appropriate. In a few

instances such as the measurement of stage 1 and 2 heart rate in the exercise tolerance data however Bonferroni should be used if there were a discrepancy between the results of these two parameters. For wall motion data, one might expect to find changes confined to certain regions. The use of the Bonferroni correction for such results would serve only to mask them. Since the possibility of disparate regional results is acknowledged from the outset, the use of the Bonferroni correction was not necessary. One must nonetheless acknowledge the possibility of spurious results in such instances and this has been done where required.

Other statistical tests have been used in individual studies and these are discussed in the appropriate subsections of section 2.

SECTION III

RESULTS

In this section the results of the investigations described in the previous section will be considered in the order in which they were described in that section. A general consideration of the clinical outcome of the study covering patient performance and symptomatic improvement in addition to specific clinical events will be dealt with in section IV as part of the general discussion of the study. Although the same study group is involved throughout the investigations covered in this section, each of those investigations will be dealt with separately in its own sub section, the whole being considered in more detail also in section IV. The description of each sub section will consist of a brief summary of the method detailed previously, the results obtained using that method and a discussion of the interpretation of those results with appropriate references. It is the aim of this section to deal with the investigations in a manner which provides a step-wise answer to the central question regarding the effect of exercise training on the hearts of individuals with angina pectoris.

THE EFFECT OF EXERCISE TRAINING ON TREADMILL PERFORMANCE

Methods

The technique of treadmill exercise tolerance testing has been described in detail already. All patients underwent a familiarisation treadmill test prior to measurement of treadmill values which were obtained between 9.00 a.m. and 10.00 a.m. after 12 hours fasting and 24 hours after the last dose of plain nifedipine or isosorbide dinitrate. The treadmill protocol produced a linear increase in workload and heart rate, the rate of change of each being 1 MET and 4 to 5 beats per stage respectively. This allowed accurate measurement of end points. The parameters measured fall into three groups:

a) those which measure degree of fitness

b) those which measure disease severity

c) those which measure the combined effect of a) and b).

a) Parameters of physical fitness: These consist of resting and sub maximal heart rates. An improvement in physical fitness is manifest by a fall in resting heart rate and a fall in heart rate at a given level of exercise. Conversely a deterioration in fitness e.g. due to prolonged bed rest, leads to a rise in resting and sub maximal heart rates. All patients were able to exercise at least to stage II of the treadmill protocol on both occasions. The parameters of resting, stage I and stage II heart rates are therefore used for intra and inter group comparisons.

b) Parameters of disease severity: In patients with angina

pectoris ischaemia occurs when myocardial oxygen demand exceeds the ability of the stenosed coronary artery to supply that demand. Myocardial oxygen demand measured at the end of an exercise tolerance test is therefore equivalent to maximal myocardial oxygen supply. The maximum treadmill heart rate and double product of maximum heart rate x systolic blood pressure can be used as measures of myocardial oxygen demand and hence maximum myocardial oxygen supply at peak exercise.(77-79) Myocardial oxygen demand measured in this way has been shown to be a reproducible end point in stable angina pectoris.(80-82) Since the exercise test is symptom limited however, one requires, in addition, a more objective measurement of disease severity. The degree of ST depression is believed to reflect the severity of underlying ischaemia. In addition to measuring maximum heart rate and double product therefore, maximum ST depression is also assessed. Finally these two types of measurement can be combined in the double product/ST threshold which is the double product at which 1 mm of ST depression is first recorded. These four parameters of disease severity are therefore measured.

c) Combined parameters: Physical fitness and disease severity combine to produce the two most basic treadmill parameters of treadmill time and treadmill workload. Both improvements in fitness and disease severity will increase these parameters.

Statistical Analysis

A Student's 't' test (two-tailed) was used to compare baseline data for training and control groups. Where data did

not conform to a normal distribution or where variances differed by an 'F' test, the data were transformed to logarithms to allow the use of the Student's 't' test. In such cases the log results are given in addition to the actual results. Intragroup comparisons of baseline and one year data were made using a paired 't' test (two-tailed), again with log transformation where necessary. For this data the 95% confidence intervals for the difference between the means is also given where differences were statistically different.

Interval change was also measured for all data in both groups. Intergroup comparison of this data was made using a Mann Whitney 'U' test since three sets of interval data could not be normalised and the variances between groups differed significantly for five of the ten parameters. For those parameters where baseline data for the exercise group differed substantially from that of the control group, a scatter plot of initial measurements against interval change was made. Linear regression analysis was carried out to check for a correlation between interval change and baseline measurements. In no case was such a correlation found. The above statistical comparisons of interval change were therefore deemed valid.

Results

Randomisation produced groups where baseline measurements differed statistically in only one respect. The mean maximum ST depression for the control group (1.5 $\pm$ 0.8 mm) was significantly less than that for the exercise group (1.9 $\pm$ 0.9 mm). However, as shown in Table 2 other parameters did show quite large variations which were nevertheless not statistically significant.

Most notable among these differences is the time to 1 mm ST depression, that for the controls being double the result for the exercise group. The overall trend was for the exercise group to be less fit as measured by resting and sub maximal heart rate and to have more severe disease as measured by maximum heart rate and double product, maximum ST depression and double product ST threshold. As a result the combined parameters of performance showed a trend for poorer performance among the exercise group at the outset. These trends are most important when one considers the extent of change after training since one might postulate that irrespective of training effect the extent of change might be proportional to the severity of abnormality at the outset. It was important therefore to examine this relationship. The graph of time to 1 mm ST depression against change in time to 1 mm ST depression is shown in Figure 12. For this and all other parameters as mentioned in the statistical analysis section, no linear relationship was found.

Table 3 shows the comparison of measured variables before and after training. Resting and sub maximal heart rates were lower after training, although the fall in resting heart rate just

Table 2

Baseline exercise tolerance parameters

Variable	Training group (mean±SD)	Control group (mean±SD)	'p' value ('t'test)
Resting HR	81 ± 12	74 ± 10	NS
Stage I HR	111 ± 19	106 ± 16	NS
Stage II HR	116 ± 19	110 ± 18	NS
Max HR	128 ± 17	136 ± 22	NS
Max DP ($x10^2$)	219 ± 55	259 ± 74	NS
Max ST dep (mm)	1.9 ± 0.9	1.5 ± 0.8	< 0.05
DP/ST threshold	183 ± 51	227 ± 75	NS
Time to 1 mm ST dep (sec)	374 ± 369*	719 ± 560	-
Log time to 1 mm ST dep	2.37 ± 0.44	2.68 ± 0.46	NS
Treadmill time (sec)	741 ± 356	1006 ± 504	NS
METS	6.3 ± 1.9	7.8 ± 2.8	NS

* Non-normal data by "goodness of fit" test

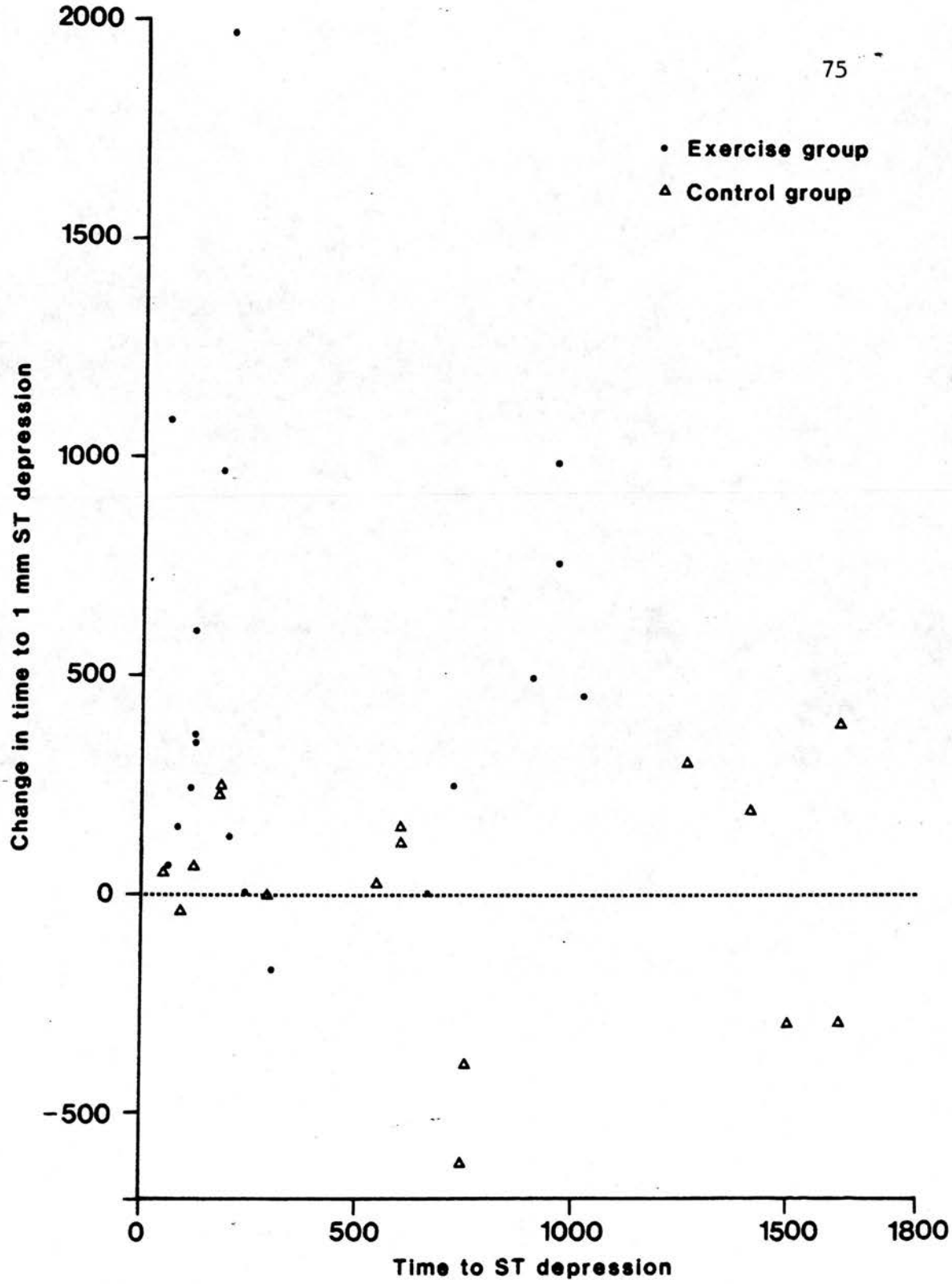


Figure 12 Graph of baseline time to 1 mm ST depression against interval change in time to 1 mm ST depression

Table 3

Pre and post study exercise tolerance parameters - training group

Variable	Pre (mean±SD)	Post (mean±SD)	'p' value (paired 't'test)	95% C.I.
Resting HR	81 ± 12	76 ± 10	NS	-
Stage I HR	111 ± 19	98 ± 15	< 0.001	6 - 20
Stage II HR	116 ± 19	103 ± 16	< 0.01	5 - 21
Max HR	128 ± 17	138 ± 21	< 0.05	2 - 18
Max DP ($x10^2$)	219 ± 55	244 ± 67	NS	-
Max ST dep (mm)	1.9 ± 0.9	1.6 ± 1.2	< 0.05	0.1 - 0.7
DP/ST threshold	183 ± 51	205 ± 64	NS	-
Time to 1 mm ST dep (sec)	374 ± 369*	881 ± 668	** -	-
Log time to 1 mm ST dep	2.37 ± 0.44	2.79 ± 0.41	< 0.001	0.23 - 0.61
Treadmill time (sec)	741 ± 356	1272 ± 514	< 0.001	303 - 759
METS	6.3 ± 1.9	9.5 ± 2.9	< 0.001	2.0 - 4.4

* Non-normal data by "goodness of fit" test
** Variances differ by 'F' test

failed to achieve statistical significance. Figure 13 shows an extended graph of heart rate against workload before and after training showing that the relationship is linear and a reduction in heart rate is maintained at higher workloads.

Maximum heart rate increased by ten beats per minute with a corresponding rise in maximum double product which nonetheless failed to reach statistical significance. While the individual increases in maximum heart rate were in most cases modest, the graph of individual results in Figure 14 shows that some patients achieved large increases. Despite the overall increase in maximum heart rate, this was associated with a decrease in maximum ST depression from 1.9 $\pm$ 0.9 mm to 1.6 $\pm$ 1.2 mm. There was a trend towards improvement in the double product/ST threshold which failed however to reach statistical significance.

Combining the above parameters produced highly significant increases in time to 1 mm ST depression (374 $\pm$ 369 seconds to 881 $\pm$ 668 seconds), treadmill time (741 $\pm$ 356 seconds to 1272 $\pm$ 514 seconds) and treadmill workload (6.3 $\pm$ 1.9 METS to 9.5 $\pm$ 2.9 METS).

Over the one year period the control group showed consistent results with respect to all parameters. There were no significant changes in any of the measured variables (Table 4).

Intergroup comparison of the one year interval change data confirmed that in all parameters, the results for the training group were better than those for controls. (Table 5)

With respect to resting and sub maximal heart rates, the difference between the groups reached statistical significance

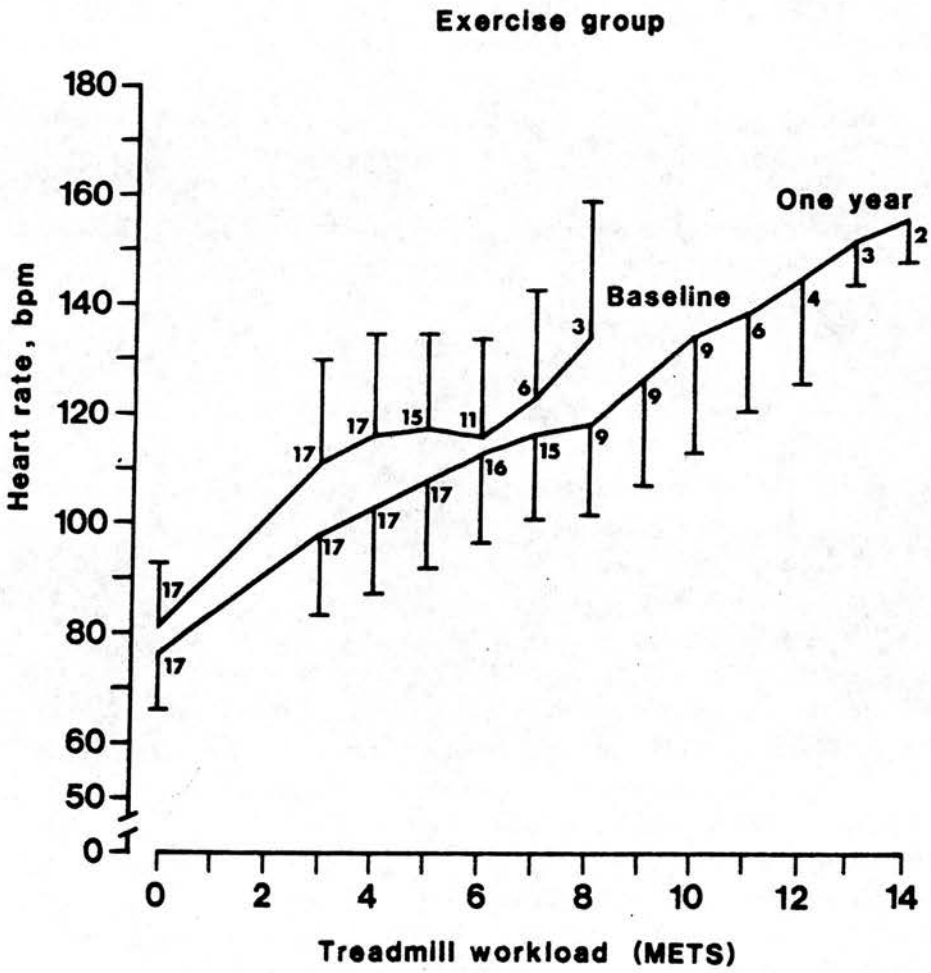


Figure 13 Graph of heart rate against treadmill workload

Exercise group

Number at each point refers to number of patients who achieved that workload

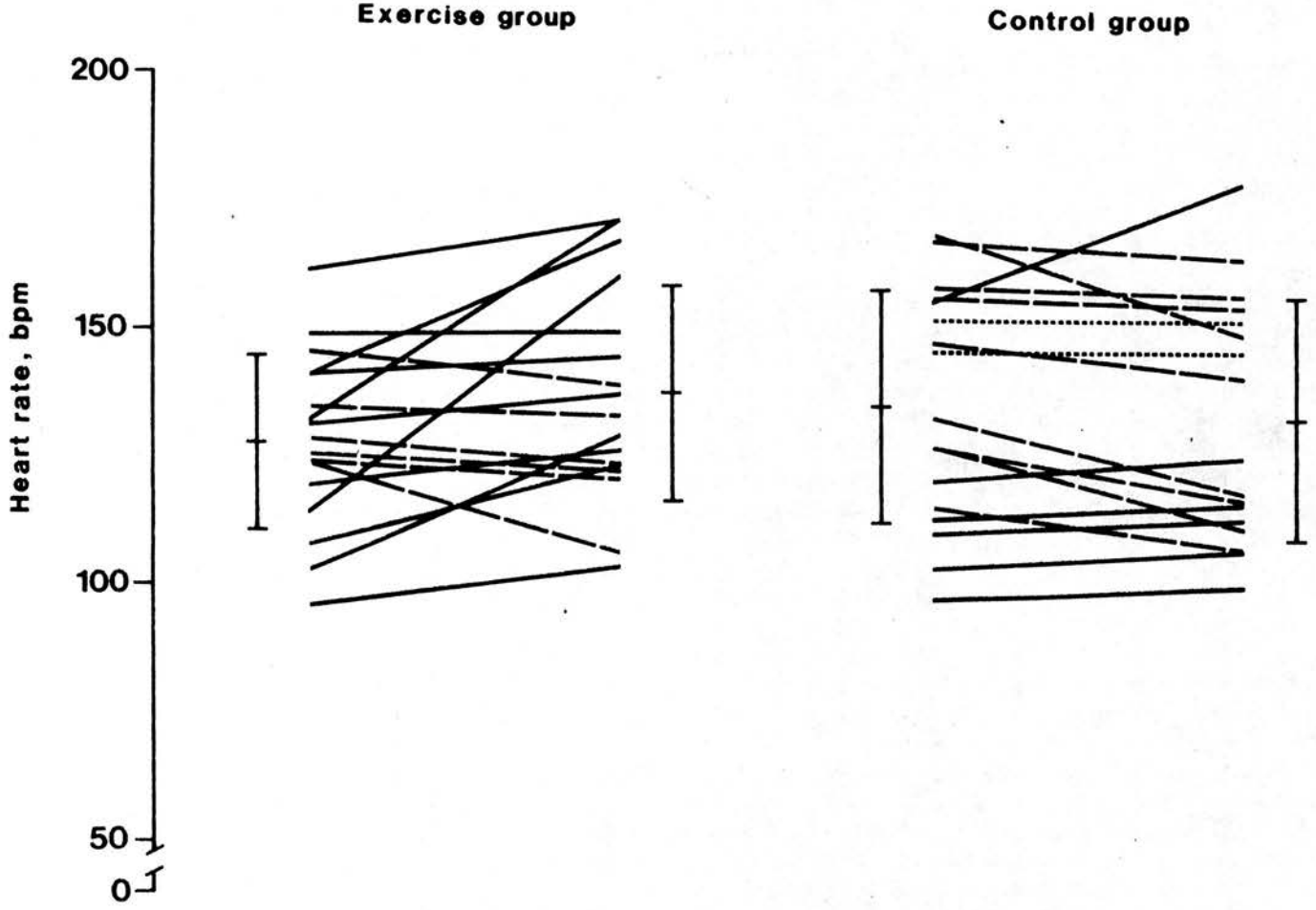


Figure 14 Individual change in maximum heart rate from baseline to one year

Dotted line = no change Hatched line = decrease in maximum heart rate
Closed line = increase in maximum heart rate

Table 4

Pre and post study exercise tolerance parameters - Control group

Variable	Pre (mean±SD)	Post (mean±SD)	'p'value (Paired 't'test)
Resting HR	74 ± 10	75 ± 9	NS
Stage I HR	106 ± 16	102 ± 10	NS
Stage II HR	110 ± 18	106 ± 10	NS
Max HR	136 ± 22	134 ± 24	NS
Max DP (10^2)	259 ± 74	248 ± 74	NS
Max ST dep (mm)	1.5 ± 0.8	1.4 ± 0.8	NS
DP/ST threshold	227 ± 75	206 ± 60	NS
Time to 1 mm ST dep (sec)	719 ± 560	715 ± 580	NS
Treadmill time (sec)	1006 ± 504	1010 ± 546	NS
METS	7.8 ± 2.7	8.0 ± 3.1	NS

Table 5

Interval change parameters of exercise tolerance

Variable	Interval change - training	Interval change - control	'p'value (Mann Whitney 'u'test)
Resting HR	-4.5 ± 14	+1.1 ± 10.4*	NS
Stage I HR	-13.4 ± 13.4	-4.6 ± 13.3	< 0.02
Stage II HR	-12.3 ± 16.2*	-3.9 ± 13.4	NS
Max HR	+9.5 ± 17	-2.0 ± 9.7	** < 0.02
Max DP ($x10^2$)	+25.6 ± 55.3	-10.9 ± 26.6	** < 0.02
Max ST dep (mm)	-0.4 ± 0.7	-0.1 ± 0.6	NS
DP/ST threshold	+23 ± 58	-17 ± 35	** < 0.02
Time to 1 mm ST dep (sec)	+507 ± 520	+6 ± 268	** < 0.002
Treadmill time (sec)	+531 ± 461	+4.6 ± 307	< 0.001
METS	+3.2 ± 2.5	+0.2 ± 1.5*	** < 0.0005

* Non-normal data by "goodness of fit" test
** Variances differ by 'F' test

only for stage I heart rate, the resting heart rate change being small, while the sub maximal heart rate change was partially offset by improvement in the control group.

For the parameters of disease severity the differences both for maximum heart rate and double product were significant at the 2% level. The changes in ST depression were not significantly different again due a slight improvement in controls. However, whereas the improvement in double product ST threshold in the exercise group failed to reach statistical significance by paired 't' test, the interval change data do show a significant difference between the groups at the 2% level.

As before the combined parameters again show a highly significant difference in all three when interval change data are studied.

Discussion

The common factor in all training schedules leading to improved exercise tolerance is the reduction in sub maximal heart rate. It has long been recognised that the origin of this reduction is peripheral and not cardiac. Figure 15 shows the control mechanism which is responsible for those changes. The cardiovascular control area in the mid brain modulates heart rate via vagal and sympathetic efferents. Among the afferents to this control area are fibres originating in stretch receptors in skeletal muscle. Use of these muscles leads to a reflex rise in heart rate. The more work the muscle has to do the greater the rise in heart rate. A trained muscle will respond with a smaller

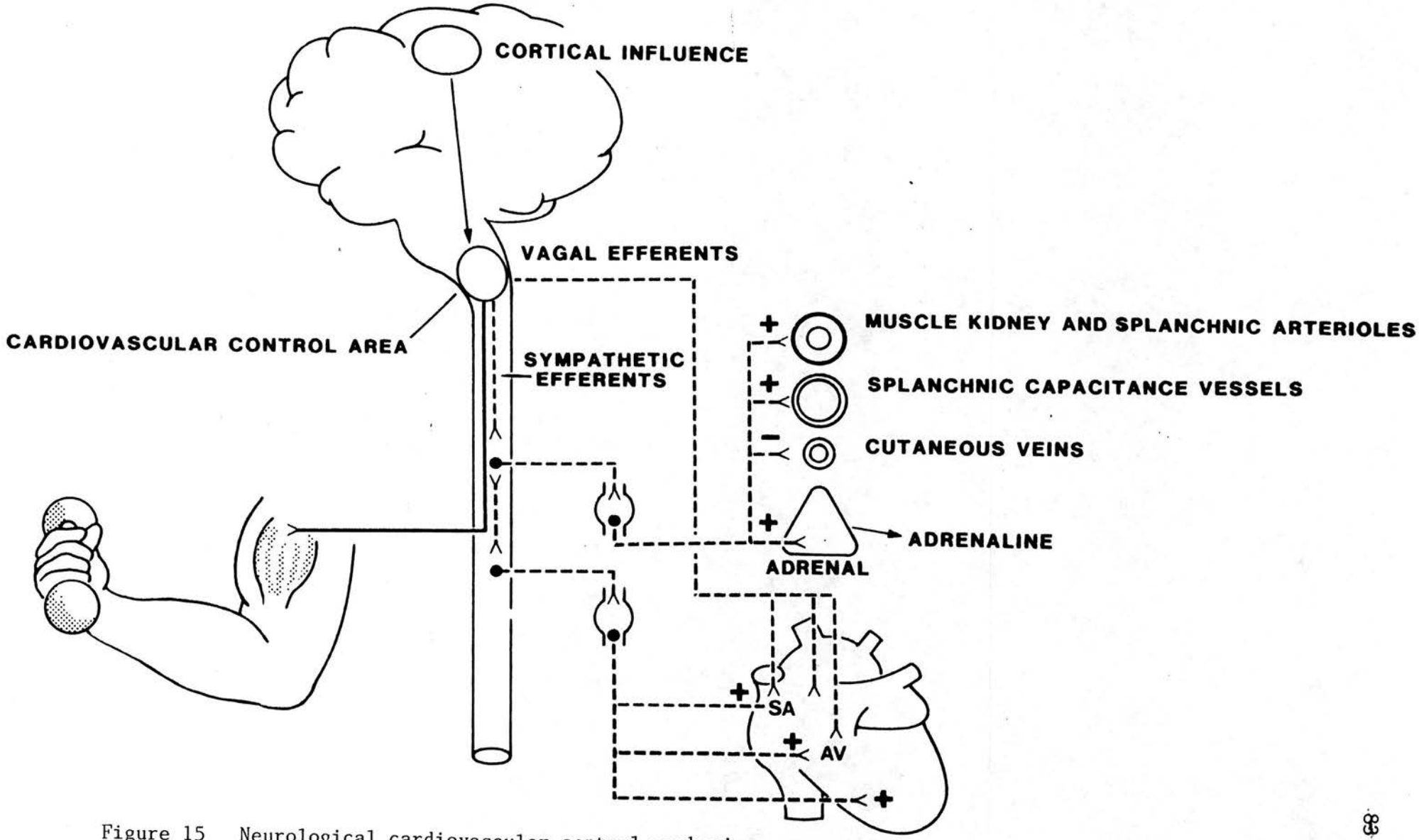


Figure 15 Neurological cardiovascular control mechanisms

incremental rise. It is clear also from this description that the training effect is muscle specific i.e. training of leg muscles only will have no effect on the heart rate response to arm exercise.(83) Early work suggested that minimum durations of exercise were necessary in order to achieve such reductions in heart rate, (84,85) and the guidelines for exercise training were established.(86,87) As a result the norm for programmes has been three sessions per week of 35 minutes minimum duration at 70% of maximum heart rate. This programme chose a more practical regime of 11 minutes of exercise each day. In addition supervision was kept to a minimum. It was important therefore that it should be shown to be effective in lowering sub maximal heart rate. The reduction in stage I and stage II heart rate of 13 beats per minute is comparable to that achieved by other programmes. Using gymnasium exercise to 60 to 70% of maximum heart rate for five hour long sessions per week Nolewajka et al reported a reduction in sub maximal heart rate of 14 beats per minute after seven months.(88) The same degree of reduction was found by Ehsani et al (89) using jogging and bicycle ergometry for similar periods each week up to 80 to 90% of VO2 max over a one year period. Such changes may be demonstrated by periods of training as short as six weeks.

While it is clear that the reduction in sub maximal heart rate, which is of peripheral origin, is the major factor responsible for the improvement both in symptoms and in exercise tolerance, it is those parameters which reflect disease severity which we must look at more closely if we are to consider changes

in myocardial perfusion. As mentioned earlier maximal treadmill heart rate or the double product of heart rate times systolic blood pressure is proportional to maximal myocardial oxygen consumption and for patients with angina pectoris has been shown to be reproducible. An improvement in these parameters would imply a greater maximal myocardial oxygen consumption and therefore an increase in myocardial oxygen supply provided there is no reduction in wall tension or contractility since these parameters also effect myocardial oxygen consumption. Endurance training causes left ventricular dilatation and this would tend if anything to increase wall tension. Evidence from other studies would also suggest that contractility on maximal exercise is likely to be increased or unchanged.(90-91) Do we therefore have evidence for a greater degree of maximum myocardial oxygen consumption? This study has shown a statistically significant rise in maximum heart rate of 10 beats per minute, but although double product increased by 11.4% after training this failed to reach statistical significance due to a lack of rise in maximum blood pressure. While the intergroup comparison of maximum double product did show a significant difference between the groups it is nonetheless disappointing that we have failed to demonstrate a greater rise in maximum double product.

One of the earliest studies to show a rise in maximum heart rate and triple product (heart rate x systolic pressure x ejection time) was reported by Redwood et al in 1972.(92) After only six weeks training they were able to show a 13.4% increase in triple product. It is interesting to note that all patients in the

study had angina and that exercise training was carried out at an intensity sufficient to produce angina, a theme central to the studies in this thesis. Redwood suggested that the increase in myocardial oxygen consumption may have three alternative explanations. It may indeed indicate improved myocardial perfusion. Alternatively alterations in the haemoglobin oxygen dissociation curve may allow a greater release of oxygen to the myocardium. The third possibility was that trained individuals might have a higher pain threshold. He noted that only three of seven patients had ST depression on exercise testing and none of the three increased triple product.

With the exception of Sim in 1974 (93) the majority of studies carried out in the next decade showed no improvement in maximum heart rate or double product.(88,94,95) It is tempting to suggest that this failure is related to the trend towards lower levels of exercise according to the guidelines outlined earlier. Certainly it was the aim of the studies throughout this period to keep exercise below the ischaemic threshold. During the last decade however, a number of authors have again reported an increase in maximum heart rate and double product.(27,59,61,62, 89,96,97)

While most of these studies have concentrated on the assessment of left ventricular function or perfusion, some have considered other ECG criteria of disease severity. In this study, the maximum ST depression decreased from 1.9 $\pm$ 0.9 mm to 1.6 $\pm$ 1.2 mm, despite an 11.4% increase in maximum double product. Ehsani et al (89) reported very similar figures in a

small group of patients on a one year high intensity programme. Such a reduction in ST depression makes it unlikely that a decreased pain threshold was responsible for the modest improvement in maximum heart rate shown here. However perhaps a more objective measurement is to look at the double product ST threshold. The double product/ST threshold is the double product at which 1 mm of ST depression occurs. The intra group comparison shows a 12.6% improvement in this parameter in the training group with a 7.5% deterioration among the controls. As with maximum double product, neither of these changes achieves statistical significance, although the intergroup comparison of interval change is significant. It would appear that there is some benefit in participation in this exercise training programme in terms of parameters of disease severity but the changes were small and the reason for them is unclear.

Raffo et al (27) and Winter et al (96) have studied patients on the Canadian Airforce PBX schedule in Leeds. The initial paper reported a six month study of 12 patients on the programme and 12 controls, while the second study looked at longer periods of training in nine of the original 12 in addition to a further eight patients. They did not measure symptom limited exercise tolerance but did report improvements in the heart rate/ST threshold and double product/ST threshold. Improvements in these parameters were found among the training group with deteriorations among the controls. This of course was the trend shown in this study. Both studies from Leeds and Ehsani's study used exercise of relatively high intensity in patients with ischaemic ST

depression and angina pectoris. The conclusions of both groups are similar. The finding of less ST depression at the same or greater cardiac workload implies better myocardial oxygenation, either secondary to improved perfusion or to biochemical changes allowing greater release of oxygen to the myocardium or more efficient usage of available oxygen.

The combination of improvement in fitness, in addition to improvement in the parameters of disease severity results in increases in exercise tolerance which are highly significant. An increase in time to 1 mm ST depression and treadmill time of 8 - 9 minutes represents a large improvement in exercise tolerance. An improvement in treadmill workload from 6.3 to 9.5 METS as shown by the training group has important implications in terms of patient activity. Table 6 shows activities estimated to be in the 5 - 7 METS and 9 + METS range.(98) It is therefore not surprising that patients on the exercise programme reported marked improvements in physical work capacity and in many cases a lack of exercise induced angina.

In summary therefore the exercise tolerance data has shown that a training effect can be obtained using this programme. This effect as in other studies is due mainly to peripheral adaptations which lead to a reduction in the chronotropic response to sub maximal exercise. It would appear that any improvement in maximal myocardial oxygen consumption is small. There is insufficient evidence here to support the hypothesis of improved myocardial perfusion, but equally the results do not exclude the possibility. It is conceivable that the treadmill parameters of

Table 6

Approximate energy requirements of selected activities

Category	Self-care or home	Occupational	Recreational	Physical Conditioning
Very light	Washing, shaving, dressing	Sitting (clerical, assembling)	Shuffleboard, horseshoes	Walking (level at 2 mph)
3 METS	Desk work, writing	Standing (store clerk, bartender)	Bait casting	Stationary (bicycle
10 ml/kg/min	Washing dishes	Driving truck, crane operator	Billiards, archery	(very low resistance)
4 kcal	Driving auto		Golf (cart)	Very light calisthenics
Light	Cleaning windows	Stocking shelves (light objects)	Dancing (social & square)	Walking (3-4 mph)
3-5 METS	Raking leaves, weeding	Light welding	Golf (walking)	Level bicycling (6-8 mph)
11-18 ml/kg/min	Power lawn mowing	Light carpentry	Sailing	Light calisthenics
4-6 kcal	Waxing floors (slowly)	Machine assembly	Horseback riding	
	Painting	Auto repairs	Volleyball (6 man)	
	Carrying objects (15-30 lbs)	Paper hanging	Tennis (doubles)	
Moderate	Easy digging in garden	Carpentry (exterior home building	Badminton, tennis	Walking (4.5-5 mph)
5-7 METS	Level hand lawn mowing	Shovelling dirt	Skiing, backpacking	Bicycling (9-10 mph)
18-24 ml/kg/min	Climbing stairs (slowly)	Pneumatic tools	Basketball, football	Swimming (breast stroke)
6-8 kcal	Carrying objects (30-60 lbs)		Skating, riding (gallop)	
Heavy	Sawing wood	Tending furnace	Canoeing	Jog (5 mph)
7-9 METS	Heavy shovelling	Digging ditches	Mountain climbing	Swim (crawl stroke)
25-32 ml/kg/min	Climbing stairs (moderate	Pick and shovel	Fencing, Paddleball	Rowing machine
8-10 kcal	speed)		Touch football	Heavy calisthenics
	Carrying objects (60-90 lbs)			Bicycling (12 mph)
Very heavy	Carrying loads upstairs	Lumber jack	Handball, squash	Running (>6 mph)
>9 METS	Carrying objects (>90 lbs)	Heavy labourer	Ski touring over hills	Bicycle (>13 mph or up
>32 ml/kg/min	Climbing stairs (quickly)		Vigorous basketball	steep hill)
>10 kcal	Shovelling heavy snow			Rope jumping
	Shovelling 10/min (16 lb)			

disease severity are determined not by the overall area of ischaemia but by that portion which is most ischaemic and which relates presumably to the degree of stenosis in the supplying vessel. In such circumstances one would expect a process such as angioplasty which reduces the severity of the culprit lesion to improve that most ischaemic region and hence those parameters of treadmill performance which reflect disease severity. Collateralisation within the vessel may likewise, by bypassing the lesion, effectively increase the blood supply down the vessel and hence should improve these parameters. Collaterals which pass from a donor vessel into the periphery of the ischaemic region may reduce the extent of that ischaemic region without materially altering the most significant area at its core. In these circumstances one would not necessarily expect to improve maximum myocardial oxygen consumption. Drawing on the analogy of coronary angioplasty again, in circumstances where two similar significant lesions exist, successful angioplasty to one lesion may reduce the area of ischaemia on exercise but if it is the other lesion which is the "culprit" lesion then treadmill performance may not be significantly altered despite a reduction in the area of ischaemia. Considering the wide variation in change in maximum heart rate in the exercise group shown in Figure 14 it is therefore possible that those patients who have shown a large increase in maximum heart rate have produced collaterals within the most severely diseased vessel and have to some extent bypassed the "culprit" lesion. The majority of patients have not produced such large improvements yet it is possible that they will

have reduced the extent of their ischaemic area by intervessel collateralisation. Clearly an assessment of changes in myocardial perfusion may yet hold the key to this question.

THE EFFECT OF EXERCISE TRAINING ON MYOCARDIAL PERFUSION

Methods

The technique of Thallium 201 scintigraphy has already been described in section II. In addition the further development of a computer assisted method of circumferential profile analysis has also been described. This programme generates a range of data and it was necessary to evaluate firstly which data were suitable for use in this study and secondly how to use such data. The two curves of immediate interest were the initial or stress profile and the washout profile. The BBC microcomputer programme which generates these curves superimposes them on a curve representing two standard deviations below the mean for a group of individuals with low probability of coronary disease. Each of the three views is subdivided into the outflow tract area and three regions of myocardium. A figure representing the number of degrees in each region for which the patient's curve falls below the normal curve is printed for stress and washout curves. The number of abnormal regions is also given. Since there are very few areas of operator input to this analysis programme and all scans were analysed by the author it was reasonable to expect that reproducibility of analysis would be high. However ten scans were analysed on two separate occasions by the author to confirm this view. For the stress curves the number of degrees of abnormality was found to be highly reproducible. The programme generates points at 6° intervals round the circumference. For five of the ten patients repeat analysis produced identical results. Four of the ten patients showed a difference of 6°

between the two analyses, confined to either one or two views. One patient only produced a 12° difference on one view. This patient had a large defect of some 192° in the view in question. In addition the curves on each occasion were of similar shape. The washout curves however were found to vary considerably when analysed on two occasions. Differences of 30 - 40° were commonly found. This was most probably related to variations in background subtraction. Each scan is background subtracted automatically after the observer uses a light pen to draw a region of interest around the heart. The amount of background subtracted may vary according to the position of this region of interest, in particular how close it is to the myocardium. Since each stress curve is drawn relative to its maximum rather than as absolute counts, then variability in extent of background subtraction has little effect on that curve. However the three hour curve is expressed as a percentage of the stress curve maximum also. If the areas of interest for stress and three hour curves are drawn identically on two separate occasions resulting in an equivalent amount of background subtraction on each curve, then the three hour curve will be reproducible. If however more or less background subtraction is carried out on either one or both of the stress and three hour curves, then the three hour curve will vary. Since washout is calculated by subtracting the three hour values from the stress values and expressing this difference as a percentage of stress values then the washout will also vary.

In addition eight patients underwent repeat Thallium

scintigraphy on two occasions, one month apart. In six of those cases, stress profiles were strikingly similar on two occasions an example being shown in Figure 16. Two patients however showed distinct changes in certain regions of the scans, while the rest of the scan showed little difference. This was interpreted as representing genuine day to day variation in regions of ischaemia, perhaps related to dynamic changes in stenoses of various vessels. Such a finding is shown in Figure 17. This finding limits the value of Thallium scintigraphy for the sequential analysis of individual patients and furthermore stresses the importance of having a control group with which to compare group changes. Regional washout analysis in this group of patients showed marked variability between the two occasions. Since washout has been shown to be affected by numerous factors (42,97,100) including heart rate, myocardial uptake relative to uptake in other organs, activity prior to and timing of the three hour scan and blood glucose and since it is affected by analysis method as described above, this finding is not surprising.

For the purposes of this study however, only the stress curve was used. While it has been shown that areas of myocardium supplied by diseased vessels may have normal stress values with low washout, these generally represent less severe stenosis and the washout curve is most useful in patients with totally normal stress curves but abnormal washout due to balanced triple vessel disease. All the patients in this study had abnormalities of stress curves. Analyses of these areas therefore represented analysis of the areas of more significant ischaemia. Furthermore

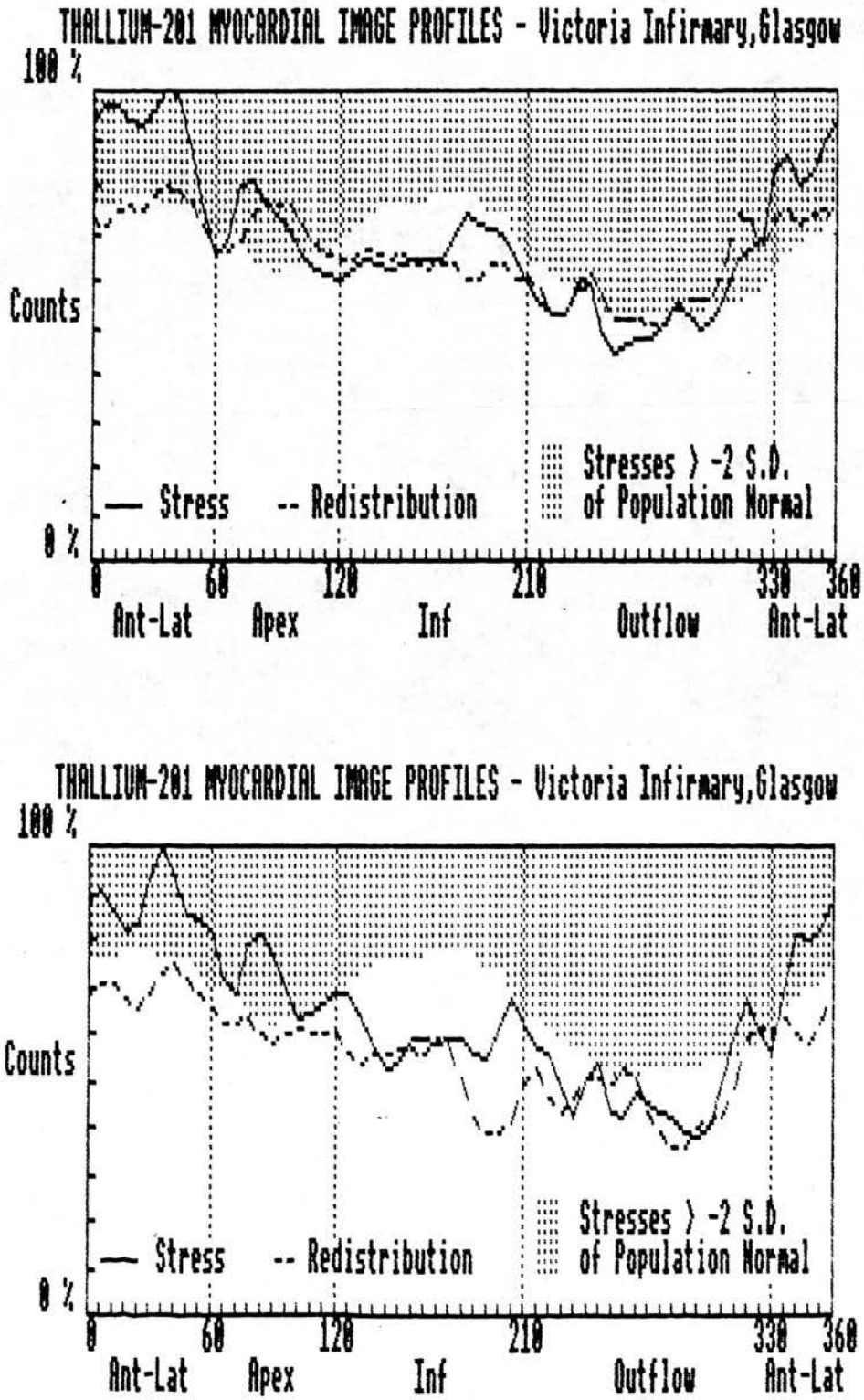


Figure 16 Reproducibility of stress Thallium circumferential profiles

(Anterior views taken 6 weeks apart)

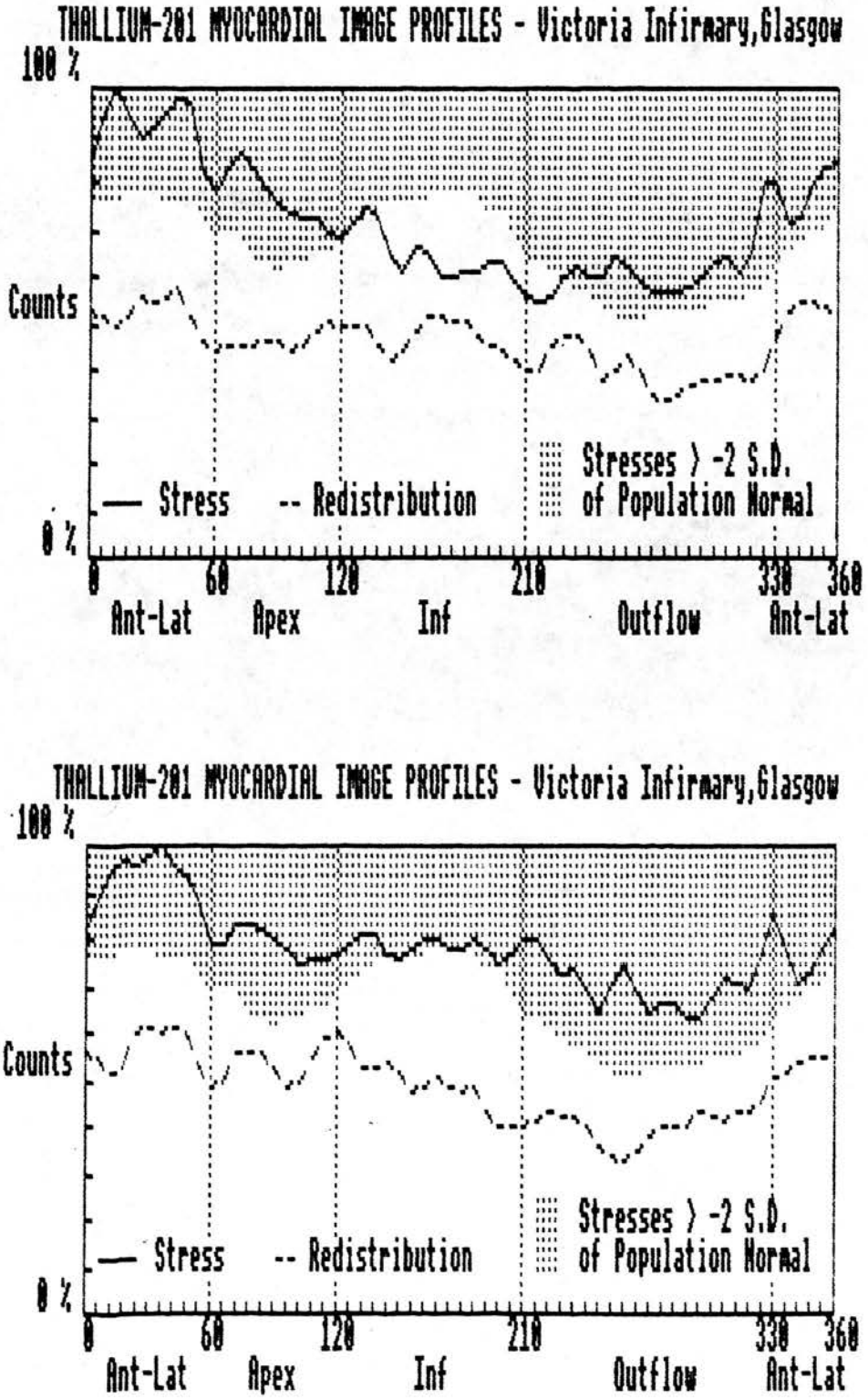


Figure 17 Variability of stress Thallium circumferential profiles (Anterior views taken 6 weeks apart)

since no patient had sustained prior myocardial infarction, these areas represent reversible ischaemia. Bearing in mind the hypothesis central to these studies i.e. that exercise induces ischaemia and that this in turn leads to improved collateral function, then these areas are precisely the ones which should be studied.

There are potentially two ways in which improvements in ischaemia may occur. There may be a reduction either in the extent of ischaemia, as measured by degrees of abnormality, or in the severity of ischaemia which may be related to either the depth of the defect or overall area of abnormality. In addition therefore to measuring the number of degrees by which the patient's curve fell below the "normal" curve the integrated area of that defect (Figure 18) was also calculated by subtracting the patient's curve area for the abnormal region from the normal curve area for that region. There are two ways in which the repeat Thallium study at one year could be carried out. Either the patient is exercised to the same heart rate on the second occasion as on the first (if possible) or the patient exercises maximally on both occasions irrespective of heart rate. Since adequate Thallium scanning relies on maximal exercise, the latter method was chosen. However since other authors have used the alternative method, those patients who exercised on the second occasion to a double product greater than 110% of the initial level were retested on a subsequent occasion to a level equivalent to that on their first test. It was found however that this produced in many cases a stress curve which bore little

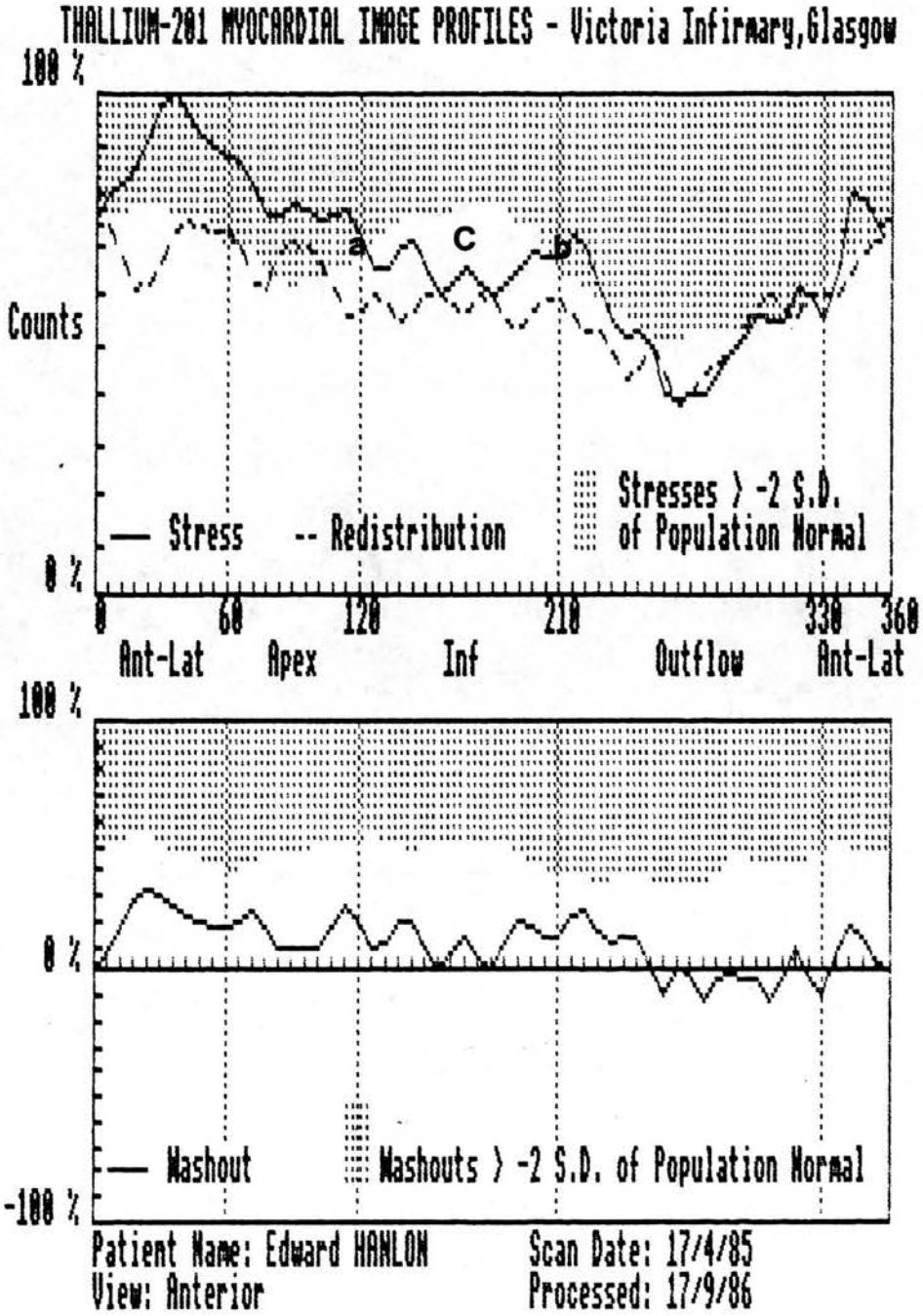
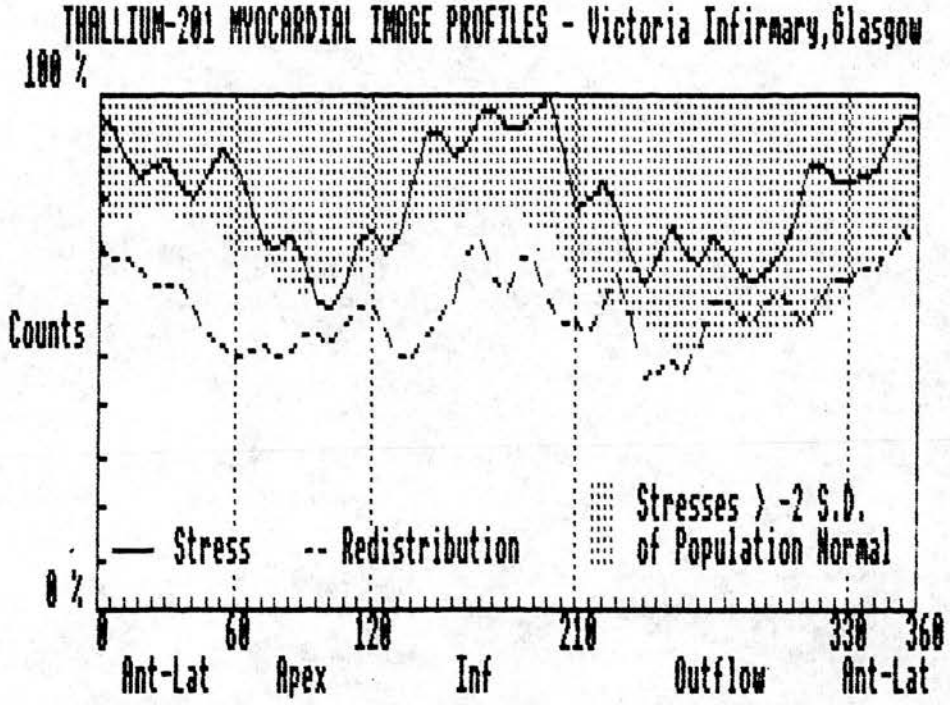


Figure 18 Calculation of ischaemic degrees and area from circumferential profile

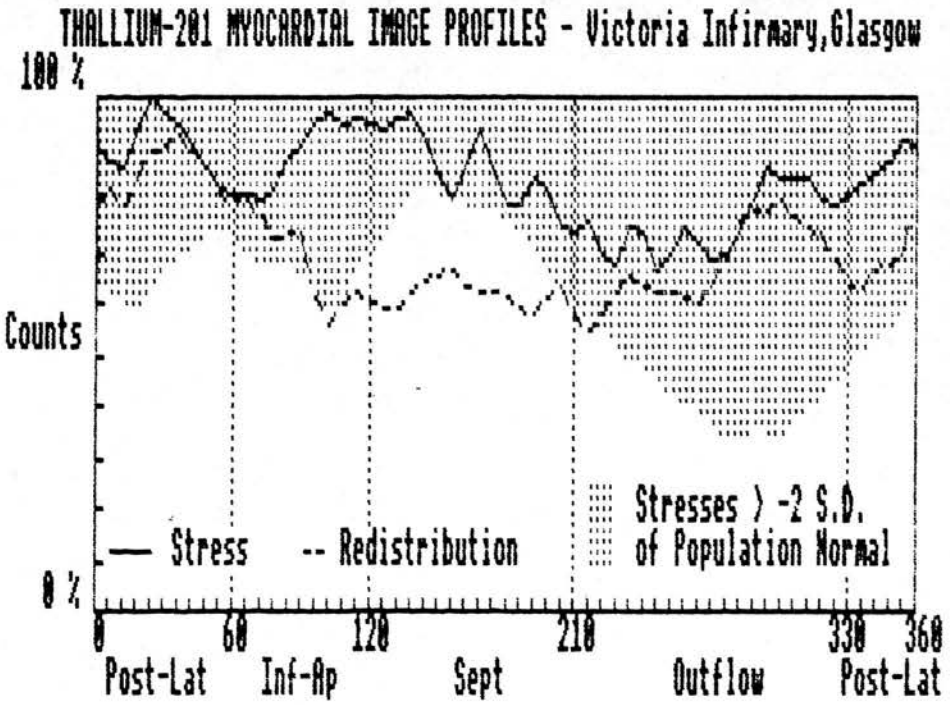
a - b = Ischaemic degrees
Area c = Ischaemic area calculated by subtracting area under patient's curve between a and b from area under normal curve between a and b

relationship to the original curve. In particular the point of maximal value was often entirely different making comparison of the curves impossible. Figures 19, 20 and 21 show three curves obtained in this way illustrating this finding. It seems therefore that the initial method used of maximal exercise is the most appropriate one for further analysis of degree and area of abnormality. In view of the variation in maximum double product and the possibility that the depth of abnormality might be constant for a given individual at onset of pain and therefore unchanged in a study to maximal exercise tolerance, a third parameter was assessed by correcting the area of abnormality by dividing it by the percentage of maximum heart rate achieved. This parameter is labelled the SIS score. A similar technique has been used by other authors.(101) They did not measure the "abnormal" area but measured the redistribution area between independently normalised stress and three hour curves plus the area of abnormal washout and corrected this for percentage maximum heart rate and treadmill time. They found that this correlated well with the extent of angiographic disease and commented that normalisation for treadmill time was probably unnecessary.

In summary therefore this study has measured degrees of abnormality, area of abnormality and SIS score for both groups at one year intervals. The total values of these parameters are compared looking at the intragroup changes over one year and then by calculating interval change, comparing that parameter between the two groups in a similar fashion to the method used for the exercise tolerance data. Where a difference was found further

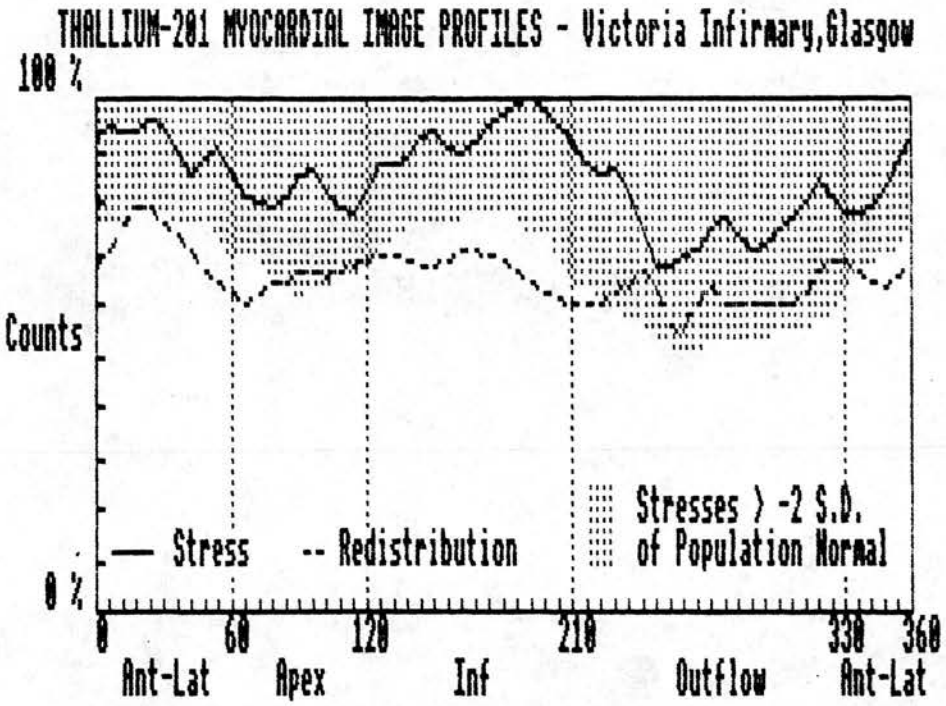


Anterior view

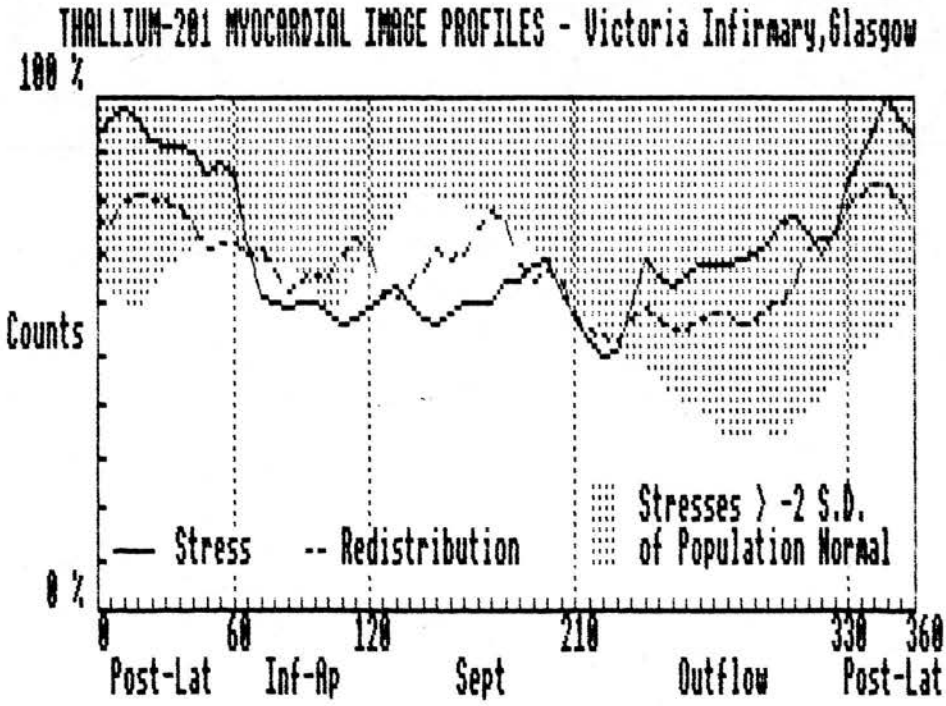


45° LAO view

Figure 19 Patient J.F. Baseline anterior and 45° LAO stress curves

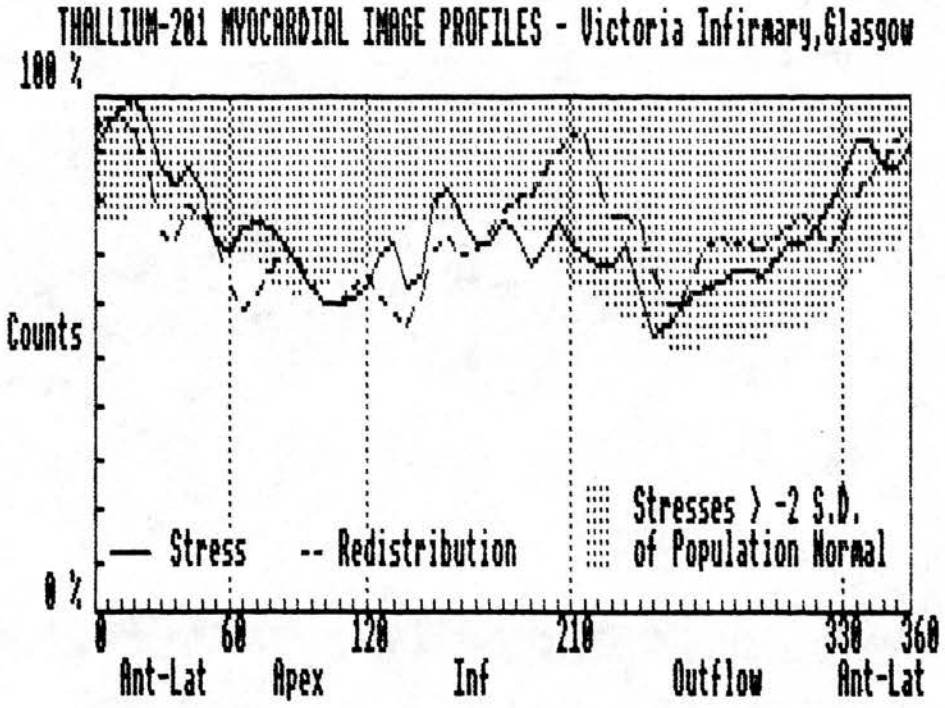


Anterior view

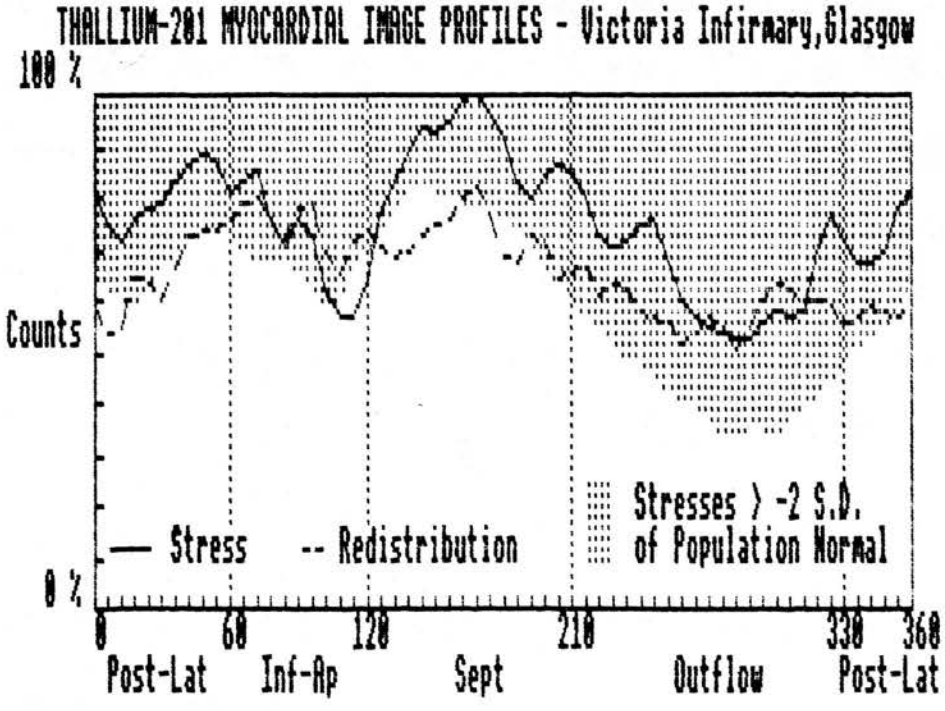


45° LAO view

Figure 20 Patient J.F. One year maximal exercise anterior and 45° LAO stress curves



Anterior view



45^{o} LAO view

Figure 21 Patient J.F. One year baseline matched submaximal exercise anterior and 45^{o} LAO stress curves

analysis of the three views used (anterior, 45° LAO and 65° LAO) and of the three regions within each view was carried out to identify whether these changes occurred in specific regions of the myocardium.

Statistical methods

For all three parameters the global data were found to conform to a "normal" distribution. Intragroup comparison of means was therefore made using a Student's 't' test for paired data. Intergroup comparison of interval change data was made using an unpaired Student's 't' test. The view and regional data was not normally distributed. Where this was analysed the Wilcoxon signed rank test was used for paired data. All results are expressed as mean and standard deviation with p values and for normal data 95% conference intervals.

Results

Of the 40 patients randomised at the start of the study, 17 of the exercise group and 16 controls were successfully studied on two occasions. In addition one patient from each group was found to have sustained a full thickness myocardial infarction during the study. These two patients were not studied further since the circumferential profiles were not comparable after infarction and since it was intended from the outset only to study the effects of training on reversible ischaemia. Results given therefore apply to 16 exercise patients and 15 controls.

Table 7 lists the results of the three parameters of global

Table 7

Global Thallium Data

Exercise Group

Patient	Deg Pre	Deg Post	Area Pre	Area Post	SIS Pre	SIS Post
1	234	156	1352	1212	18.8	17.1
2	120	150	793	1296	10.4	17.3
3	210	234	2666	3214	37.0	44.0
4	42	96	202	919	3.1	9.9
5	96	48	1979	139	20.0	1.3
6	402	156	8345	745	98.2	8.8
7	294	108	1879	1013	34.8	15.6
8	246	228	2372	2111	37.1	27.1
9	78	0	554	0	7.5	0
10	180	12	1930	10	25.7	0.1
11	60	108	187	512	2.1	5.8
12	204	72	1602	480	26.7	6.3
13	318	270	4451	4690	60.2	60.9
14	54	36	298	114	3.2	1.2
15	276	216	2952	2512	36.0	25.6
16	312	156	3727	2313	47.8	29.7
Mean	195	128	2206	1330	29.3	16.9
S.D.	111	82	2060	1327	25	17.2
95% C.I.	20 - 114		-		0.2 - 24.6	
'p' value	< 0.02		NS		< 0.05	

Control Group

Patient	Deg Pre	Deg Post	Area Pre	Area Post	SIS Pre	SIS Post
21	276	138	2259	1552	34.8	24.6
22	300	264	5067	3267	84.5	51.9
23	192	108	1902	1022	23.8	14.2
24	36	102	245	470	3.7	6.5
25	390	318	6837	3656	91.2	55.4
26	144	192	984	1461	10.7	15.7
27	174	156	1438	1140	20.3	16.3
28	78	96	859	1850	9.5	20.3
29	18	84	35	285	0.5	4.3
30	30	114	111	718	1.1	7.2
31	210	90	2755	295	32.8	3.5
32	330	384	7821	9056	122.2	137.2
33	12	96	55	334	0.6	3.5
34	168	180	1710	1500	17.6	17.4
35	84	48	1011	277	11.6	3.3
Mean	163	158	2206	1792	31.0	25.4
S.D.	121	96	2460	2260	37.7	34.9
95% C.I.	-		-		-	
'p' value	NS		NS		NS	

perfusion. The exercise group produced a 34% reduction in the mean extent of ischaemia as measured by the degrees of circumference involved. This was reduced from 195° initially to 128° after training, the 95% confidence limits for the difference before and after training being 20° to 114°. The ischaemic area was reduced by 40% after training from a mean of 2206 units to 1330 units. The standard deviations for these measurements however were much wider and this difference, although extensive, just failed to achieve statistical significance. When the ischaemic area was corrected for heart rate however, the reduction in SIS from 29.3 to 16.9 was significant at the 5% level.

The results for the control group were not significant for any of these three parameters. The degrees of abnormality at baseline and one year differed by 5° only from a mean of 163° initially to 158° at one year. Such a difference represents less than one point on a profile. The mean area of abnormality fell from 2206 to 1792 units over the year, the SIS falling by a similar extent from a mean of 31 to 25.4, neither fall being significant.

Intergroup comparison of interval change data shows the reduction in ischaemic degrees of 68° after exercise training to be significantly better than the reduction of 5° among controls. (Table 8) However the improvements in area and SIS are offset by smaller improvements in these parameters in the control group.

Table 8

Interval change Thallium Data-Means

Parameters	Exercise Group Mean	Stand Dev	Control Group Mean	Stand Dev	p value
DEG	-68	89	-5	74	0.05
AREA	-875	1937	-414	1256	NS
SIS	-12.4	23.2	-5.6	15.7	NS

In view of the above global results the ischaemic degrees data for the exercise group were further broken down to show whether the improvements demonstrated could be ascribed to any of the three views used or to any of the nine vascular regions. The "view" data is presented in Table 9, while the regional data is shown in Table 10. The anterior view was the only one to show a significant fall in mean number of ischaemic degrees, the figures before and after training being 72° $\pm$ 59° and 30° $\pm$ 35° respectively. Though neither achieved statistical significance the 45° LAO and 65° LAO views also shows reductions in mean number of ischaemic degrees, the former producing a fall from a mean of 66° $\pm$ 51° to 58° $\pm$ 56° while the latter fared slightly better with a fall from 58° $\pm$ 61° to 40° $\pm$ 43°.

The regional data demonstrated which vascular regions produced significant improvement. The anterolateral and apical regions on the anterior view both showed significant improvements in number

Table 9

'View' Thallium Data

EXERCISE GROUP

Patient	Ant Pre	Ant Post	45° Pre	45° Post	65° Pre	65° Post
1	78	72	42	0	114	84
2	0	0	48	72	72	78
3	84	102	114	120	12	12
4	30	0	0	84	12	12
5	6	0	96	42	0	6
6	192	42	78	30	132	84
7	96	96	102	12	96	0
8	120	0	102	102	24	126
9	30	0	42	0	6	0
10	150	0	0	12	30	0
11	0	0	48	60	12	48
12	132	12	42	42	30	18
13	0	0	186	192	132	78
14	54	12	0	24	0	0
15	102	84	120	132	54	0
16	72	66	36	0	204	90
Mean	72	30	66	58	58	40
S.D.	59	35	51	56	61	43
'p'value	< 0.05		NS		NS	

Table 10

Regional Thallium Data

EXERCISE GROUP

	Anterior						45° LAO						65° LAO					
Patient	A-L Pre	A-L Post	Ap Pre	Ap Post	Inf Pre	Inf Post	P-L Pre	P-L Post	Inf Ap Pre	Inf Ap Post	S Pre	S Post	Inf Pre	Inf Post	Ap Pre	Ap Post	A-S Pre	A-S Post
1	0	0	24	0	54	72	18	0	18	0	6	0	66	60	18	24	30	0
2	0	0	0	0	0	0	48	66	0	6	0	0	72	78	0	0	0	0
3	0	12	0	30	84	72	12	12	12	36	90	72	12	54	0	0	0	0
4	12	0	18	0	0	0	0	0	0	0	0	84	0	0	0	0	12	12
5	6	0	0	0	0	0	0	0	6	0	90	42	0	6	0	0	0	0
6	90	0	60	0	42	42	0	0	0	0	78	30	0	0	42	0	90	84
7	0	0	24	30	72	66	0	0	42	6	60	6	66	0	64	0	24	0
8	60	24	42	12	18	0	78	66	24	36	0	0	24	78	0	48	0	0
9	0	0	12	0	18	0	0	0	0	0	42	0	0	0	0	0	6	0
10	30	0	30	0	90	0	0	0	0	0	0	12	30	0	0	0	0	0
11	0	0	0	0	0	0	30	36	18	24	0	0	12	48	0	0	0	0
12	24	12	60	0	48	0	0	0	0	0	42	42	18	18	12	0	0	0
13	0	0	0	0	0	0	54	42	60	60	72	90	60	48	60	30	12	0
14	0	0	0	0	54	12	0	24	0	0	0	0	0	0	0	0	0	0
15	36	0	66	0	0	84	0	0	18	42	102	90	0	0	24	0	24	0
16	0	0	0	0	72	66	24	0	12	0	0	0	78	78	54	12	72	0
Mean	16	3	21	4	35	26	17	15	13	13	36	29	27	29	17	7	17	6
S.D.	26	7	24	10	34	34	24	24	17	20	39	36	30	33	24	14	27	21
p'value	< 0.05		< 0.02		NS		NS		NS		NS		NS		NS		< 0.05	

of ischaemic degrees, the anterolateral region falling from a mean of 16° ± 26° to 3° ± 7° with the apical region showing a similar reduction from 21° ± 24° to 4° ± 10°. On the 65° view the anteroseptal region improved significantly from 35° ± 34° to 6° ± 21°. While no other region showed statistically significant improvements, the apical region on the 65° view did demonstrate a large fall from 17° ± 24° to 7° ± 14°. The figures for the inferior region on the anterior view and the septal region in the 45° view showed smaller improvements, the former decreasing from 34° ± 34° to 26° ± 34° while the latter decreased from 36° ± 39° to 29° ± 36°. The three remaining regions showed little change between the two occasions. The figures for the posterolateral region were 16° ± 24° before and 15° ± 24° after, those for the infero-apical region were 13° ± 17° before and 13° ± 20° after and those for the inferior region on the 65° LAO view actually increased from 27° ± 30° to 29° ± 33° after training.

Discussion

Before considering the above results it is perhaps useful to place them in context by considering the few studies which have sought to address this question previously. Thallium scintigraphy has been used in a number of studies in recent years to investigate the effect of exercise training on myocardial perfusion.(60,61,97,102,103) Its use however has been hampered by poorly developed techniques and in particular by the lack of quantitative analysis. The first study of this kind was reported in 1981 by Verani et al (60) who studied 16 patients before and

after a 12 week training programme using treadmill and bicycle exercise tolerance testing, exercise Technetium 99 ventriculography and Thallium 201 scintigraphy. There are various limitations in the study in terms in duration of training programme and lack of control group. In addition however they chose to exercise patients to the same level of cardiac work before and after training during Thallium scintigraphy. This technique has theoretical advantages in that one can compare perfusion at comparable work loads. If however maximal cardiac work is improved by training, as one might expect assuming the improved perfusion, then by definition the repeat scan is carried out below the ischaemic threshold, a situation which has been found to produce erroneous results and which is not generally recommended for routine assessment of Thallium scans. As mentioned previously we have found this method to produce scans which are quantitatively not comparable. The pre and post training scans were assessed by Verani in two ways. Firstly pairs were assessed blindly and graded as to the presence of an increase or decrease in perfusion or no change. Secondly anatomical regions of individual scans were scored on a 0 - 4 semiquantitative scale. Using this technique three patients were scored as improved, three worse and ten unchanged. Verani concluded that there was no improvement in myocardial perfusion He recognised the limitations of his study in terms of patient selection but did not comment on the short duration of study or the limitation of his analysis technique.

The year after Verani's paper Taubau (61) and colleagues

reported a study with similar design incorporating the same investigations but with a mean duration of training of 5.6 months and using circumferential profile analysis of Thallium scans. The use of quantitative analysis was limited however. They established the presence of defects in various regions and produced an estimated variability for each region due to methodology. Observers analysed paired scans to assess differences in profiles which were outside this range of variability. These were defined as improved or worse. As a result, although they detected 132 abnormal regions initially, only 13 of these regions were adjudged to have changed. Five patients improved, one was worse and 11 were unchanged. This study too failed to show that exercise training can improve perfusion, although the authors suggested that the improvement in five patients pointed to the need for a controlled study in a more carefully selected group.

In 1984 Froelicher's group reported the results of one of the largest studies of exercise training to date.(102) In a randomised controlled study of 146 patients over a one year period they reported the results of Thallium-201 scintigraphy using a technique similar to that described above for Verani. For side by side analysis of paired scans however observers had to score any change detected on a 0 - 3 scale. For independent regional scoring, a scale of 0 - 10 was used where Verani had used a 0 - 4 scale. This side by side comparison failed to demonstrate a significant difference, but the regional scoring system showed a significant interval change difference between the exercise group

and control group with improved perfusion in the exercise group. Analysis of variance demonstrated that improved perfusion following training depended also on the presence of angina. The extent of improvement demonstrated was small and although statistically significant was of limited clinical significance. The authors were unable to strongly recommend this therapy on the basis of their results.

In 1986 Sebrechts subjected the results of a sub group of Froelicher's study to further analysis.(103) He took those patients whose Thallium studies were suitable for circumferential profile analysis and measured the area under the profile curve, excluding the outflow tract. This area was divided by the number of points on the curve to produce an index of perfusion. The same process was applied to the wash-out curve. In addition to producing global indices, view and regional indices were produced. Again comparison of interval change data revealed a statistically significant difference between trained and control patients. The global indices were significantly different and analysis of views revealed this to be related mainly to differences between the anterior views, although the 45° LAO views were also found to be significant. Regional analysis revealed significant improvements in the anterolateral wall, inferior wall and posterolateral wall. While these results are superficially attractive, they are rather disappointing. The parent study by Froelicher had already pointed to improvements in perfusion and had made the more significant point that angina was an important prerequisite for improvement. This study simply applied a

figure which did not reveal any new information about the improvement. Indeed the results of regional analysis serve only to confuse the picture, revealing as they do three regions of improvement in three different vascular territories on three different views. The improvement in the LAD territory on the anterior view for example is not backed up by improvements in other LAD regions. This suggests that the results may be spurious and not genuine indicators of improved perfusion. Bearing in mind the use of non maximal scanning on the repeat testing, one must ask whether the alterations in perfusion in the exercise group may be related to this technique. The rather patchy results certainly raised more questions about method than convincing answers about perfusion changes.

The final study in recent years was by Schuler in 1988. (97) He studied 18 patients with stable angina pectoris and hyper-lipidaemia and observed the changes induced by low fat diet and exercise training over a one year period. These were matched with 18 patients with similar severity of coronary artery disease. Thallium scanning in this group was carried out at maximal exercise on both occasions, that for the intervention group being higher at one year than at baseline. He measured degrees of circumference of left ventricle with reversible ischaemia from reconstructed cross sectional images of stress and redistribution scans. Stress induced myocardial ischaemia measured in this way was reduced by 54% ($p < 0.05$) despite higher workload. This data of all studies is the most convincing evidence of reduction in ischaemia. The study is limited by lack

of regional data and by the dual pathology of one group and the dual nature of intervention within that group. Nonetheless in the currently published literature it is one paper where it is difficult to provide an alternative explanation for the changes, other than genuine improvements in perfusion. The technique of Thallium scintigraphy used in Schuler's paper cannot be criticised and is supported by a control group.

The study reported here suggests that myocardial perfusion may indeed be improved after exercise training. The reduction in number of degrees of ischaemia by 34%, despite an increase in cardiac work is comparable to the result in Schuler's study. Schuler however was unable to produce a statistically significant intergroup comparison, nor did he have data on the area of abnormality. In this study reduction in ischaemic degrees is significant both by intra and inter group analysis, strengthening the case that this is due to the intervention and not due to natural change as a result of the disease. While the area data show a larger percentage change, this does not imply a reduction in depth of ischaemia. For curves of this sort, a decrease in degrees of ischaemia of 34% without any alteration in depth of ischaemia would produce a reduction in area of ischaemia of approximately 40% as shown here. The major change therefore appears to be a reduction in the size of the ischaemic zone as measured by the degrees of circumference involved, rather than in depth of ischaemia within that zone as measured by area of ischaemic curve. This would suggest that if collateralisation is occurring then it is most effective around the periphery of the

ischaemic zone. The depth of the ischaemic zone may possibly bear a relationship to the onset of chest pain and therefore be unchanged in a symptom limited test such as this. Alternatively like maximum heart rate it may be related to the severity of the underlying stenosis and so remain unchanged.

Analysis of the three views shows that the anterior view provided the only significant improvement. Sebrechts also found this view to have the most significant change. He speculated that this might be related to the proximity of scanning to the end of the exercise test i.e. redistribution of Thallium occurring after cessation of exercise may mask the ischaemic change on the views carried out later. However in this study, the improvement in the 65° LAO view, although not significant, was greater than that in the 45° LAO, although this was recorded earlier. While redistribution of Thallium may be a factor, this suggests an alternative reason. The nine regional views help explain this and provide further evidence for genuine regional improvement in ischaemia and hence support the hypothesis of collateralisation. Those regions with improved perfusion fit into the territory of the LAD with significant changes anterolaterally on the anterior view, but also anteroseptally on the 65° LAO view, despite the fact that the latter was recorded 20 - 30 minutes after exercise. Furthermore the apical improvements are significant in the anterior view and, though not significant on the 65° LAO view, are substantial here also. That these apical changes may also be subscribed to the LAD is supported by the lack of change inferolaterally, posterolaterally and inferiorly. It is

interesting that the septum, though slightly improved, was less improved than the anterior wall. One must conclude from these studies that exercise training has induced changes in myocardial perfusion and that in this group of patients these changes have occurred in the anterior wall of the left ventricle in the territory of the left anterior descending coronary artery. The localised nature of these improvements supports the hypothesis that collateralisation is the mechanism of improvement, rather than some general effect on the heart which might be expected to have a more global effect on perfusion. The consistency of these results in all three views adds to the conviction that these changes are genuine and not simply spurious results.

The group studied here were more carefully selected than in any of the previously mentioned studies. Angina pectoris was a prerequisite for entry into this study. All patients therefore conformed to the sub group found by Froelicher to have more benefit. In addition the exclusion of patients with infarcts not only increased the likelihood of improvement but also allowed the investigative technique to be simplified. It was possible to say that all abnormalities detected on stress were potentially reversible. In the previously mentioned studies, comparisons have been made either of a perfusion figure which combines reversible and irreversible ischaemia or of a redistribution area which introduces other variables in terms of extent of redistribution at three or four hours and factors which might influence this. By comparing the patient's curve with a "normal" curve, it is possible to concentrate on the area of interest,

rather than on the whole curve. A weakness in Sebrecht's study was that although it produced a quantitative figure which could be studied sequentially, it said nothing about the extent of abnormality and significance of that change clinically. The technique used here has been more precisely tailored to answer the question posed than any of the studies published to date and despite the reservations about Thallium scintigraphy mentioned in Section II it is encouraging that it appears to have produced a positive result.

Why then has this study demonstrated changes confined to the distribution of the LAD? Perhaps it is simply that this region is most easily studied by Thallium scintigraphy. There are however a number of alternative possible explanations. While the group of patients studied included those with ischaemia in all vascular regions, it is possible that the underlying anatomy favoured collateralisation only in those patients with LAD territory ischaemia. Collateralisation depends on the availability of potential sources of collaterals. Post mortem angiographic studies have shown that collaterals are present between the LAD and RCA in 95% of cases, between the LAD and circumflex in 81% of cases and between the RCA and circumflex in 55% of cases.(104) There is therefore a higher probability of a diseased LAD receiving collaterals from either the RCA or circumflex. Furthermore studies of intracoronary collaterals in disease of each of the three vessels revealed intracoronary anastomoses in 78% of cases of LAD stenosis, 45% of RCA stenosis and 61% of circumflex stenosis.(104) The increased incidence of

collaterals in the LAD territory may simply reflect the complex nature of this vessel and the many branches of it, each acting as a potential route of collateral supply. It is likely also that the distribution of disease within the vessels is also significant. Gensini reports that 53% of RCA lesions are proximal and that 90% of circumflex lesions occur either at the origin of the circumflex or of the obtuse marginal.(105) Proximal lesions of this sort allow intercoronary anastomosis with retrograde flow through the vessel but have little potential for intracoronary collateral channels. The commonest site of lesion in the LAD however is in the mid portion after the first septal perforator, accounting for 47%, with a further 25% sited in the first diagonal. Such lesions have many potential sources for inter and intracoronary anastomoses. It is also self evident that single vessel disease is the most amenable to collateralisation since the supply from other vessels is uncompromised. Gensini reports the incidence of single vessel disease to be 14.2% in the LAD, 8.7% in the RCA and 5.2% in the circumflex.(105) Taking all of the above factors into account it is clear that on anatomical grounds one would choose the LAD as the vessel most likely to be effectively collateralised. Furthermore disease in the mid portion and first diagonal would have the greatest potential. Such disease would produce ischaemia in the anterior and anterolateral walls, precisely those areas which have demonstrated improvement in this study.

Thallium studies have demonstrated that disease in the LAD territory produces larger defects than in either of the other two

vessels.(106,107) This may affect not only the potential for collateralisation, but also the ease with which it can be detected. Iskandrian demonstrated in single vessel disease that the presence of collaterals was associated with significantly smaller perfusion defects.(108) Although the numbers in this study were limited it is of interest that separate analysis of the three vessels demonstrated the above findings to be significant only for ischaemia in the LAD territory. Tubau also showed that in single vessel disease the presence of collaterals was associated with a reduced incidence of perfusion defects and a smaller number of defects per patient.(109)

Bearing in mind the limited capabilities of Thallium scintigraphy it would be dangerous to draw too firm conclusions from this study. However it does seem that improved uptake of Thallium does occur in areas of abnormality as a result of exercise training. These improvements take the form of a reduction in the extent of the abnormal region rather than the depth of that region. Furthermore in this group of patients these improvements appear localised rather than generalised and the region to which they are localised corresponds to that region where one would most expect to find improvements based on anatomical and scintigraphic studies of collaterals. These changes support the opinion expressed in the preceding study on exercise tolerance data that while we cannot claim to have made significant alterations in blood flow through or around the critical stenosis we may indeed have encouraged collateral blood flow into the periphery of the ischaemic region thereby reducing the area at risk.

THE EFFECT OF EXERCISE TRAINING ON GLOBAL LEFT VENTRIUCLAR FUNCTION

Methods

The technique used is described in detail in section II. Gated Technetium bloodpool angiography was carried out in the 30° - 45° LAO view with a 10° caudal tilt. A resting scan was recorded followed by stress scans. As previously described cold pressor stress was chosen as the most applicable technique.

The 16 patients in the exercise group whose Thallium results were discussed in the previous subsection underwent gated Technetium bloodpool angiography on both occasions. However the baseline scans of one patient were lost due to computer failure and one cold pressor scan of a further patient was also lost leaving 15 paired rest studies and 14 paired stress studies in the exercise group. Of the 15 control patients whose Thalliums have been discussed, one declined to undergo repeat Technetium scanning and in one case a rest scan only was achieved since cold pressor induced ectopic activity led to a failure of gating. Two other patients had incomplete data due to computer failure. This left 12 rest scans and 11 stress scans in the control group.

During the cold pressor test heart rate and blood pressure were monitored at one minute intervals using a Hitachi HME-20 automatic pulse and blood pressure monitor. The mean heart rate and systolic blood pressure at rest and during cold pressor at baseline and one year are shown in Figures 22 and 23. There were no significant inter group or intra group differences in either

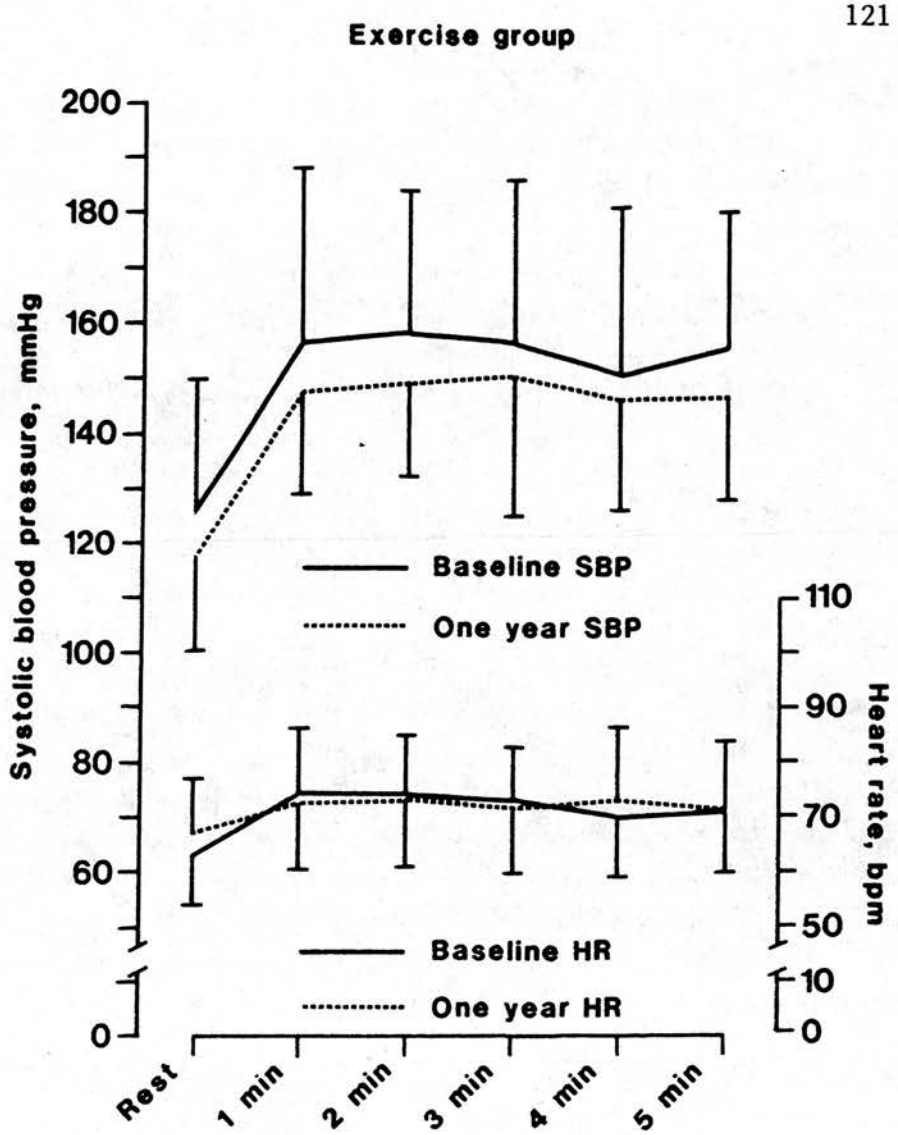


Figure 22 Mean heart rates and systolic blood pressures at rest and during cold pressor stress - exercise group

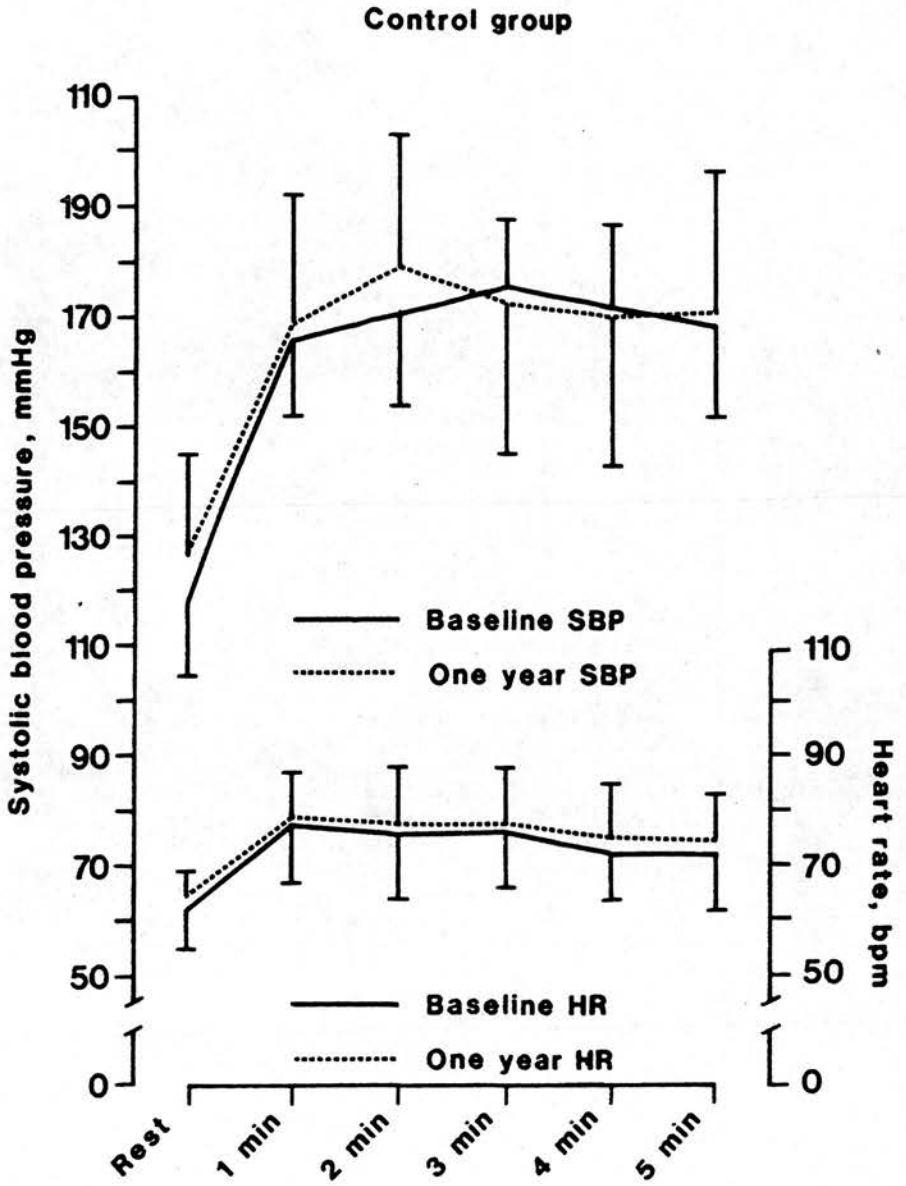


Figure 23 Mean heart rates and systolic blood pressures at rest and during cold pressor stress - control group

heart rate or blood pressure at any time during the test. For both groups however there was a significant rise in heart rate and blood pressure within the first minute of cold pressor. This increase in cardiac work was maintained throughout the five minutes. These results are in keeping with previous work in the Victoria Infirmary demonstrating that the technique of cold pressor used is both effective and reproducible. For the purposes of this study therefore the left ventricular function results shown at baseline and one year reflect equivalent levels of stress on both occasions.

Statistics

The various parameters of global left ventricular function were found to conform to a normal distribution and therefore a Student's paired t-test was used for intra group analysis of baseline and one year data and an unpaired Student's t-test was used for inter group comparisons. The eight parameters which describe the left ventricular function curve could not be considered as independent or pre-selected variables and as such the Bonferonni correction was applied to the calculation of p values. The "proportion" data was analysed using a Fisher's exact test. All results are expressed as mean and standard deviation with appropriate p values.

Results

a) Resting values

The mean baseline values at rest for the nine parameters of

left ventricular function are shown in Table 11. There were no significant differences between the groups for any of the parameters studied. Table 12 shows the baseline and one year values for the training group. Fast ejection time increased at rest from 16.7 ± 1.7% to 18.0 ± 1.9%, this increase being significant at the 5% level. All other parameters remained unchanged at one year, although there was notably a small but non significant increase in resting ejection fraction from 54.9 ± 10.5% to 56.9 ± 8%. The equivalent values for the control group are shown in Table 13. Most of these parameters showed a high degree of consistency over the one year period. In this group however ejection fraction fell by 5% from 56.9 to 51.9%. This difference was not statistically significant however since the standard deviations within this group were broad.

The inter group comparison of interval change data is shown in Table 14. Again there are no statistically significant differences in any of the parameters and indeed in most cases again there is a high degree of consistency over the one year period.

b) Stress values

Tables 15 to 18 show the corresponding results during cold pressor to those discussed at rest. Again the baseline intergroup comparison shows that randomisation was successful. The baseline and one year parameters for the training group with the exception of ejection fraction show, if anything, an even greater consistency than the resting values. Ejection fraction during cold pressor however improved from 48 ± 8.4% to 54.9 ±

Table 11

Baseline parameters of resting global left ventricular function

Variable	Training Group mean ± SD	Control Group mean ± SD	'P' value
FET	16.7 ± 1.7	16.9 ± 1.2	NS
DVs/DT	4.5 ± 0.5	4.6 ± 0.5	NS
FEL	34.5 ± 3.9	32.3 ± 5.1	NS
ST	38.9 ± 3.6	37.6 ± 4.3	NS
SL	43.1 ± 6.2	42.4 ± 5.4	NS
FFT	59.8 ± 7.0	59.3 ± 4.8	NS
DVd/DT	3.7 ± 0.6	3.6 ± 0.5	NS
FFL	30.9 ± 6.0	31.3 ± 6.3	NS
EF	54.9 ± 10.5	56.9 ± 15.8	NS

Table 12

Pre and post study parameters of resting global left ventricular function - training group

Variable	Pre (mean ± SD)	Post (mean ± SD)	'P' value
FET	16.7 ± 1.7	18.0 ± 1.9	NS
DVs/DT	4.5 ± 0.5	4.4 ± 0.4	NS
FEL	34.5 ± 3.9	33.6 ± 4.2	NS
ST	38.9 ± 3.6	39.1 ± 3.8	NS
SL	43.1 ± 6.2	41.5 ± 6.2	NS
FFT	59.8 ± 7.0	59.5 ± 5.8	NS
DVd/DT	3.7 ± 0.6	3.5 ± 0.4	NS
FFL	30.9 ± 6.0	31.5 ± 6.0	NS
EF	54.9 ± 10.5	56.9 ± 8.0	NS

Table 13

Pre and post study parameters of resting global left ventricular function - control group

Variable	Pre (mean ± SD)	Post (mean ± SD)	'P' value
FET	16.9 ± 1.2	16.6 ± 1.6	NS
DVs/DT	4.6 ± 0.5	4.7 ± 0.3	NS
FEL	32.3 ± 5.1	33.7 ± 4.2	NS
ST	37.6 ± 4.3	38.8 ± 3.8	NS
SL	42.4 ± 5.4	43.3 ± 4.4	NS
FFT	59.3 ± 4.8	59.8 ± 3.9	NS
DVd/DT	3.6 ± 0.5	3.8 ± 0.4	NS
FFL	31.3 ± 6.3	31.1 ± 4.4	NS
EF	56.9 ± 15.8	51.9 ± 10.4	NS

Table 14

Interval change parameters of resting global left ventricular function

Variable	Interval change Training	Interval change Control	'P' value
FET	+1.3 ± 2.3	-0.3 ± 1.9	NS
DVs/DT	-0.03 ± 0.58	+0.08 ± 0.48	NS
FEL	-0.9 ± 6.1	+1.3 ± 6.1	NS
ST	+0.2 ± 5.4	+1.2 ± 4.7	NS
SL	-0.9 ± 9.6	+0.8 ± 6.1	NS
FFT	-0.2 ± 9.7	+0.5 ± 4.7	NS
DVd/DT	-0.2 ± 0.6	+0.2 ± 0.7	NS
FFL	+0.6 ± 8.7	-0.3 ± 4.7	NS
EF	+2.0 ± 13.7	-5.0 ± 12.6	NS

Table 15

Baseline parameters of global left ventricular function during cold pressor stress

Variable	Training group (mean ± SD)	Control Group (mean ± SD)	'P' value
FET	18.3 ± 3.2	17.9 ± 2.5	NS
DVs/DT	3.8 ± 0.6	4.1 ± 0.6	NS
FEL	40.4 ± 6.6	39.0 ± 7.3	NS
ST	44.2 ± 5.4	43.6 ± 5.8	NS
SL	45.8 ± 5.2	51.0 ± 10.7	NS
FFT	64.1 ± 7.5	68.9 ± 10.2	NS
DVd/DT	3.5 ± 0.5	3.3 ± 0.6	NS
FFL	33.9 ± 8.9	36.0 ± 12.0	NS
EF	48.0 ± 8.4	49.4 ± 14.2	NS

Table 16

Pre and post study parameters of global left ventricular function during cold pressor stress - training group

Variable	Pre (mean ± SD)	Post (mean ± SD)	'P' value
FET	18.3 ± 3.2	18.8 ± 2.9	NS
DVs/DT	3.8 ± 0.6	3.8 ± 0.5	NS
FEL	40.4 ± 6.6	40.1 ± 6.3	NS
ST	44.2 ± 5.4	44.1 ± 5.2	NS
SL	45.8 ± 5.2	45.1 ± 7.0	NS
FFT	64.1 ± 7.5	63.9 ± 7.7	NS
DVd/DT	3.5 ± 0.5	3.4 ± 0.3	NS
FFL	33.9 ± 8.9	31.9 ± 8.1	NS
EF	48.0 ± 8.4	54.9 ± 10.1	< 0.05

Table 17

Pre and post study parameters of global left ventricular function during cold pressor stress - control group

Variable	Pre (mean ± SD)	Post (mean ± SD)	'P' value
FET	17.9 ± 2.5	19.4 ± 3.4	NS
DVs/DT	4.1 ± 0.6	3.8 ± 0.5	NS
FEL	39.0 ± 7.3	41.8 ± 4.3	NS
ST	43.6 ± 5.8	45.7 ± 4.0	NS
SL	51.0 ± 10.7	49.7 ± 7.0	NS
FFT	68.9 ± 10.2	69.1 ± 8.1	NS
DVd/DT	3.3 ± 0.6	3.4 ± 0.6	NS
FFL	36.0 ± 12.0	38.2 ± 11.1	NS
EF	49.4 ± 14.2	45.1 ± 12.1	NS

Table 18

Interval change parameters of global left ventricular function during cold pressor stress

Variable	Interval change - training (mean ± SD)	Interval change - controls (mean ± SD)	'P' value
FET	+0.5 ± 4.9	+1.5 ± 4.2	NS
DVs/DT	+0.04 ± 0.67	-0.22 ± 0.6	NS
FEL	-0.3 ± 6.7	+2.8 ± 5.9	NS
ST	-0.1 ± 4.9	+2.1 ± 4.4	NS
SL	-0.6 ± 6.8	-1.3 ± 10.7	NS
FFT	-0.1 ± 9.0	+0.2 ± 9.8	NS
DVd/DT	-0.09 ± 0.66	+0.06 ± 0.68	NS
FFL	-1.9 ± 11.1	+2.2 ± 15.0	NS
EF	+6.9 ± 11.7	-4.3 ± 6.8	< 0.01

10.1% at one year, this improvement being significant at the 5% level. In the control group the same parameters fell from 49.4 ± 14.2 to 45.1 ± 12.1%. Although this reduction was not statistically significant, it means that the intergroup comparison of interval change in the cold pressor induced ejection fraction is significant at the 1% level.

c) Ejection fraction response to cold pressor stress

Since the degree of change in ejection fraction from rest to stress has been said to be related to the presence of coronary artery disease and its extent, the rest to stress values are shown in Figure 24 and in Table 19. The mean change in ejection fraction from rest to cold pressor in the exercise group was -6 ± 6.9% at baseline and -2.4 ± 8.4% at one year. This positive change does not attain statistical significance. Over the same period the control values were -7.2 ± 5.4% at one year, again demonstrating consistency. Intergroup comparison of the interval change was not significant. If however we define a one year improvement in ejection fraction response to cold pressor as a positive interval change in that response, then nine out of 14 exercise patients demonstrated a positive change while only four out of 11 controls demonstrated a positive change. These proportions were significantly different at the 5% level.

Discussion

In order to understand the results of this part of the study it is important for us to appreciate firstly the value of the parameters measured and secondly the mechanism of stress test

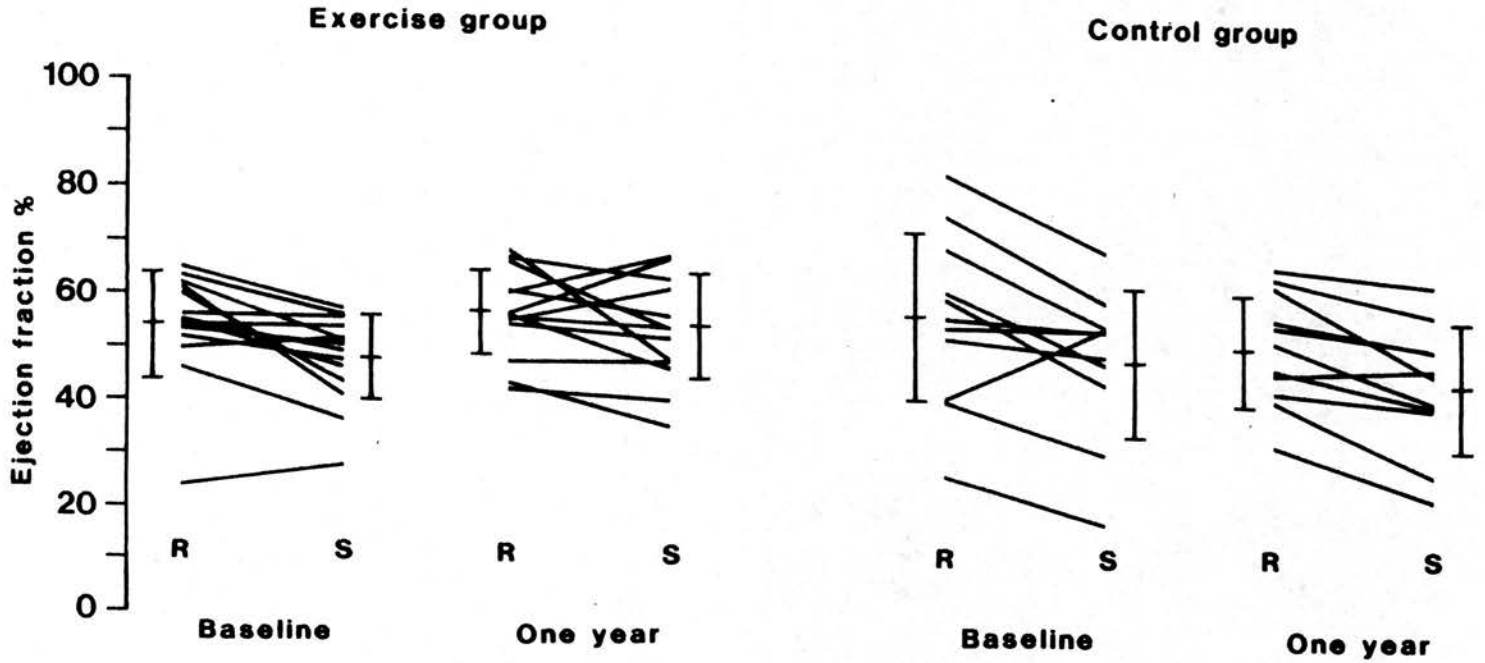


Figure 24 Individual change in global ejection fraction from rest to stress

Table 19

Rest to stress change in global ejection fraction during radionuclide ventriculography pre and post training

Exercise Group

Pat no.	R-S change in E.F.	
	Pre	Post
1	0	-12
2	-11	-10
3	-16	-2
4	-7	+7
5	+4	+6
6	-10	-8
7	-3	-5
8	-4	-20
9	-7	-4
10	+2	-1
11	-7	+6
12	-4	+11
13	0	0
14	-21	-2
Mean	-6.0	-2.4
S.D.	6.9	8.4
'p'value	NS	

Control Group

Pat no.	R-S change in E.F.	
	Pre	Post
21	-14	-3
22	-10	-14
23	+14	-11
24	0	-7
25	-9	-10
26	-16	-17
27	-14	-7
28	-3	-4
29	-16	+1
30	-14	-5
31	-2	-2
Mean	-7.6	-7.2
S.D.	9.2	5.4
'p'value	NS	

used. If we consider the parameters first, then with the exception of the ejection fraction which is perhaps the most clinically applicable measurement, the others are mathematically derived values obtained from a time/activity curve of left ventricular function. As such they are perhaps in isolation of limited value but together they define the geometry of the ventricular function curve. This in turn reflects the inotropic state of the left ventricle. There are two main regions of interest on the time/activity curve. Fast ejection and fast filling are the major components of systole and diastole respectively. The former is preceded by a short period of isovolumetric contraction, while the latter is preceded by a short period of isovolumetric relaxation. These brief flat regions of the curve are of little interest however other than as markers of end diastole and end systole. In the calculation of the parameters given in this study, fast ejection length is measured from the point at which isovolumetric contraction ends and ejection begins to end systole at which point fast filling begins. End systole is defined from the first derivative curve where it passes through the zero point. Fast filling ends at another "flat" area of curve called diastasis during which the rate of filling slows to near zero as shown by the second trough on the first derivative curve before atrial systole produces a surge in filling again. Diastasis and atrial systole were not analysed by the programme used in this study. The two periods of fast ejection and fast filling can yield a number of measurable values. Three were chosen for use in this programme, namely the

length of the period (FEL and FFL), the maximum rate of change of volume during the period (DVs/DT and DVd/DT) and the time at which the maximum rate of volume change occurs (FET and FFT). These parameters are measured automatically from the time activity curve and its first derivative, the points of maximum rate of emptying and filling being the trough and peak of the first derivative curve respectively. Systolic length (SL) is a value obtained not from systole but by subtracting FET from FFT i.e. it is the time from maximum rate of volume change in systole to maximum rate of volume change in diastole. Systolic time (ST) includes the short period of isovolumetric contraction as well as the fast ejection period.

Ejection fraction is, of course, also derived from the time activity curve being calculated from the minimum and maximum count values, but it is very much a separate entity which does not describe the curve morphology, if ejection fraction is taken in conjunction with the end diastolic counts then it can be used to define the depth of the time activity curve. It is however affected by such factors as preload and afterload as well as the inotropic state and also by regional contractile abnormalities. As mentioned it is the most studied of all parameters from a clinical point of view and it therefore merits separate consideration and can shed additional light on changes in left ventricular function in this study.

A number of groups have looked at parameters similar to those used in this study and have investigated the effect of coronary artery disease and of drugs which alter the inotropic state of the

ventricle on those parameters. Sapru et al (110) studied left ventricular function in normal individuals and the effect of infusions of isoprenaline or propranolol on various parameters derived from the left ventricular function curve. These parameters included left ventricular ejection and filling times (equivalent to FEL and FFL) mean and maximum rates of filling and emptying as well as ejection fraction. The times quoted in their study are given as absolute values in milliseconds. Changes in these values therefore have to be considered in conjunction with changes in heart rate. They do however quote the appropriate RR interval which enables the values to be corrected. They found that isoprenaline infusion reduced both left ventricular ejection and filling times but had a proportionately much greater effect on left ventricular ejection than on filling. It was also found to increase both mean and maximum ejection rates but not mean and maximum filling rates. Beta blockade increased left ventricular filling time and decreased the mean ejection rate. In order to consider these changes in isolation from the chronotropic response the authors also examined the effect of heart rate changes on left ventricular filling and emptying times using infusions of atropine. They found that an increase in heart rate alone reduced left ventricular filling time proportionately more than ejection time. The conclusion of the authors was therefore that left ventricular ejection and filling times and rates were sensitive indicators of changing inotropic state in normal individuals. As one might expect in this group the ejection fraction was increased by isoprenaline. The maximum rate of

volume change was however felt to be an insensitive measurement since it was affected by the filtering technique used to produce the time activity curve.

Marshall et al (111) and Peterson et al (112) using first pass radionuclide angiography and cine angiography respectively reached similar conclusions. They stated that left ventricular ejection rate was a more sensitive indicator of inotropic state than ejection fraction alone since it combined a measure of volume change and ejection time. In a study of this sort therefore one might expect a change in inotropic state to affect not only the ejection fraction but also the ejection time and to a lesser extent perhaps filling time.

Peak filling rate and time to peak filling rate have been studied by other authors.(63,113-116) It has been found by all these authors that in the presence of coronary artery disease peak filling rate is reduced and time to peak filling is prolonged. Polak et al (113) reported in addition a trend towards a progressive reduction in peak filling rate in proportion to disease severity. He and other authors also noted a trend toward lower peak filling rates in those patients with low ejection fractions at rest. This might suggest that these measures would be useful indicators of changing disease state. However, the values obtained by the various authors do show considerable disparity with mean values in normal individuals ranging from 2.1 to 5.98 end diastolic volumes per second and in patients with coronary artery disease from 1.6 to 2.7 end diastolic volume per second. It appears therefore that peak filling rate and time to

peak filling rate are affected by coronary artery disease but whether they are sensitive enough indicators of change in inotropic state or coronary perfusion is debatable.

The effect of cold pressor stress on the above parameters of left ventricular function has not been adequately studied. The test itself has however been investigated by a number of authors who have drawn conclusions about the haemodynamic mode of action of the cold pressor test. Bearing in mind the above discussion regarding the parameters of LV function, one can therefore deduce what changes might be expected. The topic is made more difficult by the varied methodology in carrying out the test. In the present study the hand and arm were immersed to the elbow in a mixture of crushed ice and water. Throughout the test water was continuously passed through the mixture to ensure adequate contact. A fresh ice and water mixture was used for each patient. An adequate sustained cold stimulus was therefore ensured. Early decay in the haemodynamic response to cold pressor has been noted by some authors (52,117,118) and this can in some cases by attributed to less adequate cold stimulus. It is clear that a technique of this sort has many variables and is unlikely to be consistently applied by different observers. This may account for the marked disparity both in haemodynamic response and ejection fraction results obtained by the various authors. This further emphasises the importance of consistency in technique and in particular the use of one observer (the author) throughout this study. In our own laboratory, as well as in others, the response of normal individuals to cold pressor stress has included

a fall in ejection fraction and while some authors have shown that the ejection fraction response can be used to separate normal individuals from those with coronary artery disease (50,51,117), others have found no difference.(52,118,120) If the various studies are considered as a whole however, then the ejection fraction has been found to fall more in individuals with coronary artery disease. It would appear therefore that the presence of coronary artery disease does at least effect the ejection fraction.

While the cold pressor test was originally described by Hines and Brown in 1932 (121) the haemodynamic responses were not described until the 1960's.(122-124) These authors have attributed the response to a predominant increase in alpha adrenergic stimulation associated with a rise in both systemic and pulmonary vascular resistance. Such an increase in peripheral resistance will tend to prolong left ventricular ejection as measured by fast ejection length and systolic time and this is indeed the case for both groups in the present study and for normal individuals and those with coronary artery disease in previous studies from this hospital. It is equally not surprising that the peak rate of left ventricular ejection is both reduced and delayed by cold pressor stress. Changes in the diastolic parameters are less easily attributed to this mechanism. However it is notable that the peak rate of diastolic filling was only minimally reduced during cold pressor stress. Although the time to peak filling (PFT) appears to be prolonged by cold pressor stress, one must bear in mind that this time is

measured, not from end systole but from end diastole. It therefore includes the systolic time component. The true fast filling time measured from end systole may be obtained by subtracting systolic time from fast filling time and this can be seen to be unchanged by cold pressor stress. In both groups the trend was for fast filling to be prolonged during cold pressor stress. However this response was variable and not always significant. Buonanno et al (125) have found left ventricular end diastolic pressure to be increased by 60% during cold pressor stress and it is conceivable therefore that this increased preload would lead to a prolongation in the length of the fast filling period. Clearly in normal individuals the ejection fraction response to cold pressor may depend on a balance between the increase in afterload which would tend to decrease ejection fraction and the increase in preload which would tend to increase it. The same mechanisms may apply in individuals with coronary disease. However in addition afterload increases will lead to an increase in myocardial work while an increase in end diastolic pressure may also adversely effect coronary filling by its effect on wall tension. These additional factors could explain the further reduction in ejection fraction response in individuals with ischaemic heart disease. It has however been shown by Dymond et al (117) that the maximal changes in left ventricular function do not necessarily coincide with the haemodynamic responses. This suggests an additional mechanism. This may be a direct effect on coronary vascular resistance since Mudge et al (126) during cardiac catheterisation found a 27% increase in

coronary vascular resistance in patients with coronary artery disease 50 seconds after cold pressor stress. This did not occur in normal individuals. Feldman et al (127) confirmed these findings.

In summary therefore the ejection fraction response to cold pressor in any individual is a balance between the positive effect of increases in end diastolic pressure and circulating catecholamines and the negative influences of an increase in peripheral resistance. In individuals with ischaemic heart disease all these factors tend, in addition, to have a deleterious effect on the balance between myocardial oxygen supply and demand and in conjunction with the direct effect on coronary tone this may further reduce ejection fraction. It is self evident that such a change is likely to be mediated by local changes in regional left ventricular function in areas supplied by diseased vessels.

How then may the above factors help us to explain the results of this study? There are two possible areas which can be addressed. Exercise training may have a global effect on the myocardium which could lead to an alteration in left ventricular function at rest and/or during stress. Alternatively exercise training may effect myocardial perfusion and hence ameliorate the effects of impaired perfusion on the ejection fraction response to cold pressor stress. The heart rate and blood pressure response has already been discussed and the results would support the assertion that these studies have been carried out at equivalent levels of cold pressor stress. It is valid therefore to compare

those results at baseline and one year directly. Ignoring the ejection fraction for the moment, whether one considers the resting or the stress values the striking feature is the lack of change in the left ventricular function parameters. There are two possible explanations for this lack of change. The first very real possibility is that the techniques used are not sufficiently sensitive to demonstrate subtle change in the left ventricular function parameters. As mentioned in the methods section the gamma camera used does not allow high count rates and therefore the cardiac cycle was divided into 16 segments. This allowed a reasonable number of counts per point but was clearly less than ideal. This being the case it would be dangerous to read too much into the left ventricular function curve parameters. However, if one is prepared to accept this lack of change as genuine then it implies that resting and stress left ventricular function is unaltered by exercise training whether one considers diastolic or systolic parameters. Of particular interest are those parameters of systolic function which have been shown to be sensitive indicators of inotropic change. In the training group fast ejection length and systolic length at rest, and more particularly during stress, show negligible difference. This would suggest that no significant inotropic change has taken place as a result of the training programme.

In contrast the improved ejection fraction response to cold pressor is highlighted by the lack of change in the other parameters. As discussed above one explanation is that those factors related to impaired perfusion which tend to reduce

ejection fraction during cold pressor stress tests have been ameliorated in this study by exercise training. It is reasonable to suggest that the mechanism of improvement in cold pressor ejection fraction after exercise training may be related to improvements in regional myocardial perfusion and function. An alternative factor must be considered however. Exercise training has been shown to increase end diastolic volume. This in turn by the Starling mechanism may increase ejection fraction. The effect of changes in end diastolic volume on the various parameters of left ventricular function has not been investigated. However since increased end diastolic volume is present both at rest and on exercise, and since the improvement in ejection fraction in this study is only during stress, it is unlikely that end diastolic volume is a major factor. A recent study by Ehsani (62) demonstrated an improved ejection fraction response to supine exercise at higher workloads after training. In his study end diastolic volume was also measured by radionuclide ventriculography and found to be greater both at rest and on exercise, yet an improved ejection fraction was present only on exercise. The authors concluded that the improved ejection fraction response to exercise was independent of cardiac loading conditions. Previous studies of limited duration and exercise intensity however have failed to demonstrate these results (60,61,101), though Jensen in 1980 showed no change in rest or maximal ejection fraction but at matched levels of sub maximal exercise a greater mean ejection fraction was achieved.(59)

It would be wrong to overstress the results in this section. The gamma camera used was not ideal for a study of this sort. In addition the method of stress chosen is controversial and not well understood. It would have been better to have carried out an assessment of left ventricular function by invasive means and perhaps during rapid atrial pacing. Nonetheless with these reservations in mind this study has at least shown that the ejection fraction response to cold pressor stress is improved after exercise training. Such an improvement would be consistent with the effects of improved myocardial perfusion. The next stage in the hypothesis therefore is to see whether an improvement in regional left ventricular function can also be demonstrated. This question will be dealt with in the next sub section.

THE EFFECT OF EXERCISE TRAINING ON REGIONAL LEFT VENTRICULAR FUNCTION: REGIONAL EJECTION FRACTION USING TECHNETIUM 99 VENTRICULOGRAPHY

Methods

The method used is as described for global function analysis and the results apply to the same group of patients analysed in that sub section. As part of the analysis of Technetium 99 ventriculography in addition to global left ventricular function regional left ventricular function is also measured. The end diastolic image is divided into eight equal 45° segments measured clockwise commencing at 12 o'clock, and using the left ventricular boundary previously established by the automatic programme. The segments thus derived are superimposed on the end diastolic and and systolic images and the segmental counts are thus calculated. Regional ejection fraction is therefore calculated as for global ejection fraction by expressing the difference between end diastolic and end systolic counts as a percentage of end diastolic count for the region. This was measured both at rest and during cold pressor stress. The results given below are for resting values, cold pressor stress values and rest to stress difference.

Statistics

The results for the three parameters described above are expressed as mean and standard deviation. While the data for the majority of regions were found to conform to a normal distribution this was not always the case. All data were analysed by parametric and non parametric statistics. The baseline and one year results for each region were compared by intragroup analysis using a Student's paired 't' test and a Wilcoxon signed rank test. Those results which did show statistical significance by the Student's 't' test were for normally distributed data. Since it was felt that the results for various regions were interdependent and that there was little validity in statistical comparison of similar regions between the two groups, no intergroup analysis was carried out.

Results

The resting baseline and one year values for the exercise group are shown in Table 20, while the corresponding results for the control group appear in Table 21. There were no statistically significant changes in regional ejection fraction in either group. The maximum positive change in the exercise group occurred in region 2, where resting ejection fraction improved by 7.1%, however the values of regional ejection fraction of 57.8 at baseline and 64.9 at one year are both normal. The greatest fall in ejection fraction at rest in the exercise group occurred in region 6, a region with low resting ejection fraction. The difference between baseline and one year however was only 2.5%

Table 20

Resting regional ejection fraction values at baseline and one year

EXERCISE GROUP

	Region 1		Region 2		Region 3		Region 4		Region 5		Region 6		Region 7		Region 8	
Patient	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	57	75	67	84	60	79	56	73	42	62	34	43	29	26	52	48
2	52	46	59	50	69	44	68	59	73	59	41	34	28	31	42	42
3	37	40	62	59	79	58	87	56	85	55	59	42	36	24	28	30
4	62	64	67	68	67	67	64	66	62	69	36	40	32	41	49	51
5	23	39	20	65	31	71	43	67	40	62	15	36	11	31	16	22
6	41	37	39	34	36	45	39	49	49	56	38	35	30	26	44	36
7	59	58	72	77	73	74	69	74	66	78	45	49	29	38	32	32
8	42	52	53	63	48	57	43	53	42	61	33	31	27	34	35	48
9	51	54	81	79	78	77	73	75	79	68	52	43	36	34	36	46
10	35	43	48	61	56	64	57	47	56	35	29	25	29	25	36	35
11	43	55	69	81	67	78	65	65	59	56	39	43	26	25	33	34
12	36	44	54	65	69	74	60	65	62	63	41	38	22	34	26	37
13	36	37	36	62	57	67	66	64	57	62	36	39	28	25	35	33
14	61	46	69	54	66	54	56	49	59	41	48	25	36	24	48	35
15	48	56	71	72	64	66	61	70	69	58	45	31	28	18	36	29
Mean	45.5	49.7	57.8	64.9	61.3	65	60.5	62.1	60	59	39.4	36.9	28.5	28.9	36.5	37.2
S.D.	11.4	10.8	16.4	13.1	14.0	11.3	12.5	9.4	13.3	10.4	10.3	6.9	6.2	6.2	9.5	8.2
'p'value 't'test	NS		NS		NS		NS		NS		NS		NS		NS	
'p'value Wilcoxon	NS		NS		NS		NS		NS		NS		NS		NS	

Table 21

Resting regional ejection fraction values at baseline and one year

CONTROL GROUP

	Region 1		Region 2		Region 3		Region 4		Region 5		Region 6		Region 7		Region 8	
Patient	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
21	66	64	68	69	75	60	76	72	78	73	55	46	52	40	62	51
22	44	47	50	59	45	47	37	43	24	37	28	26	26	29	35	40
23	47	42	63	57	58	57	60	50	54	46	30	35	24	24	38	33
24	45	56	61	42	71	47	65	62	66	56	32	40	26	49	29	60
25	34	39	43	49	40	41	18	32	26	34	13	17	10	15	19	36
26	48	55	52	52	63	67	68	63	58	58	40	36	39	39	54	45
27	42	47	49	65	74	62	80	57	80	59	57	36	43	22	31	26
28	48	45	58	69	57	74	57	70	61	63	34	37	26	25	34	39
29	55	34	47	49	65	50	73	53	84	52	64	33	44	26	49	31
30	48	49	71	72	78	71	69	57	69	62	60	50	38	29	37	36
31	45	38	55	49	54	48	61	48	52	43	30	29	25	20	40	34
32	21	38	43	58	60	60	53	50	55	51	39	36	37	23	1	45
Mean	45.3	46.2	55.0	57.5	61.7	57.0	59.7	54.7	58.9	52.8	40.2	35.1	32.5	28.4	35.8	39.7
S.D.	10.8	8.8	9.3	9.6	11.8	10.5	17.4	11.3	19.0	11.4	15.6	8.6	11.6	9.7	15.9	9.4
't'test	NS		NS		NS		NS		NS		NS		NS		NS	
Wilcoxon	NS		NS		NS		NS		NS		NS		NS		NS	

(39.4 at baseline, 36.9 at one year). In the control group region 8 showed the maximum positive change of 3.9% from 35.8 at baseline to 39.7 at one year. The greatest negative change in the control group occurred in region 5 where ejection fraction fell from 58.9 to 52.8 over the period of one year.

During cold pressor stress two regions showed statistically significant improvements in regional ejection fraction by parametric and nonparametric statistics. A further region showed an improvement by nonparametric statistics alone. The results for the exercise group are shown in Table 22. It is notable firstly that all eight regions show a positive change from baseline to one year in regional ejection fraction. Indeed regions 1 - 5 all show an improvement of 6 to 8%. However region 4 which improved from 54.4% to 61.1% showed the most significant improvement statistically, closely followed by region 6 which improved from 35.2 to 40.1%. These two regions were significant by both the Student's 't' test and Wilcoxon signed rank test. Region 3 which improved from 58.2 to 64.4% was significant by the Wilcoxon signed rank test only. In contrast to these results the control group showed a negative change in regional ejection fraction during cold pressor for five of the eight regions with a statistically significant reduction from 52% to 45.6% in region 4. (Table 23)

Tables 24 and 25 show the rest to stress change in regional ejection fraction at baseline and one year. For both groups seven of the eight regions show an improvement in the rest to stress response in regional ejection fraction. However only in

Table 22

Cold pressor regional ejection fraction at baseline and one year

EXERCISE GROUP

	Region 1		Region 2		Region 3		Region 4		Region 5		Region 6		Region 7		Region 8	
Patient	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	52	70	58	77	65	73	55	70	48	55	31	35	28	19	49	46
2	48	49	55	44	53	49	57	50	49	42	35	34	33	25	43	25
3	41	43	58	67	55	60	52	57	60	71	36	46	15	26	35	28
4	54	47	64	60	61	64	61	72	55	80	36	47	30	37	43	52
5	11	60	22	81	33	69	41	73	45	79	29	51	7	35	11	30
6	42	30	35	30	24	25	28	37	33	45	29	29	27	16	30	32
7	59	65	69	69	70	65	58	56	59	57	36	34	29	31	34	46
8	47	39	56	46	42	51	42	51	38	54	30	37	29	26	32	37
9	48	62	74	86	76	85	69	78	71	75	44	50	29	36	34	38
10	49	54	68	83	66	81	58	64	65	50	48	38	41	26	38	40
11	54	65	74	92	72	84	50	69	42	62	37	53	28	33	29	39
12	37	56	71	83	69	75	69	68	68	75	36	39	24	36	23	42
13	51	47	66	60	69	72	69	67	71	62	38	42	33	24	44	31
14	40	39	52	53	60	49	52	44	45	38	28	27	33	20	34	35
Mean	45.2	51.9	58.7	66.5	58.2	64.4	54.4	61.1	53.5	60.4	35.2	40.1	27.6	27.9	34.2	37.2
S.D.	11.6	11.8	14.9	18.5	15.4	16.6	11.7	12.2	12.5	14.0	5.7	8.2	8.2	6.9	9.6	7.7
't'test	NS		NS		NS		0.035		NS		0.04		NS		NS	
Wilcoxon	NS		NS		< 0.05		< 0.05		NS		< 0.05		NS		NS	

Table 23

Cold pressor regional ejection fraction at baseline and one year

CONTROL GROUP

	Region 1		Region 2		Region 3		Region 4		Region 5		Region 6		Region 7		Region 8	
Patient	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
21	61	53	70	54	68	64	62	63	76	73	47	50	56	48	60	52
22	35	36	52	47	43	31	29	25	19	17	22	16	18	25	31	37
23	38	47	57	62	55	55	48	47	53	55	23	34	16	18	28	26
24	50	52	68	58	67	43	63	46	62	67	40	48	36	64	36	66
25	22	38	28	46	21	30	18	9	8	17	17	15	9	14	9	30
26	55	54	50	62	56	61	49	52	38	45	28	31	30	20	36	44
27	45	40	59	59	52	50	50	47	54	68	49	35	31	13	34	13
28	54	59	73	78	68	72	60	63	59	61	45	47	33	30	32	36
29	46	39	49	57	61	61	64	51	74	50	52	32	44	24	41	33
30	47	54	63	71	68	67	65	51	66	56	50	42	26	24	32	30
31	54	46	67	53	61	48	64	48	64	52	37	30	31	20	44	33
Mean	46.1	47.1	57.8	58.8	56.4	52.9	52.0	45.6	52.1	51.0	37.3	34.5	30.0	27.3	34.8	36.4
S.D.	11.0	7.9	12.9	9.5	14.2	14.0	15.7	15.7	21.9	18.8	12.7	11.8	13.1	15.4	12.3	13.9
't'test	NS		NS		NS		NS		NS		NS		NS		NS	
Wilcoxon	NS		NS		NS		< 0.05		NS		NS		NS		NS	

Table 24

Rest-Cold pressor change in regional ejection fraction at baseline and one year

EXERCISE GROUP

	Region 1		Region 2		Region 3		Region 4		Region 5		Region 6		Region 7		Region 8	
Patient	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	-5	-5	-9	-7	5	-6	-1	-3	+6	-7	-3	-8	-1	-7	-3	-2
2	-4	+3	-4	-6	-16	+5	-11	-9	-24	-17	-6	0	+5	-6	+1	-17
3	+4	+3	-4	+8	-24	+2	-35	+1	-25	+16	-23	+4	-21	+2	+7	-2
4	-8	-17	-3	-8	-6	-3	-3	+6	-7	+11	0	+7	-2	-4	-6	+1
5	-12	+21	+2	+16	+2	-2	-2	+6	+5	+17	+14	+15	-4	+4	-5	+8
6	+1	-7	-4	-4	-12	-20	-11	-12	-16	-11	-9	-6	-3	-10	-14	-4
7	0	+7	-3	-8	-3	-9	-11	-18	-7	-21	-9	-15	0	-7	+2	+14
8	+5	-13	+3	-17	-6	-6	-1	-2	-4	-7	-3	+6	+2	-8	-3	-11
9	-3	+8	-7	+7	-2	+8	-4	+3	-8	+7	-8	+7	-7	+2	-2	-8
10	+14	+11	+20	+22	+10	+17	+1	+17	+9	+15	+19	+13	+12	+1	+2	+5
11	+11	+10	+5	+11	+5	+6	-15	+4	-17	+6	-2	+10	+2	+8	-4	+5
12	+1	+12	+17	+18	0	+1	+9	+3	+6	+12	-5	+1	+2	+2	-3	+5
13	+15	+10	+30	-2	+12	+5	+3	+3	+14	0	+2	+3	+5	-1	+9	-2
14	-21	-7	-17	-1	-6	-5	-4	-5	-14	-3	-20	+2	-3	-4	-14	0
Mean	-0.1	+2.6	+1.9	+2.1	-2.9	-0.5	-6.1	-0.4	-5.9	+1.3	-3.8	+2.8	-0.9	-2.0	-2.4	-0.6
S.D.	9.9	10.8	12.6	11.6	9.9	8.9	10.5	8.7	12.4	12.6	11.1	8.2	7.5	5.3	6.6	8.0
't'test	NS		NS		NS		NS		NS		NS		NS		NS	
Wilcoxon	NS		NS		NS		NS		< 0.05		0.01		NS		NS	

Table 25

Rest-Cold pressor change in regional ejection fraction at baseline and one year

CONTROL GROUP

	Region 1		Region 2		Region 3		Region 4		Region 5		Region 6		Region 7		Region 8	
Patient	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
21	-5	-11	+2	-15	-7	+4	-14	-9	-2	0	-8	+4	+4	+8	-2	+1
22	-9	-11	+2	-12	-2	-16	-8	-18	-5	-20	-6	-10	-8	-4	-4	-3
23	-9	+5	-6	+5	-3	-2	-12	-3	-1	+9	-7	-1	-8	-6	-10	-7
24	+5	-4	+7	+16	-4	-4	-2	-16	-4	+11	+8	+8	+10	+15	+7	+6
25	-12	-1	-15	-3	-19	-11	0	-23	-18	-17	+4	-2	-1	-1	-10	-6
26	-7	-1	-2	+10	-7	-6	-19	-11	-20	-13	-12	-5	-9	-19	-18	-1
27	+3	-7	+10	-7	-22	-12	-30	-10	-26	+9	-8	-1	-12	-9	+3	-13
28	+6	+14	+15	+9	+11	-2	+3	-7	-2	-2	+11	+10	+7	+5	-2	-3
29	-9	+5	+2	+8	-4	+11	-9	-2	-10	-2	-12	-1	0	-2	-8	+2
30	-1	+5	-8	-1	-10	-4	-4	-6	-3	-6	-10	-8	-12	-5	-5	-6
31	+9	+8	+12	+4	+7	0	+3	0	+12	+9	+7	+1	+6	0	+4	-1
Mean	-1.4	+0.2	+1.7	+1.3	-5.5	-3.8	-8.4	-9.6	-7.2	-2.0	-3.0	-0.5	-2.1	-1.6	-4.1	-2.8
S.D.	7.7	8.0	9.1	9.8	9.6	7.6	10.1	7.1	10.7	11.1	8.7	6.1	8.1	9.0	7.3	5.1
't'test	NS		NS		NS		NS		NS		NS		NS		NS	
Wilcoxon	NS		NS		NS		NS		NS		NS		NS		NS	

the case of the exercise group were there any statistically significant differences, region 6 showing a 6.6% improvement which was significant with a p value of 0.028 by the Student's 't' test and 0.01 by the Wilcoxon signed rank test. Region 5 showed an improvement of 7.2%. This was not however significant by the Student's 't' test although was significant at the 5% level by the Wilcoxon signed rank test. The results in table 24 show that for the exercise group seven of the eight regions showed a reduction in regional ejection fraction from rest to stress at baseline, the greatest reductions being 6.1% in region 4 and 5.9% in region 5. At one year only four regions continued to show a reduction in ejection fraction from rest to stress, the greatest reduction being 2% in region 7. Table 24 shows that seven of the eight regions for the control group showed a reduction in rest to stress regional ejection fraction, the greatest being 8.4% in region 4 and 7.2% in region 5. At one year six of these regions continued to show a fall in ejection fraction from rest to stress, region 4 being the greatest reduction at 9.6%.

Discussion

In that we have shown in the previous subsection an improvement in global ejection fraction during cold pressor, it is to be expected that this will also be reflected in regional ejection fraction. This is clearly the case as shown in the above results. However perhaps the greatest interest in studying regional ejection fraction is in seeing whether there is a difference between various regions. When regional Thallium analysis was carried out there were clear cut differences between

those regions supplied by the left anterior descending coronary artery and other regions. The results of regional ejection fraction are perhaps less clear cut. The interval change data is summarised in Table 26 and shown in histogram form in Figure 25. The improvements in cold pressor regional ejection fraction in the exercise group are striking. However on first analysis these changes appear to be quite uniformly spread throughout the regions. Why then is there this apparent discrepancy between regional ejection fraction change and regional Thallium perfusion change? There are a number of valid points to be considered. Technetium angiography was carried out in the best septal view position (30 - 45° LAO). This corresponds best to the 45° LAO Thallium view in which the improvements in Thallium perfusion were least well seen. The conclusion from Thallium perfusion was that the anterolateral regional of the left ventricle had shown the greatest improvement in perfusion. Technetium scanning in the best septal view position would be carried out with the gamma camera positioned directly over the anterolateral zone. The expected area of improvement would therefore be in the centre of the left ventricle on this view and one would therefore expect it to be reflected in all regions. The results, therefore, are not at variance with those in the rest of the study.

Although there is a uniformity of improvement throughout the various regions during cold pressor, it is interesting to note that regions 3, 4 and 6 are the regions which show statistically significant improvement. These regions are around the apex and septum and more than any might be expected to reflect left anterior descending territory.

Table 26

Interval change values for regional ejection fraction

		REGION							
		1	2	3	4	5	6	7	8
TRAINING	R	+4.2	+7.1	+3.7	+1.6	-1.0	-2.5	+0.4	+0.7
	C	+6.7	+7.8	+6.2	+6.7	+6.9	+4.9	+0.3	+3.0
	R-C	+2.7	+0.2	+2.4	+5.7	+7.2	+6.6	-1.1	-1.8
CONTROLS	R	+1.0	+2.5	-4.7	-5.0	-6.1	-5.1	-4.1	+3.9
	C	+1.0	+1.0	-3.5	-6.6	-1.1	-2.8	-2.7	+1.6
	R-C	+1.6	-0.4	+1.7	+1.1	+5.2	+2.5	+0.5	+1.3

The rest to cold pressor changes in the exercise group highlight regions 4, 5 and 6 since the improvements in regions 1, 2 and 3 during cold pressor are offset by similar degrees of improvement at rest. Again these regional improvements would tend to correlate with those shown during the Thallium study.

While the control group have shown small improvements in rest to cold pressor ejection fraction, inspection of the rest and cold pressor histograms show this to be due not to an improvement in cold pressor response but rather to a greater reduction in resting regional ejection fraction in this group. The differences between those changes noted in the exercise group and those in the control group support the concept that exercise training has produced an improved stress response.

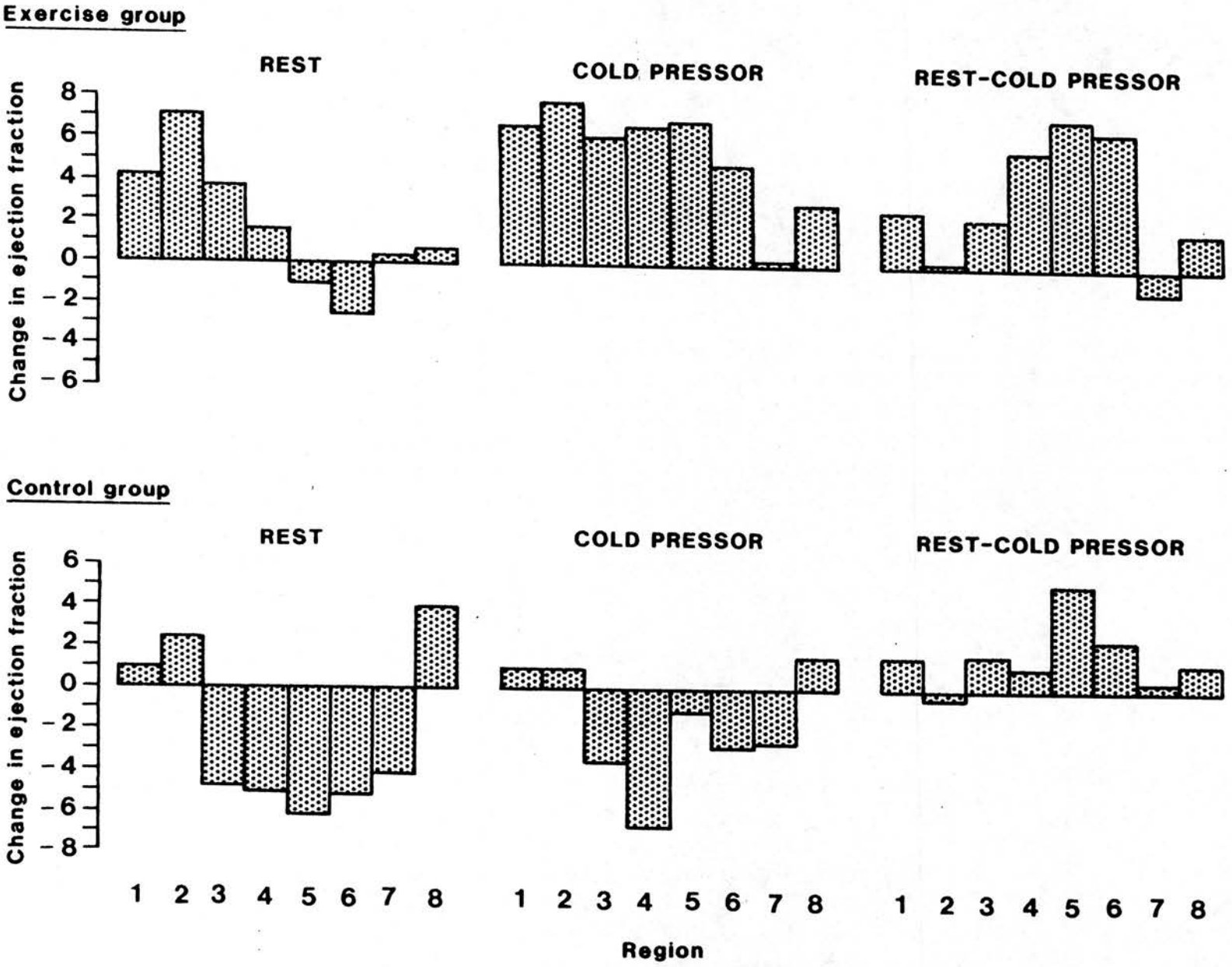


Figure 25 Interval change histogram for regional ejection fraction

There are inherent difficulties in the use of regional ejection fraction measurement which hinder its usage in this study. As has already been mentioned, unlike wall motion analysis it is a three dimensional technique. This fact improves the sensitivity for the detection of coronary artery disease, however since it is in effect less "localising" than regional wall motion then it may reduce its capability for measuring changes in regional ejection fraction over time. Changes in wall motion in one plane may for example by offset by the opposite change in the orthogonal plane leading to a cancelling out of regional ejection fraction. Furthermore the presence of isotope in vascular structures overlying the left ventricle may have a dilutional effect on ejection fraction measurement. The position of the great vessels and atria is such that persistent isotope in these regions will dilute ejection fraction in regions 7, 8 and 1. These regions therefore appear to have a lower ejection fraction. The persistence of isotope at a steady level also may account for the smaller variability in regional ejection fraction measurement in both groups in this area.

Regional ejection fraction has not been used in previous studies as a monitor of improved performance, most studies preferring to use regional wall motion.(54-56,58,60,62) It has nonetheless been shown to be a marker of coronary artery disease and in particular the presence of relative reductions in ejection fraction during isometric handgrip stress has been shown to correlate well with the presence of significant coronary artery narrowing.(67) Despite the reservations about the technique

outlined above therefore, the results do suggest that the improved ejection fraction response to cold pressor stress after training is due to regional improvements in that response, and this is in keeping with the regional improvements in perfusion shown by Thallium scintigraphy.

AN ASSESSMENT OF THE VALUE AND LIMITATIONS OF TECHNIQUES OF WALL MOTION ANALYSIS

The techniques described thus far in this thesis have used computer analysis with minimal observer input. They have in addition been quantitative. As a result their use in a controlled study of group rather than individual changes does not necessitate accurate measurement of variability, although some reference to test variability and factors contributing to it has been made where appropriate. However, at the time of this study commercially available software for automatic analysis of wall motion was limited. As previously discussed the automatic analysis of wall motion during 2-dimensional echocardiography was found to be highly variable. It was decided therefore to use a semiquantitative analysis of wall motion using a 0 - 4 scale as described in section II (0 = dyskinetic, 1 = akinetic, 2 = severely hypokinetic, 3 = mildly hypokinetic, 4 = normal). This scale may be applied to wall motion analysis using either 2-dimensional echocardiography or radionuclide ventriculography. The analysis of wall motion is however time consuming by either technique and it was therefore appropriate to evaluate these techniques during the recruitment phase of the study in order to decide which, if either, would be appropriate to use. There were in particular a number of questions to be addressed. In view of the use of regional ejection fraction in the previous section, is regional wall motion by radionuclide ventriculography of any additional value or is it simply a less accurate variation of the same technique? Does 2 - dimensional echocardiography differ

from radionuclide ventriculography bearing in mind that it allows assessment in two or more planes and uses exercise stress rather than cold pressor? Are either of the techniques "reliable" as assessed by interobserver or intraobserver variability? In order to answer these questions a series of comparisons was made. Firstly regional wall motion by radionuclide ventriculography was compared to regional ejection fraction on the same scans. Next an assessment of the interobserver and intraobserver variability of radionuclide ventriculography derived wall motion was made. Radionuclide ventriculography wall motion was then compared to 2-dimensional echocardiography wall motion and finally an assessment of interobserver and intraobserver variability for 2-dimensional echocardiography wall motion was made. These four comparisons are considered below. For the comparison of regional ejection fraction with regional wall motion Student's 't' test was used to compare the differences between normal and abnormal wall motion. For all other comparisons the results are presented as contingency tables and the percentage agreement and disagreement are discussed. Since these measurements are semiquantitative and have an inherent correlation particularly since the number of abnormal regions is relatively small, the calculation of chi squared values and correlation coefficients is of no value.

Radionuclide ventriculography: regional ejection fraction vs regional wall motion

Radionuclide regional wall motion has been assessed by other authors (54-56,58,60,62) and it is generally agreed that there are

four sites which can be assessed by gated LAO studies. These are the posterolateral region, the apex, the inferoseptal region and the septum.(Figure 26) The posterolateral regional is the largest region and this was assigned two zones while the other three regions were assigned to one zone each. In total therefore five regions of wall motion were assessed on each scan. The outflow tract area was not analysed. The position of these regions was made by identifying the apex and the outflow tract regions and assigning the five regions appropriately. The computer analysis of regional ejection fraction does not take into account variation in position of the apex and outflow tract. The eight regions in the ejection fraction analysis are assigned equally from 12 o'clock on the end diastolic image progressing clockwise. Clearly therefore the five wall motion regions would not always correspond to the same regional ejection fraction regions. Regional wall motion was assessed independently of and without reference to the results of regional ejection fraction. However, at the time of wall motion assessment a note was made of which ejection fraction regions would correspond to the appropriate wall motion regions. In general two of the ejection fraction regions corresponded to the outflow tract and were not considered. The two regions opposite corresponded to the apex and these ejection fraction values were averaged for comparison with the apical regional wall motion score. The remaining four ejection fraction regions were therefore assigned to the four appropriate wall motion regions. In the majority of cases regions one and two of the ejection fraction corresponded to the

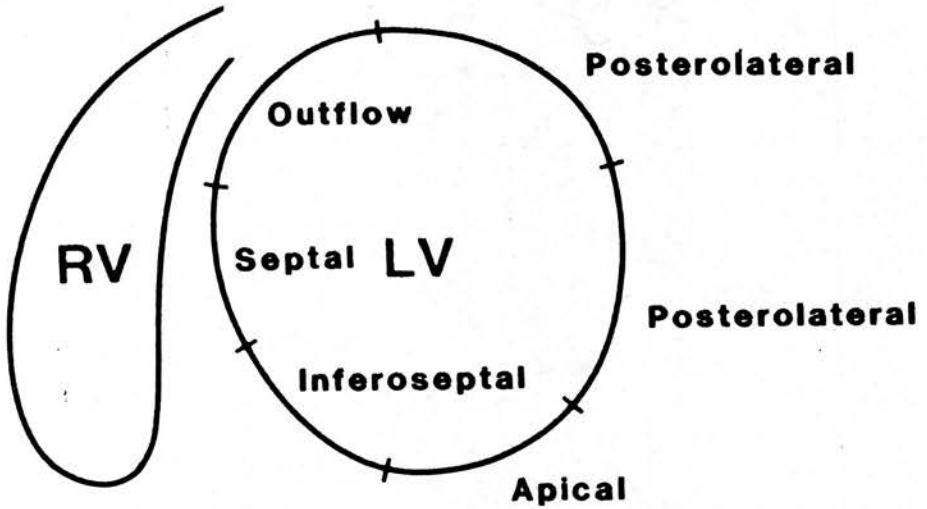


Figure 26 Regions of interest during left anterior oblique gated radionuclide ventriculography

two posterolateral regions, regions three and four corresponded to the apex, region five corresponded to the inferoseptal region, region six corresponded to the septal region and regions seven and eight were the outflow tract regions.

In order to facilitate the scoring of regional wall motion the 16 frame cyclic gated images were first processed by a spacial/temporal smoothing programme. Frame 1 (the end diastolic frame) was then visualised using an appropriate colour coding system and with appropriate adjustment of intensity to allow definition of the left ventricular edge. The intensity score was noted so that this could be reproduced during cyclical imaging. A left ventricular margin was then drawn round the end diastolic image. The 16 frame cyclical image was then played back at the same intensity setting and with the end diastolic margin drawn in. By varying the playback speed, including freeze frame, it was possible to assess the degree of motion relative to the end diastolic margin of each of the segments. An appropriate score could therefore be assigned to each segment. Scores were assigned relative to the most normal segment rather than as absolute scores.

Figure 27 shows the results of comparison of wall motion score against regional ejection fraction for 20 patients (100 regions). If the regional ejection fractions for those regions with normal (4) wall motion are compared with those with abnormal (0 - 3) wall motion, then the differences are statistically significant using a Student's 't' test ($p < 0.01$ at rest and $p < 0.01$ during cold pressor). However, as can been seen there is a

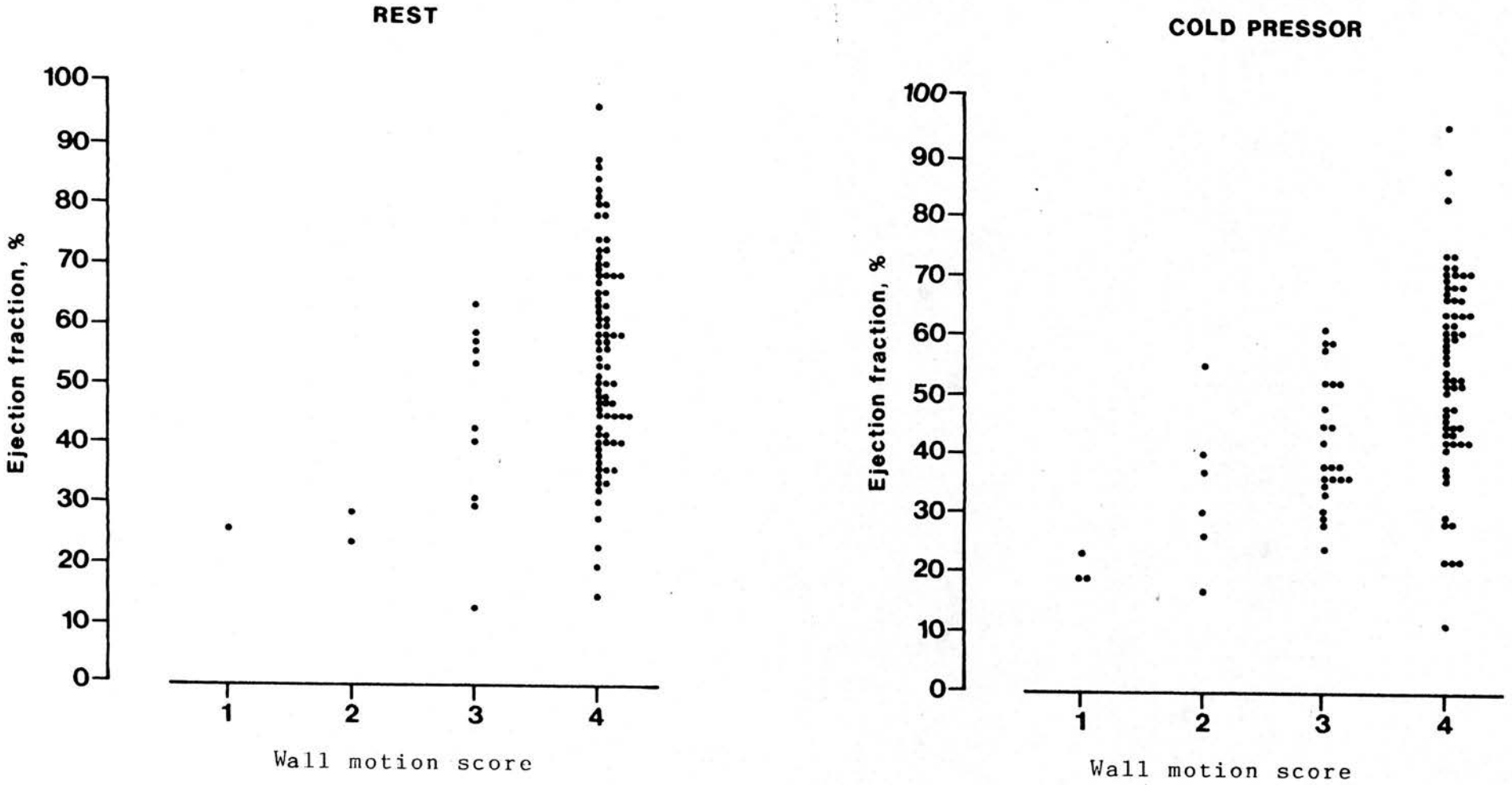


Figure 27 Radionuclide ventriculography: results of absolute regional ejection fraction compared with regional wall motion

considerable overlap both at rest and during cold pressor. Regional ejection fraction is presented as an absolute value, while wall motion as discussed above is relative to other segments. The broad scatter in ejection fraction values between patients may therefore account for the overlap. The ejection fraction values are therefore recalculated as relative values i.e. the region with the highest ejection fraction was scored 100% and all others scored relative to this. This data is presented in Figure 28.

Despite this the overlap is still evident. Why then is there this discrepancy? There are a number of reasons on consideration of the results. In none of the 20 cases was ejection fraction in the septum greater than 80% of maximum. It seems unlikely that these cases all had abnormalities in the septal region at rest and on exercise. It is likely therefore that by radionuclide ventriculography measured ejection fraction in the septum is normally lower than in the free wall. This may be partly physiological due to the contribution of the septum to right ventricular function and partly artefactual due to the overlying vascular structures in this region which have isotope persistence causing a reduction in measured ejection fraction. To a lesser extent the same finding is true for region 1. In this case due to isotope within the great vessels. While wall motion in the septum was graded as abnormal in seven cases at rest and ten cases during cold pressor the remainder had low ejection fractions but were graded 4 for wall motion. Indeed all but one of the 27 regions graded 4 with ejection fractions less than 80%

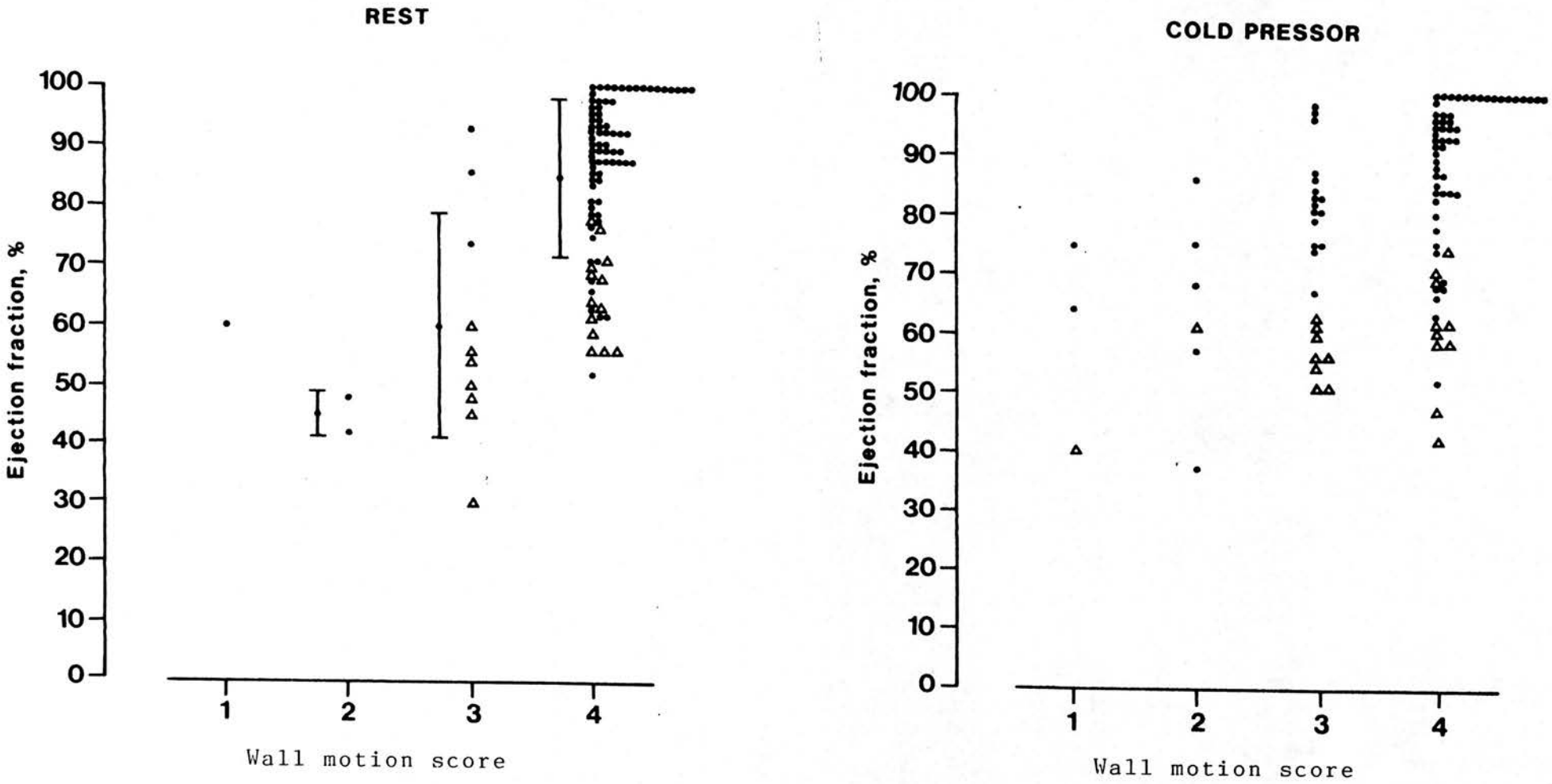


Figure 28 Radionuclide ventriculography: results of relative regional ejection fraction compared with regional wall motion

Triangles = ejection fractions in the septal region

of maximum at rest were either septal or in region 1. Similarly 19 out of 20 regions receiving similar scores during cold pressor were in these two regions. If one wished to assess normality on the basis of region ejection fraction in and individual then clearly this cannot be done without reference to the anatomical regions being considered. A relative ejection fraction of 70% in the free wall may be abnormal while in the septum it is not. This finding limits the use of measurement of regional ejection fraction as an assessment of normality or abnormality in an individual. It does not however preclude its use in group studies as we have done. In the previous section of this thesis regional ejection fraction was simply compared before and after intervention without reference to abnormality or normality of the values. In the absence of a normal reference range for each region similar to that used for the thallium study, this was clearly the most appropriate thing to do.

We can therefore explain part of the overlap between regional ejection fraction scores for regions with normal or abnormal wall motion as being due to "low" normal ejection fractions in regions 1 and 6. More disturbing perhaps are those individuals with abnormal wall motion and yet high regional ejection fractions. Two regions at rest were scored grade 3 which had ejection fractions of greater than 80% of maximum. Also one region was felt to be akinetic with an ejection fraction of 60%. Moreover the number of regions scored abnormal by wall motion with relatively high ejection fractions increases during cold pressor. These regions were re-evaluated to identify the reason

for this discrepancy. While the occasional region appeared to have been inappropriately scored, the majority were not. Two factors were evident which may account for the difference in most cases. Firstly regions next to more severe abnormalities tended to be scored as abnormal i.e. a region scored 0 - 2 often had regions scored 3 adjacent to it and in some cases these regions have normal ejection fractions. This "guilt by association" is a feature of wall motion analysis. In addition however, a number of regions, particularly during cold pressor, were noted to have delayed contraction or phase shift. Such a region would appear hypokinetic or dyskinetic compared to the other regions and yet may on its own produce a near normal ejection fraction. Such a segmental delay in contractility would impair overall ventricular function, perhaps reducing global ejection fraction if sufficiently delayed and yet not show up on regional ejection fraction analysis. In this respect wall motion analysis may detect abnormalities missed by regional ejection fraction. A final obvious consideration is the fact that regional ejection fraction is a 3 dimensional or volume assessment which measures change in count density. An abnormality in one plane may be partially offset by a normal plane at right angles to it. Wall motion analysis by this technique is more concerned with edge following and may either detect an abnormality if in the correct plane or miss it completely if not. This undoubtedly will account for some of the difference between the techniques. In summary therefore the correlation between the two suggests that the analysis of wall motion by semiquantitative means is valid but

the discrepancy between the techniques suggests that perhaps wall motion assessment is sufficiently different from regional ejection fraction to justify its use.

Radionuclide ventriculography: Interobserver and intraobserver variability

Despite the above explanation doubt remains about the reliability of wall motion analysis in the presence of this rather weak correlation with regional ejection fraction. To strengthen the case for regional wall motion assessment therefore it is necessary to show that the technique has acceptable interobserver and intraobserver error. Figure 29 shows a comparison of the wall motion scores of 26 patients by two observers scoring the scans independently. At rest there was an 85% agreement as to whether a region was normal or abnormal. Furthermore in all 110 of these regions the observers agreed exactly as to score. Nineteen regions were scored normal by one observer and grade 3 by the other. In only one region was there a discrepancy of two grades between scores. During cold pressor there was 78% complete agreement on score with 83% agreement as to normality or abnormality. In 27 regions there was a difference of opinion of one grade in score and only in two regions was there disagreement of two grades. Observer 1 analysed 12 scans on a second occasion six months after the initial analysis and complete agreement was found in 90% of cases. In no case was there disagreement of more than one grade. These results compare favourably with those published by Hecht et al using bicycle exercise in 1982.(127)

The above results suggest that wall motion analysis by radionuclide ventriculography is an acceptable technique with moderate interobserver and intraobserver variability. In addition it differs from regional ejection fraction analysis and therefore, despite the fact that it is a semiquantitative technique it may indeed be a useful adjunct to this.

Exercise echocardiography vs radionuclide ventriculography: Wall motion analysis

The technique of recording and scoring regional wall motion by 2-dimensional echocardiography has already been described in section 2. In order to compare it with radionuclide ventriculography however, it was necessary to decide which regions on echocardiography best reflected the five regions identified on radionuclide ventriculography. For the two posterolateral regions this was a straightforward choice in that they correspond to the two regions in the free wall on a four chamber echocardiographic image. Likewise the apex was taken from this view also. The septum and inferoapical regions were less easy in that there were several possible combinations from which to choose. To compare the two remaining four chamber regions directly with the two RNV regions would be to the disadvantage of 2-dimensional echocardiography in excluding the apical long axis view from comparison. Since the aim of the exercise was not simply to establish a correlation, but also to compare the different value of the tests, it was decided to average the proximal septal score on the four chamber echo view with the two septal regions on the

apical long axis view and "round" up or down the score appropriately e.g. 3 + 3 + 4 gives a score of 3.3 rounded down to 3 and 4 + 4 + 3 gives 3.6 rounded up to 4. The inferoapical region was compared to a similarly averaged score derived from the distal septum on 4C view and the inferior region on the apical long axis view. The grade of scoring 0 - 4 was identical for radionuclide ventriculography and 2-dimensional echocardiography. Figure 30 shows the results of this comparison for 23 patients in whom good quality echocardiograms and radionuclide ventriculograms were obtained. At rest there was a close correlation between the two techniques. There was total agreement on score in 100 out of 115 regions (87%) with agreement on normality or abnormality of 90%. In only two regions was there disagreement of greater than one grade. On exercise the correlation was still evident. However the number of regions with total agreement had fallen to 77 (67%) with agreement on normality or abnormality in 76% and disagreement of greater than one grading in 11 regions (10%). These results show a good correlation between techniques at rest. The resting values are as good as those achieved above when comparing observers for radionuclide ventriculography alone. The stress comparison however reveals some differences between the techniques. The pattern of scores suggests that in many cases 2 dimensional echocardiography tended to score regions lower than radionuclide ventriculography during stress but not at rest. The breakdown of results for the four regions at rest is shown in Figure 31 and during stress in Figure 32. These results show that this pattern of more severe abnormality during exercise

Figure 29

Interobserver variability of wall motion analysis by cold pressor RNV

Rest

Observer 2 \ Observer 1	0	1	2	3	4
4	–	–	–	3	93
3	–	–	–	14	16
2	–	–	2	–	1
1	–	1	–	–	–
0	–	–	–	–	–

Cold pressor

Observer 2 \ Observer 1	0	1	2	3	4
4	–	–	–	8	70
3	–	–	2	23	12
2	–	1	5	2	2
1	1	2	–	–	–
0	1	1	–	–	–

Figure 30

Wall motion analysis: RNV v exercise echocardiography

Rest

RNV \ Echo	0	1	2	3	4
4	–	–	–	5	87
3	–	1	1	12	5
2	–	–	1	1	1
1	–	–	1	–	–
0	–	–	–	–	–

Stress

RNV \ Echo	0	1	2	3	4
4	–	1	4	16	54
3	–	2	7	17	6
2	–	1	4	–	1
1	–	2	–	–	–
0	–	–	–	–	–

Figure 31

Wall motion analysis: cold pressor RNV v exercise echocardiography - Rest

Apical region

RNV \ Echo	0	1	2	3	4
4	–	–	–	3	13
3	–	1	–	3	1
2	–	–	1	1	–
1	–	–	–	–	–
0	–	–	–	–	–

Lateral region

RNV \ Echo	0	1	2	3	4
4	–	–	–	2	40
3	–	–	1	2	1
2	–	–	–	–	–
1	–	–	–	–	–
0	–	–	–	–	–

Septal region

RNV \ Echo	0	1	2	3	4
4	–	–	–	–	18
3	–	–	–	4	1
2	–	–	–	–	–
1	–	–	–	–	–
0	–	–	–	–	–

Infero apical region

RNV \ Echo	0	1	2	3	4
4	–	–	–	–	16
3	–	–	–	3	2
2	–	–	–	–	1
1	–	–	1	–	–
0	–		–	–	–

Figure 32

Wall motion analysis: cold pressor RNV v exercise echocardiography - stress

Apical region

RNV	0	1	2	3	4
4	–	1	1	3	8
3	–	1	1	4	1
2	–	1	1	–	–
1	–	1	–	–	–
0	–	–	–	–	–

Echo

Lateral region

RNV	0	1	2	3	4
4	–	–	1	9	26
3	–	–	2	6	1
2	–	–	1	–	–
1	–	–	–	–	–
0	–	–	–	–	–

Echo

Septal Region

RNV	0	1	2	3	4
4	–	–	2	1	13
3	–	1	1	3	1
2	–	–	1	–	–
1	–	–	–	–	–
0	–	–	–	–	–

Echo

Infero apical region

RNV	0	1	2	3	4
4	–	–	–	3	7
3	–	–	3	4	3
2	–	–	1	–	1
1	–	1	–	–	–
0	–	–	–	–	–

Echo

echocardiography in the post exercise scans is consistent in all regions. While it is possible that poor quality imaging after exercise may impair echocardiographic scoring, on the whole in such cases the tendency was to score regions normal rather than abnormal. A direct comparison of the regional scores for various patients with either technique suggests that the regions noted on radionuclide ventriculography tend to be picked up also on echocardiography. However the abnormalities on echocardiography tended to be more extensive e.g. an inferoseptal defect on radionuclide ventriculography would often extend laterally on echocardiography. This may reflect an advantage of echocardiography with regard to its ability to examine planes separately but it is perhaps more likely to be due to the type of stress test used. It is accepted that exercise, particularly treadmill exercise, produces a greater degree of stress than the cold pressor test. This higher degree of stress may account for the more extensive wall motion abnormalities picked up on post exercise echocardiography. There have been few published studies comparing wall motion analysis by radionuclide ventriculography with exercise echocardiography but those which have been published would support the above viewpoint. Limacher et al (71) reported a good correlation between exercise echocardiography and radionuclide ventriculography. They too found a higher pick-up rate by echocardiography. In their study treadmill exercise was used for echocardiographic assessment and bicycle exercise was used for radionuclide ventriculography. They noted that the workload achieved by treadmill exercise was greater than that

achieved by bicycle exercise and felt that this may well have contributed to the better pick-up rates by echocardiography. They did, in addition, suggest that inferior wall assessment was particularly difficult using gated radionuclide ventriculography and that this may also be a factor. They did not however report specific regional results to support this hypothesis and indeed our own study would suggest that this is not the case. Ginzton et al (129) carried out a study comparing post exercise echocardiography with first pass RAO radionuclide angiography. In this study symptom limited upright bicycle exercise was used for both techniques and the degree of exercise was found to be similar. They studied three regions (anterior, apical and inferior) and found a high degree of correlation between the techniques irrespective of region studied. Their overall figures are comparable to our own results with a similar degree of scatter, however they did not find either technique to have a higher pick-up rate. This suggests that the level of exercise achieved by the stress test is perhaps the most important factor in determining the different pick-up rates of these respective techniques. Similar findings were reported by Romijn et al.(130)

The results of this comparison would suggest therefore that exercise echocardiography may indeed be a more sensitive device for monitoring wall motion abnormalities than radionuclide ventriculography in our hospital, the main difference between the techniques being due to differences between the stress tests used. One must however bear in mind that it is not always possible to obtain good 2-dimensional echocardiograms while

radionuclide ventriculography is generally a more straight forward technique to apply.

2-DIMENSIONAL ECHOCARDIOGRAPHY INTEROBSERVER AND INTRAOBSERVER VARIABILITY

Thirty six pre and post exercise echocardiograms were analysed by two observers separately and the results of wall motion scores for the total of 360 regions are shown in Figure 33. As for the previous techniques there was a good correlation between observers at rest and on exercise. Observers agreed completely in 310 out of 360 regions (86%) at rest with 89% agreement as to normality or abnormality. In only one region was there disagreement of more than one grade. During exercise there was 75% complete agreement and 80% agreement as to normality or abnormality. Disagreement of greater than one grade was present in 11 regions. Both at rest and during stress observer 2 tended to grade abnormalities more severely than observer 1. This may be partly due to the fact that observer 1 carried out all of the echocardiograms and was perhaps more familiar with the technique. Observer 1 was also a more experienced echocardiographer and in addition was familiar with the patients. Since none of the patients had sustained a previous myocardial infarction, observer 1 might be biased towards scoring these normal at rest. It is likely that noting a resting abnormality would tend to influence scoring of that region on exercise. These difference represent true interobserver variability in analysis. While both observers continued to score all scans during the study and disagreement was

Figure 33

Interobserver variability of wall motion analysis by exercise echocardiography

Rest

Observer 2 \ Observer 1	0	1	2	3	4
4	–	–	–	3	296
3	–	1	6	13	38
2	–	–	1	2	–
1	–	–	–	–	–
0	–	–	–	–	–

Exercise

Observer 2 \ Observer 2	0	1	2	3	4
4	–	–	5	4	215
3	–	–	10	52	58
2	1	3	3	3	5
1	–	1	–	–	–
0	–	–	–	–	–

settled by consensus opinion, the "experience" of observer 1 tended to hold sway over observer 2 in cases of disagreement. Intraobserver error was assessed by observer 1 who scored 12 scans one year apart. There was 89% agreement in scoring at rest with no difference of greater than one grade and 82% agreement on exercise with only two of 120 regions scored greater than one grade apart.

The assessment of these techniques would suggest that they are all of value in the assessment of left ventricular function. The correlation between tests is generally good and where differences have been detected explanations have been provided. Furthermore the degree of variability in the technique is acceptable and comparable to that of Crawford et al.(70) One must however bear in mind that these analyses tell nothing about the sensitivity of the investigations for the detection of coronary artery disease. The generally good correlation between the techniques suggests that they are all detecting true abnormalities in wall motion i.e. that they are specific. The number of abnormalities detected by either technique of wall motion analysis is however relatively small, bearing in mind that this group of patients all have evidence of coronary artery disease. This tends to suggest a lack of sensitivity in the test or in the ability of the individual to interpret the results. Wall motion abnormalities either at rest or on exercise were detected in 84% of patients by radionuclide ventriculography and in 72% of patients by exercise echocardiography. All of these patients had abnormal exercise tests and Thallium scintigraphy and were all deemed clinically to

have ischaemic heart disease. The sensitivity of these techniques is therefore relatively low compared for example to Thallium scintigraphy. The sensitivity of exercise echocardiography in particular is lower than that reported for some authors.(71,131,132) In view of this, concern must remain that neither technique will prove sufficiently sensitive to monitor changes in abnormalities following exercise training. With this reservation however, it is nonetheless of interest that both techniques appear to have advantages over those reported in previous sections. Wall motion assessed by radionuclide ventriculography allows the consideration of regions with delayed contractility as well as those with hypokinesis and the superior stress of exercise echocardiography produces more extensive wall motion abnormalities than cold pressor stress testing. The results of these techniques in the analysis of changes in wall motion with exercise training will therefore be considered in the next subsection.

THE EFFECT OF EXERCISE TRAINING ON LEFT VENTRICULAR WALL MOTION

Methods

In the previous sub section wall motion analysis by radionuclide ventriculography and 2-dimensional echocardiography was validated. This sub section deals with the use of these techniques to assess changes in wall motion following exercise training. The method of radionuclide ventriculography has been described earlier in this thesis and the studies available for analysis are those discussed previously in the sub section on left ventricular function i.e. 15 resting and 14 stress scans in the exercise group and 12 resting and 11 stress scans in the control group. The raw data from these scans was processed as described in the previous sub section. In addition however transfer of data from floppy discs to the Winchester hard disc was carried out by an observer blinded to the group to which the patients belonged. During transfer a code was applied to the scans which could be used subsequently to identify baseline from one year. While the other observer could identify to which group the patients belonged he was not familiar with the coding. Therefore neither observer had sufficient information to "bias" his analysis of the results.

For exercise echocardiography 16 paired studies were available in each group, three patients in each group being lost to follow up and one patient in each group excluded due to myocardial infarction. It was not possible to carry out this part of the study without bias. One observer carried out all scans (the

author) and subsequently analysed them. All patients were of course known to the author. The second observer was not familiar with either the patients or the order of scanning. In this case, as with radionuclide ventriculography, a consensus score was arrived at where observers disagreed.

Statistics

The summated scores for wall motion do not correspond to a normal distribution by either radionuclide ventriculography or 2-dimensional echocardiography. For these global results, therefore a mean and standard deviation for the group is quoted. Intragroup analysis of paired data is therefore carried out using a Willcoxon signed rank test. Where significant a p value is quoted. Although intergroup analysis of regional data was considered inappropriate, the global scores were treated in the same fashion as global ejection fraction data and therefore interval change was measured and intergroup comparison was carried out using the Mann Whitney U test. The results of regional changes are also shown. However since the number of patients showing abnormalities in any given region is small no statistical analysis of this data was attempted.

Results

a) Radionuclide ventriculography

Table 27 shows the total wall motion scores for the patients in each group with the baseline (1) and one year (2) results given for rest, stress and rest to stress change. In the exercise

Table 27

Total wall motion scores by radionuclide ventriculography

EXERCISE GROUP

Pat No	Rest 1	Rest 2	Stress 1	Stress 2	R-S 1	R-S 2
1	20	20	19	19	−1	−1
2	19	20	19	19	0	−1
3	20	20	19	20	−1	0
4	20	20	18	20	−2	0
5	20	20	19	20	−1	0
6	19	19	16	17	−3	−2
7	20	20	18	20	−2	0
8	20	20	18	19	−2	−1
9	20	20	19	20	−1	0
10	19	20	19	20	0	0
11	20	20	20	20	0	0
12	20	20	18	20	−2	0
13	20	20	19	20	−1	0
14	19	20	17	18	−2	−2
15	20	20	–	–	–	–
Mean S.D.	19.7 ±0.46	19.9 ±0.37	18.4 1.02	19.4 0.94	−1.3 0.91	−0.5 0.76
'p'value Wilcoxon	NS		< 0.005		< 0.04	

CONTROL GROUP

Pat No	Rest 1	Rest 2	Stress 1	Stress 2	R-S 1	R-S 2
21	20	20	20	19	0	−1
22	17	19	15	11	−2	−8
23	20	20	18	20	−2	0
24	19	20	16	19	−3	−1
25	20	20	18	18	−2	−2
26	13	19	10	11	−3	−8
27	20	20	20	19	0	−1
28	19	20	19	19	0	−1
29	20	20	17	20	−3	0
30	20	19	20	19	0	0
31	20	20	19	20	−1	0
32	18	20	–	–	–	–
Mean S.D.	18.8 2.08	19.8 0.45	17.5 2.98	17.7 3.37	−1.5 1.29	−2.0 3.03
'p'value Wilcoxon	NS		NS		NS	

group there were few resting abnormalities on either occasion and the mean wall motion scores of 19.7 ± 0.46 and 19.9 ± 0.37 at baseline and one year reflect this. During stress at baseline however the mean score fell to 18.4 ± 1.02, while at one year the fall was much less at 19.4 ± 1.94. Comparison of the stress results shows significant improvement in wall motion score during cold pressor in this group ($p < 0.005$). No patient showed a deterioration in wall motion score during cold pressor at one year, 11 out of 14 showing an improvement. The rest to stress change at baseline in this group was -1.3 ± 0.91. By one year it had improved to -0.5 ± 0.76. This improvement was also significant ($p < 0.04$).

In the control group resting wall motion score was lower at baseline at 18.8 ± 2.08. At one year it had risen to 19.8 ± 0.45. This difference was largely due to one patient and was not statistically significant using non parametric comparison. The mean stress wall motion score in this group was lower than in the exercise group but showed consistency over the year being 17.5 ± 2.98 at baseline and 17.7 ± 3.37 at one year. The rest to stress change was -1.5 ± 1.29 at baseline and -2.0 ± 3.03 at one year. In this group four out of 11 patients showed a deterioration in stress wall motion score over the year, while five out of 11 improved. The difference in the number with improved stress scores in the exercise group compared to the control group (11 out of 14 vs 5 out of 11) was significant by the Fisher's exact test ($p < 0.05$). The interval change data is shown in Table 28. Since this data is unpaired statistical comparison of the three

Table 28

Interval change in total wall motion score by radionuclide ventriculography

	Exercise group		Control group		
Parameter	Mean	S.D.	Mean	S.D.	'p'value
Rest	+0.2	0.4	+0.9	1.8	NS
Stress	+1.0	0.7	+0.3	2.1	NS
R-S change	+0.9	0.7	-0.5	2.8	NS

parameters using the Mann Whitney test showed no significant differences. The mean change of +1 $\pm$ 0.7 in the exercise group was offset by a slight positive change (0.3 $\pm$ 2.1) in the control group. The rest to stress change of +0.9 $\pm$ 0.7 in the exercise group compares favourably with the rest to stress change of -0.5 $\pm$ 2.8 in the control group.

The mean regional scores for the exercise group at rest and during cold pressor are shown in Figure 34. The most common site for abnormalities during cold pressor at baseline was the inferoseptal region with a mean group score of 3.2. This had improved to 3.8 at one year. There were too few abnormalities in other regions to show much change, but no region deteriorated

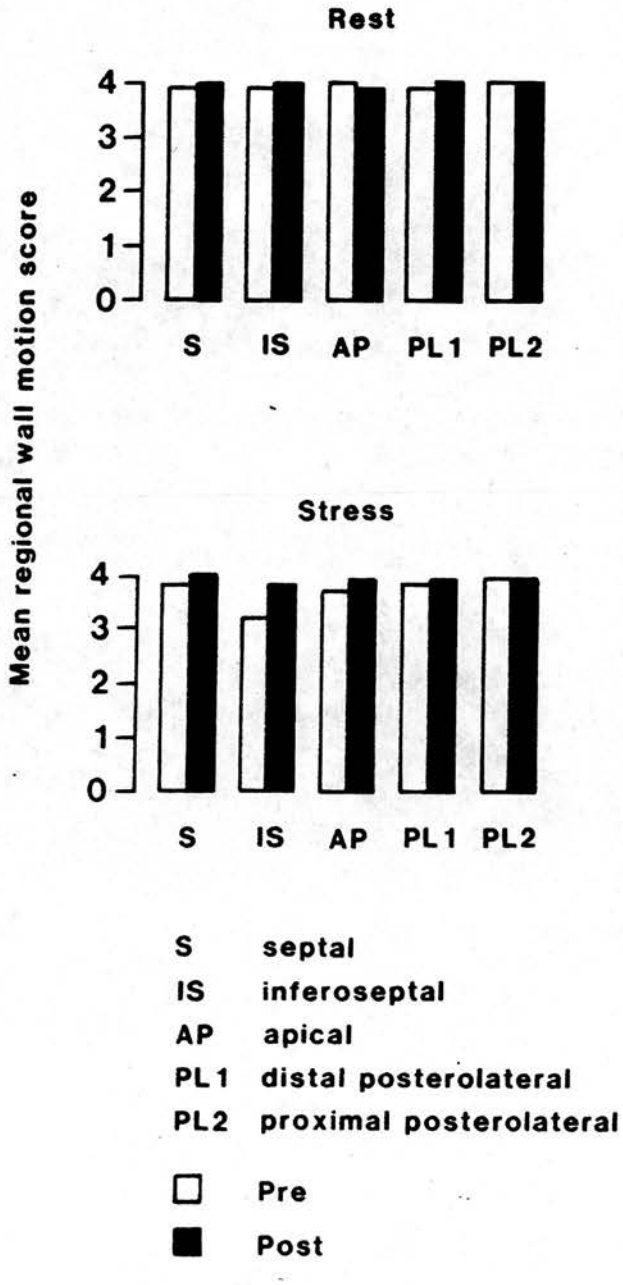


Figure 34 Mean regional wall motion scores pre and post training by radionuclide ventriculography

during stress and there were no septal abnormalities in the group at one year.

b) Exercise echocardiography

The individual results for exercise echocardiography and group means are shown in Table 29. Again there were few resting abnormalities in the exercise group, reflected in mean wall motion scores of 39 $\pm$ 2.4 and 39.2 $\pm$ 2.0 at baseline and one year respectively. After exercise the mean wall motion score at baseline fell to 36.7 $\pm$ 3.5, while it was statistically better at one year at 38.6 $\pm$ 2.3 ($p < 0.04$). The rest to exercise change was -2.3 $\pm$ 2.7. At one year this had also improved to -0.6 $\pm$ 1.5, this difference being statistically significant ($p < 0.05$). By this technique the control group's resting wall motion scores were 39.2 $\pm$ 1.9 and 38.8 $\pm$ 3.3 at baseline and one year, while the exercise scores were 36.5 $\pm$ 3.8 and 37 $\pm$ 4.2 respectively. Neither change was significant. The rest to exercise change was -2.7 $\pm$ 2.5 at baseline and -1.8 $\pm$ 1.9 at one year and again this was not significant. The proportion showing improved wall motion in the exercise group (8 out of 16) was not significantly greater however than that in the control group (6 out of 16). The interval change data for both groups is shown in Table 30 while the trend towards improvement in exercise and rest to exercise scores is greater in the training group these failed to reach statistical significance.

The regional breakdown of results for the exercise group is shown in Figure 35. Again the numbers are small, the most abnormal area at baseline being in the septum and apex on the four

Table 29

Total wall motion scores by exercise echocardiography

EXERCISE GROUP

Pat No	Rest 1	Rest 2	Ex 1	Ex 2	R-E 1	R-E 2
1	39	39	36	40	-3	+1
2	40	40	40	40	0	0
3	40	40	37	40	-3	0
4	40	40	38	40	-2	0
5	40	40	38	40	-2	0
6	39	38	29	38	-10	0
7	40	40	40	36	0	-4
8	34	38	31	38	-3	0
9	40	40	40	40	0	0
10	40	40	40	40	0	0
11	40	40	36	36	-4	-4
12	40	40	35	37	-5	-3
13	32	32	32	32	0	0
14	40	40	40	40	0	0
15	40	40	36	40	-4	0
16	40	40	39	40	-1	0
Mean	39	39.2	36.7	38.6	-2.3	-0.6
S.D.	2.4	2.0	3.5	2.3	2.7	1.5
'p'value	NS		< 0.04		< 0.05	

CONTROL GROUP

Pat No	Rest 1	Rest 2	Ex 1	Ex 2	R-E 1	R-E 2
21	40	40	40	40	0	0
22	40	40	33	38	-7	-2
23	40	40	39	39	-1	-1
24	40	40	37	36	-3	-4
25	34	28	28	23	-6	-5
26	40	40	40	40	0	0
27	40	40	38	39	-2	-1
28	40	40	39	39	-1	-1
29	40	40	35	38	-5	-2
30	40	40	40	37	0	-3
31	40	40	34	34	-6	-6
32	35	34	30	34	-5	0
33	40	40	38	38	-2	-2
34	38	38	34	37	-4	-1
35	40	40	40	40	0	0
36	40	40	39	40	-1	0
Mean	39.2	38.8	36.5	37	-2.7	-1.8
S.D.	1.9	3.3	3.8	4.2	2.5	1.9
'p'value	NS		NS		NS	

Table 30

Interval change in total wall motion score by exercise echocardiography

	Exercise Group		Control Group		
Parameter	Mean	S.D.	Mean	S.D.	'p'value
Rest	+0.2	1.0	-0.4	1.5	NS
Exercise	+1.9	3.1	+0.5	2.5	NS
R-E change	+1.7	3.0	+0.9	2.1	NS

chamber view. No area shows a deterioration at one year, the greatest improvement is also in the septum and apex.

Discussion

The results of wall motion scores by the two techniques shows consistency. Both techniques show that wall motion during stress is improved following exercise training. Furthermore the degree of improvement is very similar by the two techniques. At the same time the control group's results have remained unaltered over the year by either technique. Perhaps the only "discrepancy" between the techniques is in the assessment of resting wall motion score in the control group. However, as already mentioned, the

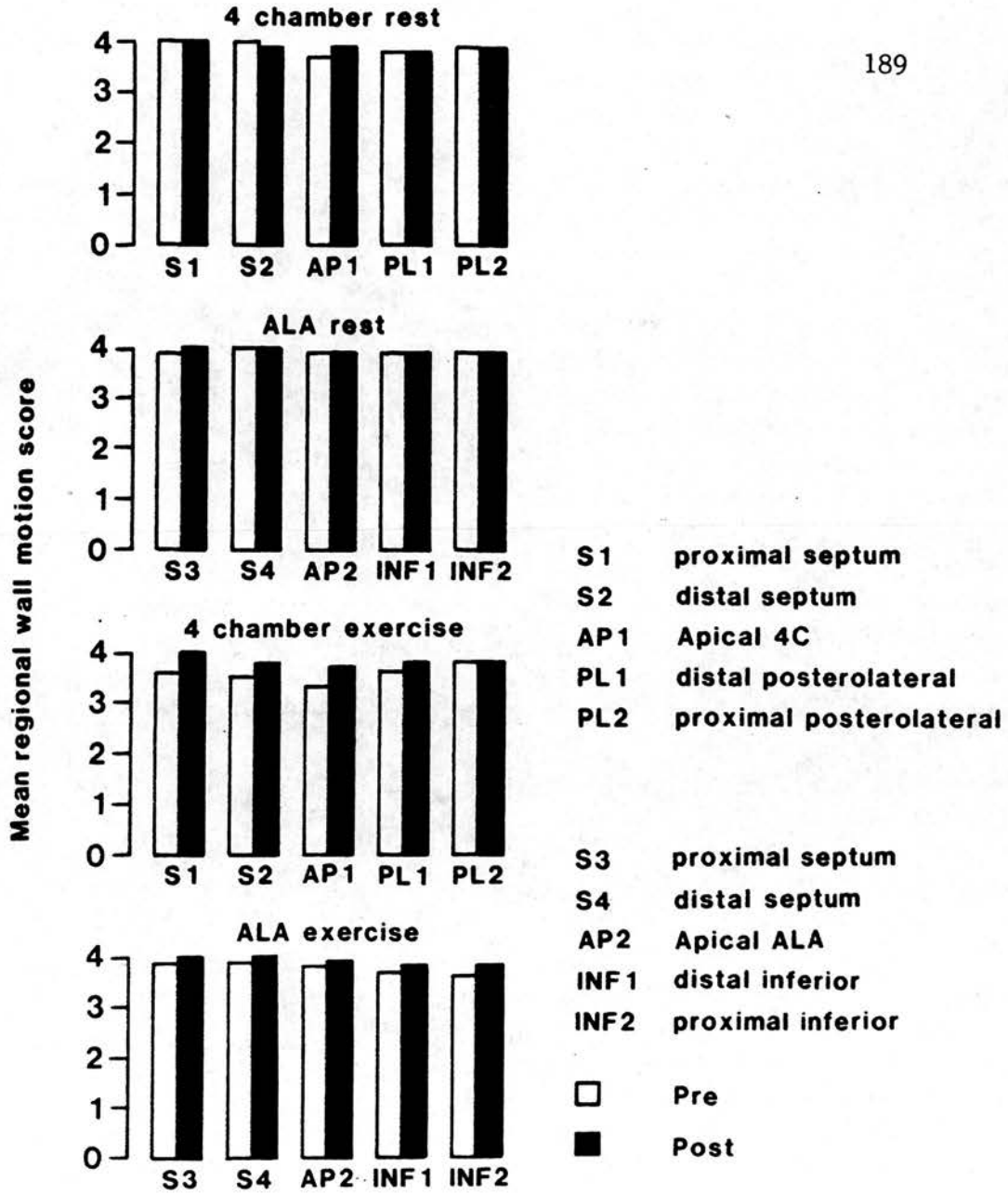


Figure 35 Mean regional wall motion scores pre and post training by two-dimensional exercise echocardiography

low resting wall motion score at baseline by radionuclide ventriculography was largely attributable to one patient. This patient had evidence of extensive disease by all methods and interestingly presented with "indigestion" after meals. This subsequently was shown to be post prandial angina. It was our practice to carry out radionuclide ventriculography at 2.00 p.m. without fasting the patient and the low resting wall motion score in this patient may therefore reflect silent post prandial ischaemia at rest. Subsequently the patient was advised to eat "little and often" which may account for the improvement at one year.

The improvements in overall stress induced wall motion score and rest to stress change are consistent by the two wall motion techniques. In addition they mirror the changes shown by the other techniques described in this thesis in that they suggest an improved stress response after exercise training. It would be wrong to draw too many conclusions from the limited regional data available. Consideration of the regions assessed by radionuclide ventriculography shows the greatest baseline abnormality to be in the region labelled as inferoseptal. In addition this region has shown the most significant improvement at one year. Broadly this is in agreement with the results of regional ejection fraction. At first consideration there seems to be some discrepancy between this finding and the findings of Thallium perfusion studies which demonstrated the greatest improvement to be in the LAD vascular territory. However consideration of the wall motion results achieved by echocardiography perhaps gives a clue to the answer.

The most abnormal region by this technique was the distal septal region on the four chamber view. Again this region showed the greatest improvement at one year. The pattern of change in regional wall motion on the four chamber view is very similar to that shown by radionuclide ventriculography. This suggests that the inferoseptal region shown on radionuclide ventriculography is indeed more septal than inferior reflecting the distal septal echocardiographic region rather than the inferior wall. It is after all appropriately sandwiched between the proximal septum and apex. Further credence to this view is given if one compares the regional wall motion results by radionuclide ventriculography and by 2-dimensional echocardiography in the four chamber view with the 45° LAO Thallium view. The pattern of change by the three techniques is similar.

Two-dimensional echocardiography was chosen on the basis that it would provide better localisation of wall motion abnormalities. The above discussion would support that viewpoint. It is disappointing therefore that the number of abnormalities detected by 2-dimensional echocardiography in the apical long axis view was small, particularly since the corresponding Thallium views had best identified the perfusion change. It is interesting to note however that the greatest wall motion improvement was in the septal region and furthermore that no abnormalities in wall motion could be detected at one year in the septum and apex on the apical long axis view. Although this data is "soft" it does perhaps support the view that the left anterior descending territory has made the greatest improvement.

Two studies have addressed the question of improved wall motion following exercise training using radionuclide ventriculography. Verani (60) failed to show any improvement in wall motion. However as previously discussed he also failed to show any improvements in perfusion and this is attributable to the short duration low intensity programme which he used. Ehsani(62), on the other hand, improved wall motion in 8 out of 10 of his exercise group using a much more intense and prolonged programme. In contrast, the control group demonstrated five wall motion abnormalities at baseline and seven at one year with only one of the original five showing an improvement.

Two dimensional exercise echocardiography has not been used to evaluate the effects of exercise training. However resting 2-dimensional echocardiography was used to assess the benefits of coronary artery bypass grafting (133) and exercise echocardiography was successfully used to demonstrate resolution of exercise induced wall motion defects after treatment with nitroglycerine.(70) In this study we have shown that exercise echocardiography can be as effective as radionuclide ventriculography in monitoring changes in stress induced wall motion abnormalities. In particular the superior spacial definition of 2-dimensional echocardiography and the ability to use this technique with high intensity treadmill exercise offer useful advantages over radionuclide ventriculography. The use of these two differing techniques has confirmed that regional myocardial function can be improved by exercise training and that this improvement is based on an improved ability of dysfunctional

myocardium to cope with stress, whether that stress be due to the cold pressor test or treadmill exercise. The nature and location of these improvements supports the hypothesis that improved perfusion may be responsible.

AN ASSESSMENT OF EXERCISE TRAINING BY AMBULATORY ECG MONITORING

Methods

The technical details of the Oxford Medilog MARS ambulatory monitoring system and details of its use in this study are contained in section II. As with the other investigations ambulatory monitoring was carried out at baseline and one year. The baseline measurements however took place one week after commencing the exercise programme so that an assessment of the response to the daily exercise programme could be made. The analysis of the completed 24 hour tapes comprised of two phases. Firstly the cassette was automatically analysed using the Oxford Medilog (MARS) replay system to produce trend graphs of heart rate, ST segment analysis and ventricular ectopic activity. In addition an hourly summary of maximum and minimum heart rates plus arrhythmias was produced. Samples of all types of complex with relative frequency was also automatically printed. The second phase of the analysis was to use this summary information to select times of ST segment shift or arrhythmias and by entering these times into the replay system print-outs of the two lead ECG's were obtained. This manual check meant that all events identified were confirmed as genuine and in no case was diagnosis of ST segment depression or arrhythmia based solely on the software used by the automatic analysis programme. This was particularly important with regard to ST segment analysis since the point of onset of ST depression could be accurately

identified, the heart rate at that point could be measured and the change in heart rate over the preceding minute could also be ascertained.

Significant ST segment depression was defined as horizontal or downsloping shift of greater than or equal to 1 mVolt from baseline occurring 80 m secs after the J point and lasting for at least 30 seconds. Individuals with obvious resting ST segment or T wave changes in the monitored lead were excluded from analysis. Ventricular ectopic or arrhythmic activity was analysed firstly as the total number of ventricular premature contractions per hour or per 24 hour period and secondly as the maximum Lown grade of ventricular ectopic activity noted on the individual's tape.(134) The Lown grading system is shown in Figure 36.

Statistics

Data relating to heart rates were normally distributed and therefore a Student's paired 't' test was used for intragroup analysis. ST segment data did not conform to a normal distribution however and this data was therefore analysed using the Wilcoxon signed rank test. Similarly the data for total ventricular ectopic activity was analysed using the Wilcoxon test.

Figure 36

Lown ventricular ectopic grading system

Grade 0 - No VPC's

Grade 1A - Occasional isolated VPC's (< 30/hr) < 1/min

Grade 1B - Occasional isolated VPC's (< 30/hr) < 1/min

Grade 2 - Frequent VPC's (> 30/hr)

Grade 3 - Multiform VPC's

Grade 4A - Repetitive VPC's; couplets

Grade 4B - Repetitive VPC's; salvos

Grade 5 - Early VPC's (R on T)

Bernard Lown MD

Sudden Cardiac Death - 1978

Circulation 1979, 60; 1539-1599

Results

a) Figures 37-42 show the hourly maximum, minimum and mean heart rates for both groups at baseline and one year. For all three parameters there was a trend towards lower heart rates in the exercise group after training. Individual results were however variable and the standard deviations large. The graphs of maximum heart rate for the exercise group demonstrate in addition maximum heart rates achieved during exercises themselves. These were carried out at the weekly class from 2.00 - 3.00 p.m. Hence the peaks at that time correspond to the maximum heart rate induced by the exercise training programme. Despite the fact that the baseline measurement was made at the lowest level of exercise (level D- on chart 1) the heart rate produced was much higher than that during greater levels of exercise at one year.

The group means for minimum, maximum, mean and nocturnal heart rate are shown in Table 31. The mean heart rate was calculated by dividing the total number of beats per 24 hours by 1440. The mean nocturnal heart rate was calculated by averaging the mean hourly heart rates over six consecutive hours while the patient was asleep, the six hour group chosen being that group between midnight and 8.00 a.m. which produced the lowest mean heart rate. Again the trend for all four measurements was towards a reduction in heart rate after exercise training. However the reductions in minimum 24 hour heart rate from 49.7 $\pm$ 5.3 to 48.2 $\pm$ 40 and mean 24 hour heart rate from 80.9 $\pm$ 8.4 to 78.5 $\pm$ 6.7 did not achieve statistical significance. Maximum heart rate was significantly lower after training at 142.2 $\pm$ 16.1 compared to

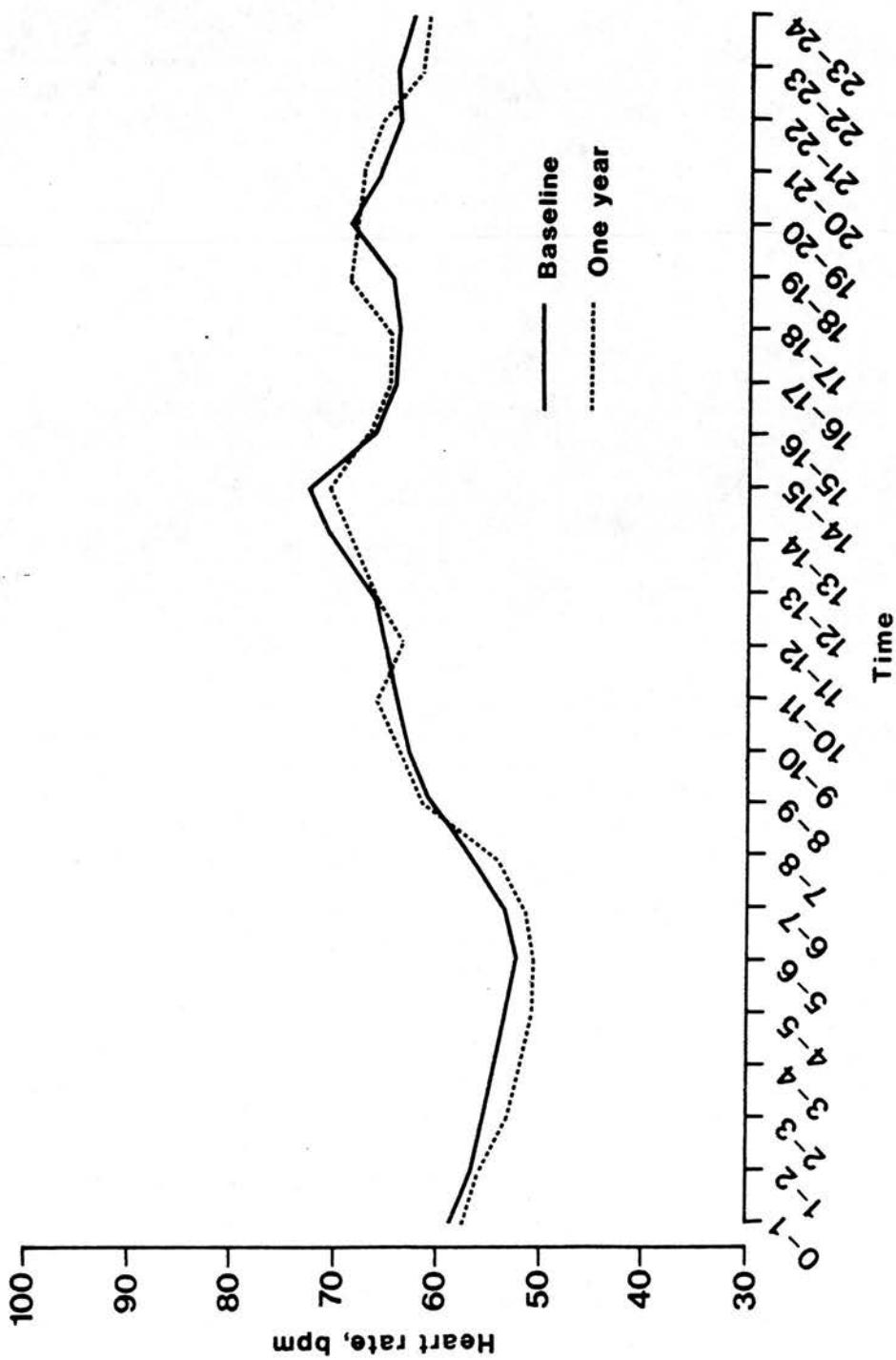


Figure 37 Minimum 24 hour heart rates - exercise group

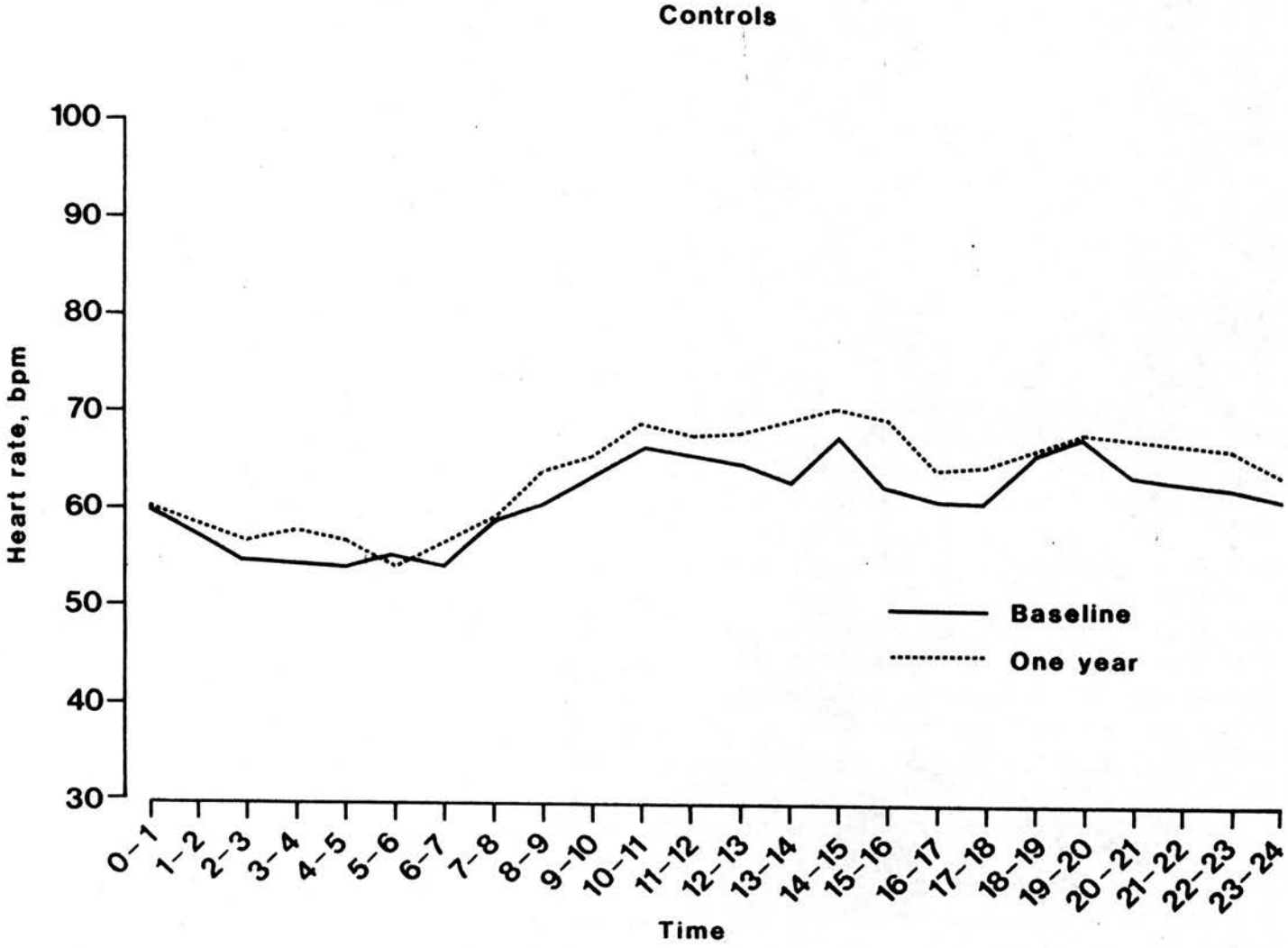


Figure 38 Minimum 24 hour heart rates - control group

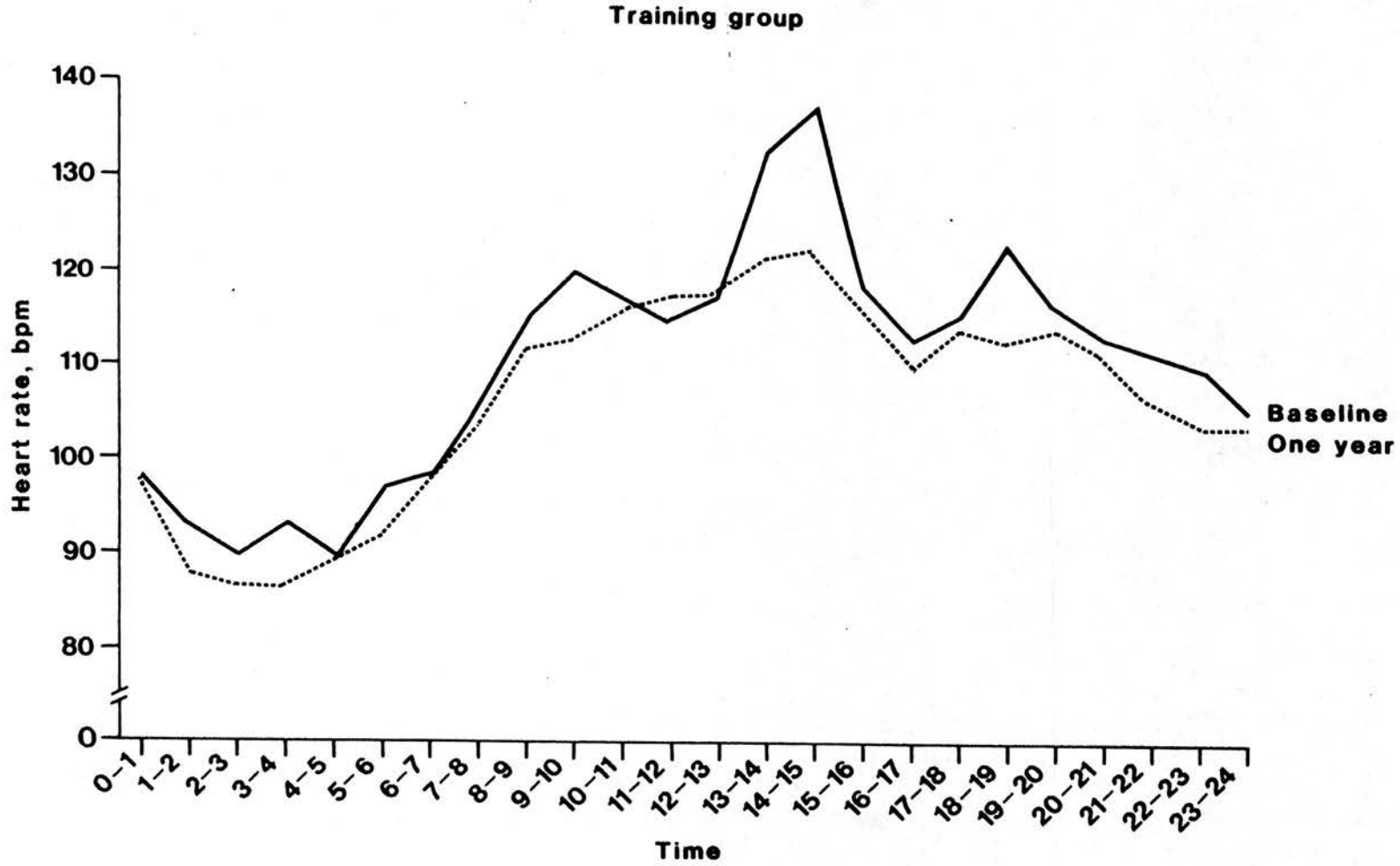


Figure 39 Maximum 24 hour heart rates - exercise group

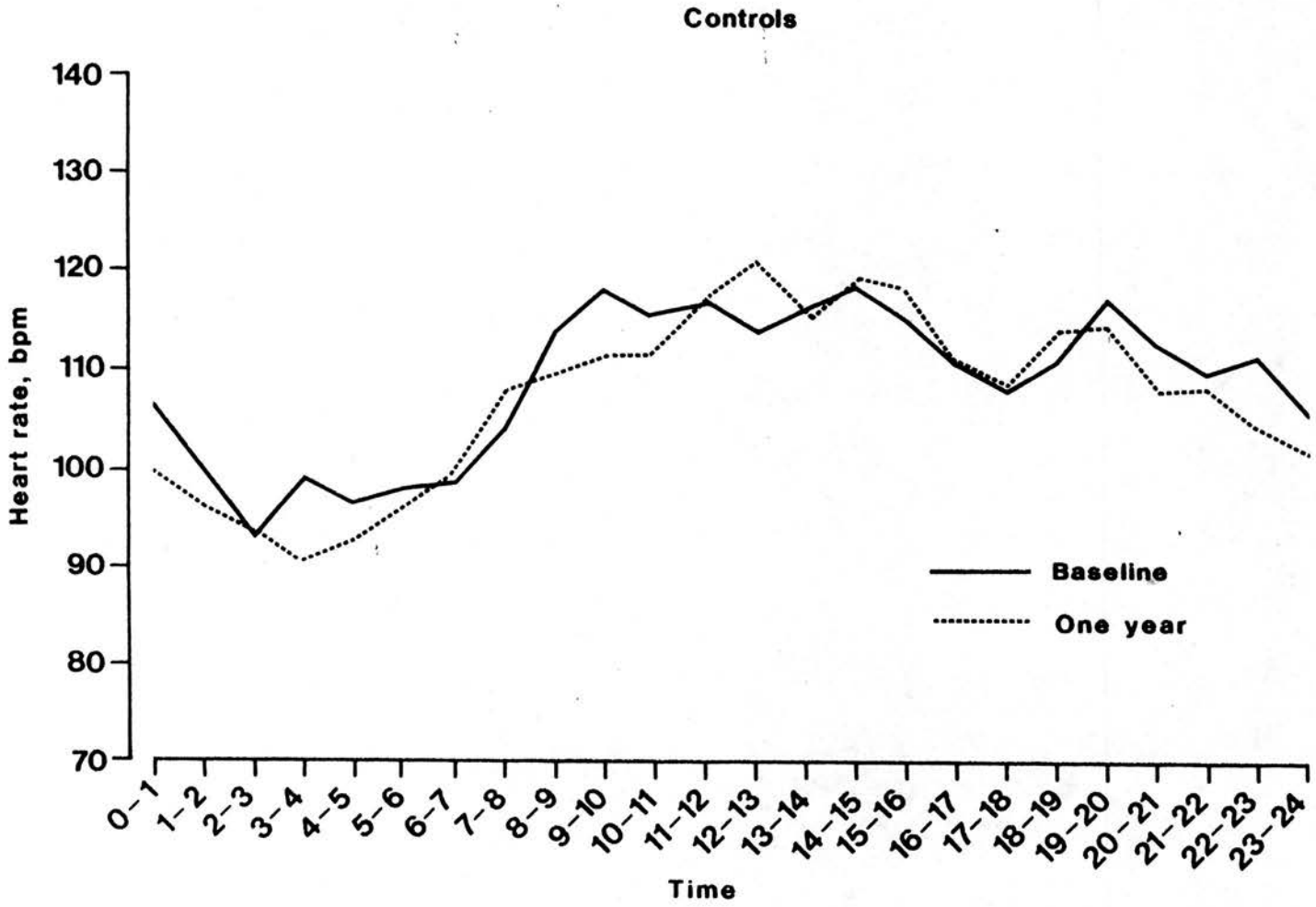


Figure 40 Maximum 24 hour heart rates - control group

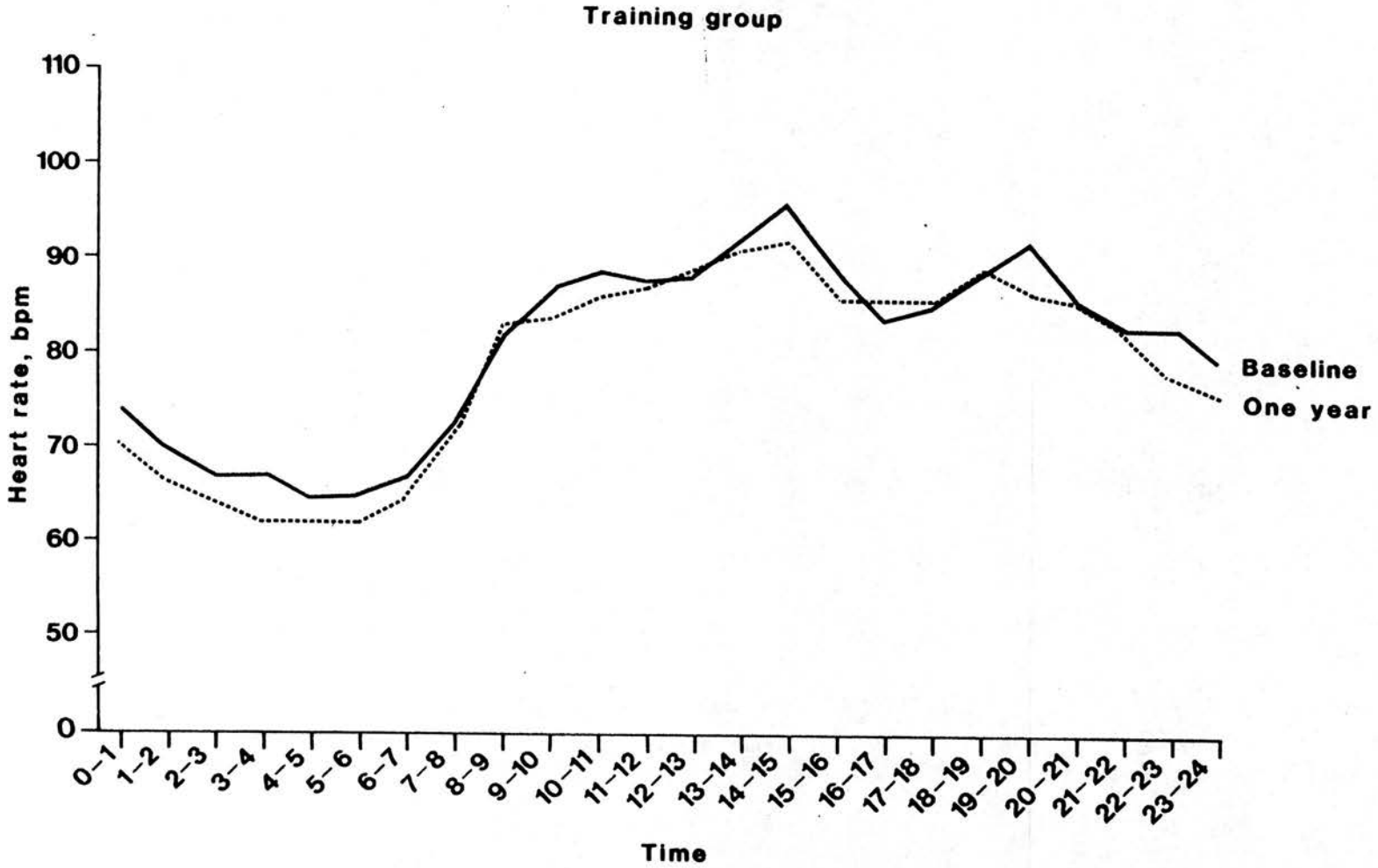


Figure 41 Mean 24 hour heart rates - exercise group

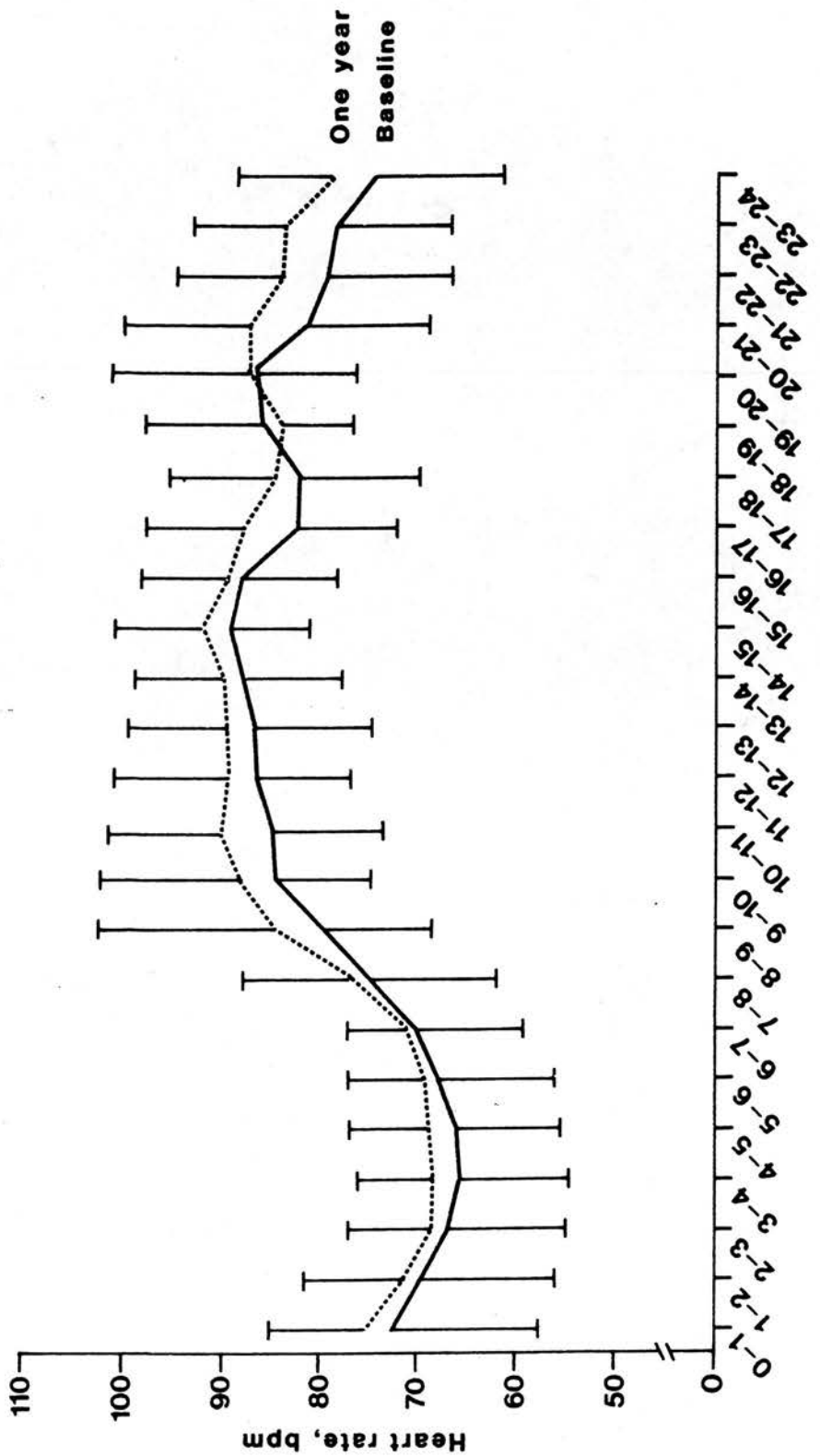


Figure 42 Mean 24 hour heart rates - control group

Table 31

Mean group 24 hour heart rates

	EXERCISE GROUP			CONTROL GROUP		
Parameter	Baseline mean±SD	One year mean±SD	'p'	Baseline mean±SD	One year mean±SD	'p'
Min HR	50± 5.3	48± 4.0	NS	49± 5.8	51±6.4	NS
Max HR	151±17.8	142±16.1	<0.05	137±14.6	139±18	NS
Mean HR	81± 8.4	79± 6.7	NS	79± 6.8	80±7.0	NS
Noct HR	66± 6.3	63± 4.6	<0.05	66± 9.1	69±7.8	NS

150.7 ± 17.8 at baseline ($p < 0.05$). Mean nocturnal heart rate was also significantly lower after training at 62.8 ± 4.6 compared to 65.9 ± 6.3 before training ($p < 0.04$).

b) ST segment analysis: the individual results for ST depression, frequency of ST depression and total duration of ST depression are shown in Table 32, in addition to group means, standard deviations and p values (Wilcoxon signed rank test). Maximum ST depression in the exercise group at baseline ranged from 0 - 6 mm with a mean maximum ST depression of 2.2 mm. This was reduced by 30% after training to 1.5 mm (range 0 - 3.8 mm). This reduction was significant with a 'p' value of 0.04. This improvement is reinforced by a reduction in frequency of ST depression from 8.3

Table 32

Individual ST segment characteristics

EXERCISE GROUP

Patient number	Maximum ST depression		Frequency of ST depression		Total durn. of ST depression	
	1	2	1	2	1	2
1	1.0	1.8	1	2	4	2
2	1.5	1.0	4	3	30	7
3	3.2	1.0	17	1	122	4
4	0	0	0	0	0	0
5	2.6	0	1	0	3	0
6	4.6	1.0	13	1	95	2
7	1.0	1.0	1	1	2	2
8	3.0	3.4	15	15	117	91
9	0	0	0	0	0	0
10	2.0	1.5	6	9	25	150
11	2.2	2.5	14	11	163	96
12	1.3	1.0	8	3	52	11
13	6.0	3.8	13	12	197	97
14	1.4	1.1	1	1	3	1
15	2.2	2.0	17	4	60	10
16	2.8	1.0	3	1	12	1
17	3.0	3.2	27	25	198	167
Mean	2.2	1.5	8.3	5.2	63.7	37.7
S.D.	1.5	1.2	8.0	7.0	71.2	57.8
'p'value	0.04		0.02		0.02	

CONTROL GROUP

Patient number	Maximum ST depression		Frequency of ST depression		Total durn. of ST depression	
	1	2	1	2	1	2
21	1.0	1.8	6	13	8	56
22	2.5	2.8	10	11	45	44
23	1.2	1.2	6	6	22	22
24	1.4	0	1	0	6	0
25	3.5	3.8	21	30	296	254
26	1.5	0	7	0	102	0
27	0	0	0	0	0	0
28	0	1.6	0	1	0	3
29	1.0	1.0	1	1	5	5
30	1.9	1.8	15	11	139	68
31	1.0	1.0	1	4	3	12
32	2.0	2.3	7	11	65	165
33	2.5	0	5	0	32	0
34	0	0	0	0	0	0
Mean	1.4	1.2	5.7	6.3	51.6	44.9
S.D.	1.0	1.2	6.2	8.5	82.2	75.4
'p'value	NS		NS		NS	

to 5.2 episodes per patient per 24 hours ($p = 0.02$). The total duration of ST depression was also reduced from 63.7 mins to 37.7 mins per 24 hours ($p = 0.02$). Over the same period the control group showed no significant change in any of the three parameters.

A breakdown of the characteristics of the episodes of ST depression is shown in Tables 33 and 34. The total number of episodes of ST depression in the exercise group was 141 at baseline and 89 at one year, a reduction of 37%. Of the initial 141 episodes, 23% were associated with pain as reported by patients in their diaries. At one year only 12% of the 89 episodes was painful. The mean number of episodes of painful ST depression had decreased from 1.9 ± 1.9 to 0.7 ± 1.0, this reduction being significant ($p = 0.02$). There were 108 silent episodes at baseline and 77 at one year, representing a mean frequency of 6.4 ± 7.6 episodes per patient at baseline and 4.5 ± 7.0 at one year. This difference however failed to achieve statistical significance. In the control group there were 80 episodes of ST depression at baseline and 88 at one year. Twenty four percent were painful initially and this had decreased to 12% at one year, the reduction in painful episodes from 19 to 12 being accompanied by an increase in silent episodes from 61 to 79. There was no significant change in the mean frequency of either painful or silent episodes in the control group.

The episodes can also be sub divided into those associated with an increase in heart rate of greater than six beats per minute during the minute preceding the onset of ST depression (heart rate triggered) and those not so associated. In the

Table 33

Characteristics of episodes of ST depression - Exercise Group

	Baseline			One year			'p'value
	Group total	%	Mean ± S.D.	Group total	%	Mean ± S.D.	
All episodes	141	100	8.3 ± 8.0	89	100	5.2 ± 7.0	0.02
Painful	33	23	1.9 ± 1.9	12	13	0.7 ± 1.0	0.02
Silent	108	77	6.4 ± 7.6	77	87	4.5 ± 7.0	NS
H.R. triggered	79	56	4.6 ± 4,6	45	51	2.6 ± 3.5	0.008
Non H.R. triggered	62	44	3.6 ± 4.9	44	49	2.6 ± 3.9	NS
Mean H.R. at onset of ST depression	-	-	107 ± 17	-	-	106 ± 14	NS
Max H.R. during ST depression	-	-	116 ± 19	-	-	112 ± 16	NS
Mean Max degree of ST depression	-	-	1.8 ± 0.9	-	-	1.6 ± 0.7	NS

Table 34

Characteristics of episodes of ST depression - Control Group

	Baseline			One year			'p'value
	Group total	%	Mean ± S.D.	Group total	%	Mean ± S.D.	
All episodes	80	100	5.7 ± 6.2	88	100	6.4 ± 8.4	NS
Painful	19	24	1.4 ± 1.8	12	14	0.9 ± 2.0	NS
Silent	61	76	4.4 ± 5.8	79	86	5.4 ± 8.3	NS
H.R. triggered	47	59	3.4 ± 4.4	59	67	4.2 ± 6.2	NS
Non H.R. triggered	33	41	2.4 ± 2.8	29	33	2.1 ± 2.9	NS
Mean H.R. at onset of ST	-	-	101 ± 11	-	-	103 ± 11	NS
Max H.R. during ST depression	-	-	114 ± 12	-	-	114 ± 14	NS
Mean max episodic ST depression	-	-	1.5 ± 0.5	-	-	1.7 ± 0.7	NS

exercise group there were 79 heart rate triggered episodes at baseline and 45 at one year, representing a frequency of 4.6 $\pm$ 4.6 at baseline and 2.6 $\pm$ 3.5 at one year. This difference was statistically significant ($p = 0.008$). The incidence of non heart rate triggered events also fell from 3.6 $\pm$ 4.9 (62 events) to 2.6 $\pm$ 3.9 (44 events). This reduction however failed to reach statistical significance. In the control group there were 47 triggered and 33 non triggered events at baseline and 59 triggered and 29 non triggered at one year with no significant change in mean frequency of either type. Figure 43 shows a frequency histogram of duration of ischaemic episodes showing that at baseline there was a relatively even distribution of frequency of episodes in the four bands up to 30 minutes duration. However at one year there was a relative reduction in frequency of episodes exceeding 5 mins duration. Therefore not only were there fewer episodes, but those episodes which did occur tended to be shorter. These two facts together account for the marked reduction in total duration of ischaemic time. Figure 44 shows similar histogram for the control group showing consistency over the one year period.

The mean heart rate at onset of ST depression, mean maximum heart rate during ST depression and mean maximum degree of ST depression per episode were all unchanged in either group over the one year period.

c) Arrhythmias: Figures 45 and 46 show the hourly total number of ventricular premature contractions for the two groups, both groups

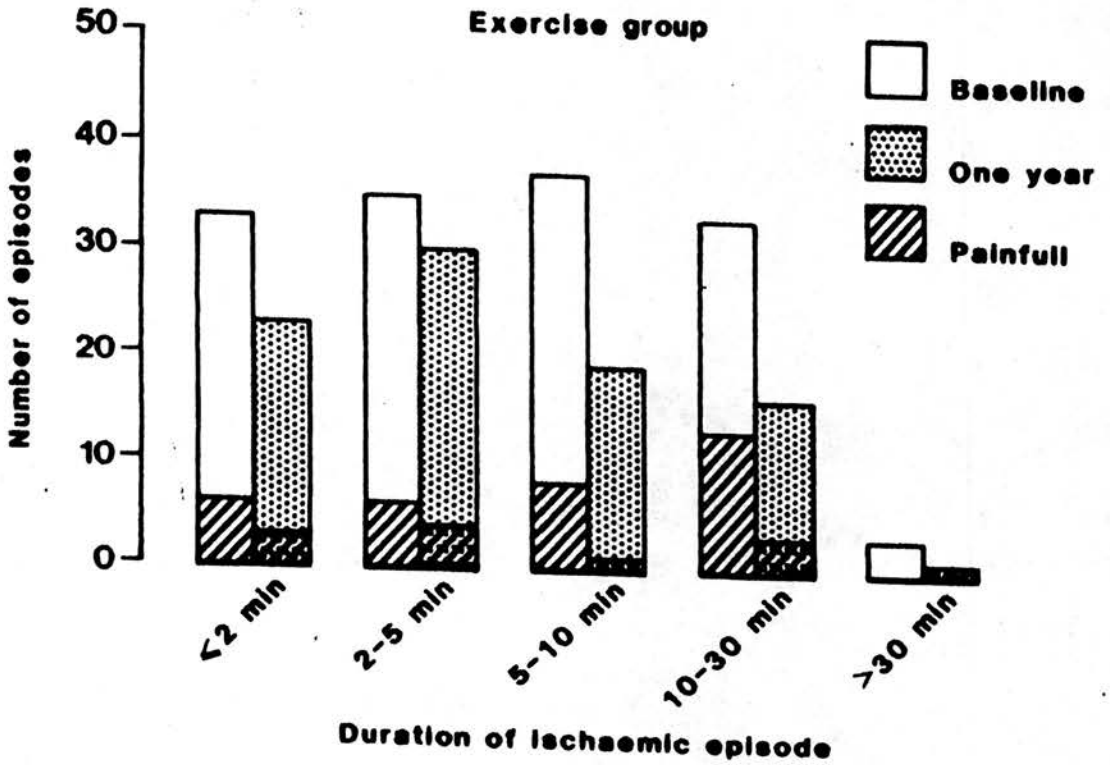


Figure 43 Frequency histogram of duration of ischaemic episodes at baseline and one year - exercise group

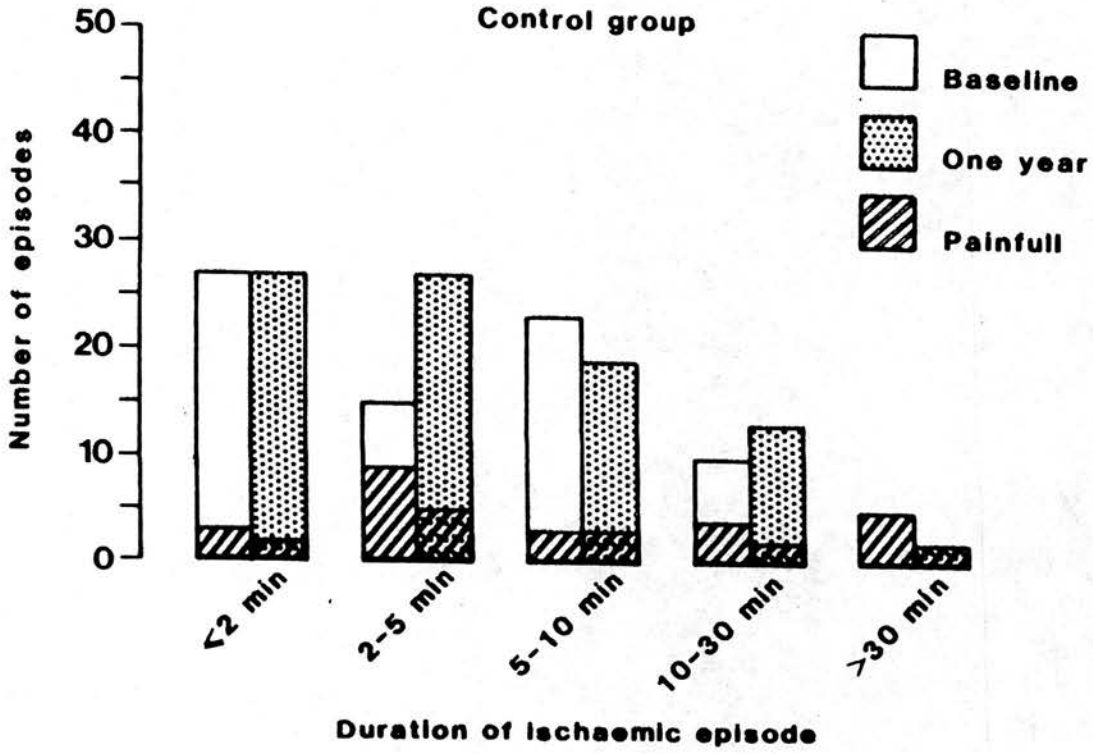


Figure 44 Frequency histogram of duration of ischaemic episodes at baseline and one year - control group

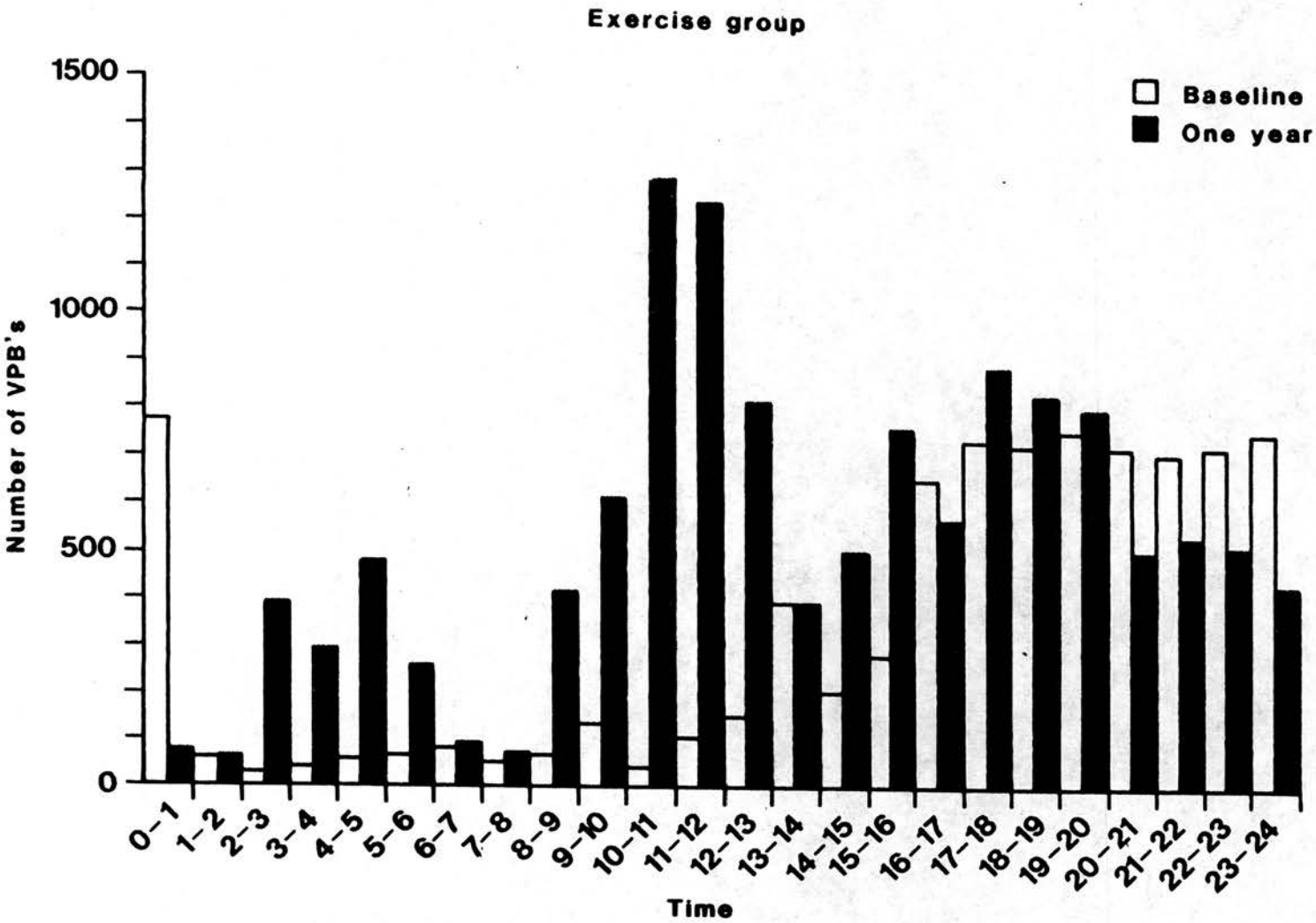


Figure 45 Frequency histogram of hourly ventricular ectopic beats - exercise group

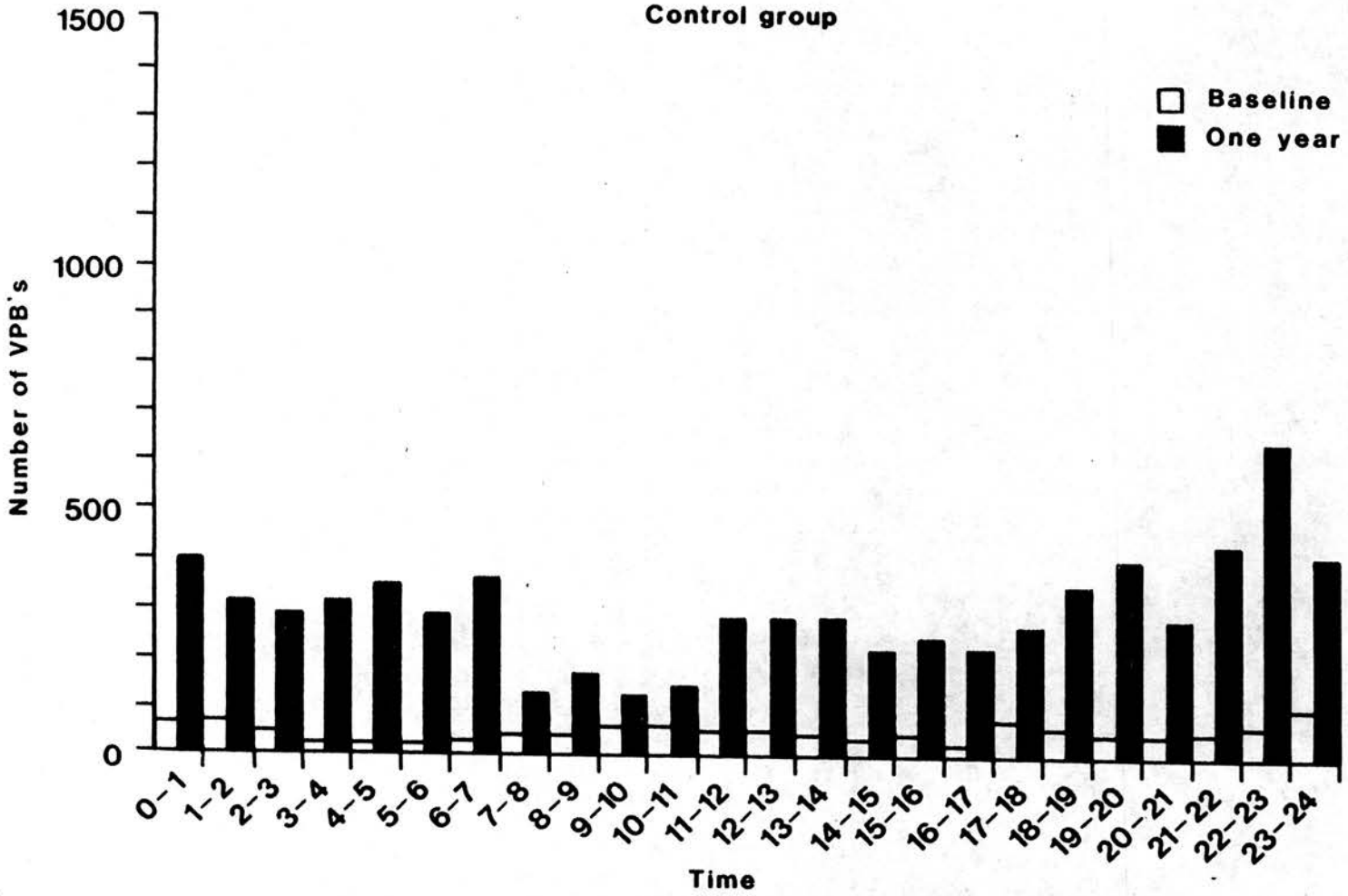


Figure 46 Frequency histogram of hourly ventricular ectopic beats - control group

showing an increased frequency of VPC's at one year. Although the total number of VPC's increased greatly in each group, these increases were accounted for by one or two patients in each group and the mean change was not statistically significant. Table 35 shows the maximum Lown grading achieved by each patient. At baseline only six of 17 patients had a Lown grading of two or greater. At one year seven patients were graded two or greater. In the control group only two of the 14 patients were graded two or greater at baseline and three at one year. Five patients in the exercise group had identical Lown gradings on both occasions while seven had improved grading and five were graded worse at one year. Among the controls ten patients showed no change, one improved and three got worse.

Discussion

There are no previous studies of ambulatory monitoring during exercise training with which to compare these results. The technique has however been used to assess drug therapy in angina pectoris (135-138) and one can therefore compare the antianginal efficacy of exercise training with drugs in these studies. The reduction in heart rate is perhaps less than might have been expected after training. Other published data from the Victoria Infirmary has compared mean hourly heart rate in veteran athletes with matched controls and shown that the athletes have significantly lower heart rates.(139) However athletes while active during sport tend to be no more physically active at other times than normal, allowing a fair comparison of heart rates

Table 35

Lown grading of ventricular ectopic activity at baseline and one year

Exercise Group		
	Baseline	One Year
Lown Grade	Number of patients	Number of patients
0	0	2
1A	10	7
1B	1	1
2	3	3
3	1	1
4A	0	1
4B	1	2
5	1	0

Control Group		
	Baseline	One Year
Lown Grade	Number of patients	Number of patients
0	1	0
1A	11	11
1B	0	0
2	0	1
3	0	1
4A	1	1
4B	1	0
5	0	0

between the two. In the group studied here however it was clear that most of the patients with angina were on medical advice relatively sedentary individuals at baseline and that by the end of the year this trend had been largely reversed and they were encouraged to be physically active as often as possible. It is possible therefore that the expected reduction in mean heart rate has been offset by an increase in activity level. The resting bradycardia of the athletic individual is evident however in the significant reduction in nocturnal heart rate implying an increase in resting vagal tone.

The graphs of maximum heart rate also provide evidence of the training effect when the heart rates between 2.00 and 3.00 p.m. on the two occasions were compared. In all cases this corresponds to peak heart rate during the exercise class. This has been significantly reduced after training despite a much higher level of exercise on that occasion. Likewise the group maximum heart rate shown in Table 31 decreased from 150.7 to 142.2 despite the overall increase in physical activity. These various heart rate parameters support the belief that the improvements in heart rate response to exercise are not confined to treadmill measurements but do genuinely carry over into normal daily activities.

What then can we say about myocardial ischaemia during daily activities? The baseline parameters for the exercise group do show a rather higher maximum ST depression and higher mean frequency of ST depression than the control group. One must remember however that this test, unlike the others, was carried out after randomisation and after exercise training had commenced.

Intergroup comparison is not relevant therefore and was not carried out. Most individuals performed their exercises on two occasions during the 24 hour period (prior to retiring to bed or rising from it and at the exercise class). In the majority of cases this represents two "deliberate" episodes of provoked ischaemia accounting to a large extent for the difference in mean baseline frequency of ST depression between the groups (8.3 vs 5.7). Since in many cases ST depression occurred during exercises this also partly explains the difference in extent of ST depression (2.2 vs 1.4). That aside however the intragroup change in the exercise group over the one year period is striking, particularly considering the apparent increase in physical activity. Not only has the maximum ST depression decreased significantly, but the frequency and duration of ST depression have decreased by 37% and 41% respectively so that at one year both parameters are less than the corresponding parameters in the exercise group. The frequency histogram in Figure 43 also demonstrates that episodes of ST depression tend to be of shorter duration after training. The antianginal effect of the training programme previously demonstrated on the treadmill is therefore clear during ambulatory monitoring also. There are fewer episodes and those which do occur are shorter such that total ischaemic duration is reduced. The argument that encouraging such physical activity in the presence of ischaemic heart disease may be dangerous since it actively provokes ischaemia is somewhat weakened in this context since paradoxically we have reached a situation where there is less ischaemia despite an increased

physical activity. The reverse side of the coin must also be true however. If the hypothesis that provoking ischaemia is effective as a mean of collateralisation is a true one, then we have also reached a situation where the control group are now being stimulated more than the exercise group. In order to maintain the stimulus therefore it may be necessary to increase exercise duration and intensity.

The antianginal efficacy of exercise training as measured by ambulatory ECG monitoring is comparable to that using drug therapy. Quiyyumi studied a group of patients with severe angina pectoris whose baseline measurements of ST depression are similar to the group studied here in terms of frequency, duration and extent of ST depression and incidents of painful and silent ischaemia.(135) They were treated with Atenolol and Pindolol in a double blind crossover study. Pindolol decreased the frequency of ischaemic episodes by 30% while Atenolol produced a reduction in frequency of 53%. Duration of ischaemia was reduced by 30% with Pindolol and 45% with Atenolol, figures not dissimilar from those produced by the exercise group studied here. Studies with calcium blockers show similar degrees of efficacy (136-138) though interestingly Nifedipine, the drug used as antianginal therapy in this study, appeared not to decrease frequency or extent of ST depression when studied by Bala Subramanyan.(138)

One of the major discoveries resulting from the use of ambulatory ST segment monitoring is that the typical heart rate provoked ischaemic painful episode of ST depression is very much in the minority. Studies have shown that the majority of

episodes of ST depression are painless (74,75,140,141) and also that most are not triggered by increases in heart rate. (75,140,142) The question of how exercise training might affect these two parameters is of great interest. It might, perhaps by increasing endogenous opiate production, reduce painful episodes. It might also, due to its effect on the heart rate response to exercise training, decrease episodes which are heart rate triggered. From the above results, these two facts appear to be true. Painful episodes were indeed decreased but there was, in addition, a reduction of 29% in silent episodes though this was not statistically significant. Since studies have shown that painless episodes are otherwise identical to painful episodes (75,76,140) this finding would suggest that the primary effect in the exercise group was a reduction in ischaemia and that superimposed on this was a tendency for fewer episodes to be recognised by the patient, whether this be due to opiate production or perhaps "denial". In the control group on the other hand, while painful episodes decreased, silent episodes increased. Though neither change was significant it is clear there was no overall decrease in ischaemia but a tendency to report pain less often.

In the exercise group the picture with respect to heart rate triggered or non heart rate triggered events was similar. Both were reduced but only the heart rate triggered were significantly reduced. As discussed above one might expect the training effect to reduce such episodes. It is likely that there would be fewer sudden increases in heart rate in trained

individuals and therefore a decrease in ischaemia induced by such changes. That there was a reduction in non heart rate triggered events, is encouraging and one would like to see such a trend studied in a larger group to see if it too would be ultimately statistically significant.

Interestingly despite the reduction in heart rate triggered ischaemia, this did not produce a fall in the mean heart rate at onset of ST depression. This parameter was unchanged over the year. Unlike the ST threshold on treadmill testing this does not appear to reflect improvements in myocardial perfusion. The mean heart rate at onset of ST depression is however relatively low as is usually found with ambulatory monitoring indicating that increases in heart rate are only part of the equation even in so called heart rate triggered episodes. Clearly also the mean maximum heart rate during episodes and mean maximum ST depression were unchanged, again failing to produce supportive evidence of a change in threshold for ischaemia. These parameters however perhaps reflect a lack of sensitivity in ST segment monitoring compared to the more rigid laboratory setting of treadmill testing. The variability of other factors in the ischaemic process and the ability to monitor only two leads limits the effectiveness of this procedure. Nonetheless in practical terms it has demonstrated a reduction in frequency and duration of ischaemia, whether this be due to an antianginal training effect or a genuine improvement in blood supply.

The monitoring of arrhythmias was always likely to be beyond the study of this sort. While early studies suggested that PVC's

were important indicators of risk of sudden death (143,144), it has since been recognised that there is a great variation in the occurrence of arrhythmias during ambulatory monitoring (134) and that while episodes in Lown class I are common, they are also therefore poor discriminators for identifying patients at risk of sudden death.(145,146) More complex arrhythmias on the other hand do seem to predict sudden death but are much more variable in their occurrence and overall are less common.(145,147) A small group such as this would inevitably produce too few serious arrhythmias and those produced would become irrelevant in the context of natural variability in their occurrence.(148) All that one can say is that training produced no evidence of a reduction in ectopic activity and little change in the more serious arrhythmias with approximately one third improved, one third worse and one third unchanged.

There is evidence that a reduction in sympathetic tone or an increase in parasympathetic tone is associated with increased electrical stability in the myocardium (149) and one might therefore expect exercise training to lead to such an improvement. Indeed one epidemiological study has suggested that in untrained individuals vigorous exercise is associated with increased risk of sudden death but that in the trained population this is not so.(150) Blackburn also showed that during stress testing, trained individuals were less likely to produce PVC's.(151) However as with most training benefits, the first real evidence of decreased susceptibility to ventricular fibrillation as a direct result of exercise training has been

shown in an animal study.(152) Billman demonstrated that training altered the barroreflex slope, an abnormality which predisposed to ventricular fibrillation. All dogs with such an abnormality pre training lost it after training and also lost their susceptibility to ventricular fibrillation.

Though this study has shown improved myocardial perfusion it has not shown any reduction in premature ventricular activity. While this is most likely to be due to the natural variability in such activity and the need for much larger numbers, it is possible that ischaemic heart disease provides the substrate for ventricular ectopic activity and that subsequent improvement in perfusion will not change that substrate. It is further possible that independent of ventricular premature activity, the changes in neurogenic activity induced by exercise training may be associated with a decreased likelihood of such ventricular premature activity degenerating into ventricular fibrillation. Such a possibility has prompted other authors to recommend the evaluation of exercise training as a treatment for individuals with increased susceptibility to sudden death.(153)

OBSERVATIONS ON THE RELATIONSHIP BETWEEN PHYSICAL FITNESS AND BETABLOCKADE

Throughout this thesis reference has been made to the anti anginal effects of exercise training. In the preceding subsection it was suggested that the efficacy of exercise training as assessed by ambulatory monitoring was comparable to traditional therapy. At the beginning of this section the effect of training on treadmill performance was evaluated, the results in the laboratory setting being even more impressive. Furthermore the mode of action of exercise training in altering sympathetic and parasympathetic tone raises a number of questions with regard to comparisons and interaction with betablocking drugs. A number of studies have investigated the efficacy of training in the presence of betablockade, (154-156) but none to date have directly compared the two. This subsection therefore compares the antianginal efficacy of exercise training with betablockade and examines the effect of betablockers before and after exercise training.

Methods

During the initial series of investigations exercise patients who had completed exercise echocardiography and Thallium scanning were prescribed 100 mg of atenolol daily for one week. An exercise test was then carried out exactly 24 hours after the final dose of atenolol. The patients then took a further 100 mg of atenolol 36 - 48 hours after the last dose to alleviate the effects of sudden withdrawal of betablockade. At the end of one year during the same stage of the repeat investigations the

process was repeated. Interestingly all but one patient tolerated the betablockade during the baseline investigations and therefore data are available for the 17 patients referred to in the subsection on treadmill performance. However at one year only 10 of these patients were able to tolerate betablockade, the remainder complaining of extreme fatigue.

Statistical analysis

As in the subsection on treadmill performance the parameters studied are expressed as mean ± standard deviation. Comparison is made using Student's 't' test for normally distributed data and the Wilcoxon signed rank test for non parametric data.

Results

a) Comparison of training and betablockade. The results of the 10 parameters measured are shown in Table 36. The reduction in resting and submaximal heart rate achieved by training is not as great as that by betablockade. Betablockade with atenolol clearly reduces resting heart rate in particular. This fell by a mean of five beats during training and 17 beats during betablockade. During exercise however the difference is less marked and the three lines are parallel as shown in Figure 47. Training decreased stage I and II heart rates by 13 beats, while atenolol decreased them by 23 beats.

Figure 48 summarises the results of those parameters which reflect disease severity. On maximal exercise training produced an increase in maximum heart rate from 128 ± 17 beats per minute

Table 36

Comparative effect of training and atenolol on parameters of treadmill performance

	Exercise group			Control group	
	Baseline (mean±SD)	Atenolol (mean±SD)	One year (mean±SD)	Baseline (mean±SD)	One year (mean±SD)
Resting HR	81 ± 12	64 ± 8	76 ± 10	74 ± 10	75 ± 9
St I HR	111 ± 19	88 ± 11	98 ± 15	106 ± 16	102 ± 10
St II HR	116 ± 19	93 ± 13	103 ± 16	110 ± 18	106 ± 10
Max HR	128 ± 17	109 ± 12	138 ± 21	136 ± 22	134 ± 24
Max DP	219 ± 55	164 ± 44	244 ± 67	259 ± 74	248 ± 74
DP/ST threshold	183 ± 51	143 ± 43	205 ± 64	227 ± 75	206 ± 60
Max ST depression	1.9 ± 0.9	1.6 ± 1.0	1.6 ± 1.2	1.5 ± 0.8	1.4 ± 0.8
Time to 1 mm	374 ± 369	749 ± 439	881 ± 668	719 ± 560	715 ± 580
Tread. time	741 ± 356	974 ± 430	1272 ± 514	1006 ± 504	1010 ± 546
Workload (METS)	6.3 ± 1.9	7.6 ± 2.2	9.5 ± 2.9	7.8 ± 2.8	8.0 ± 3.1

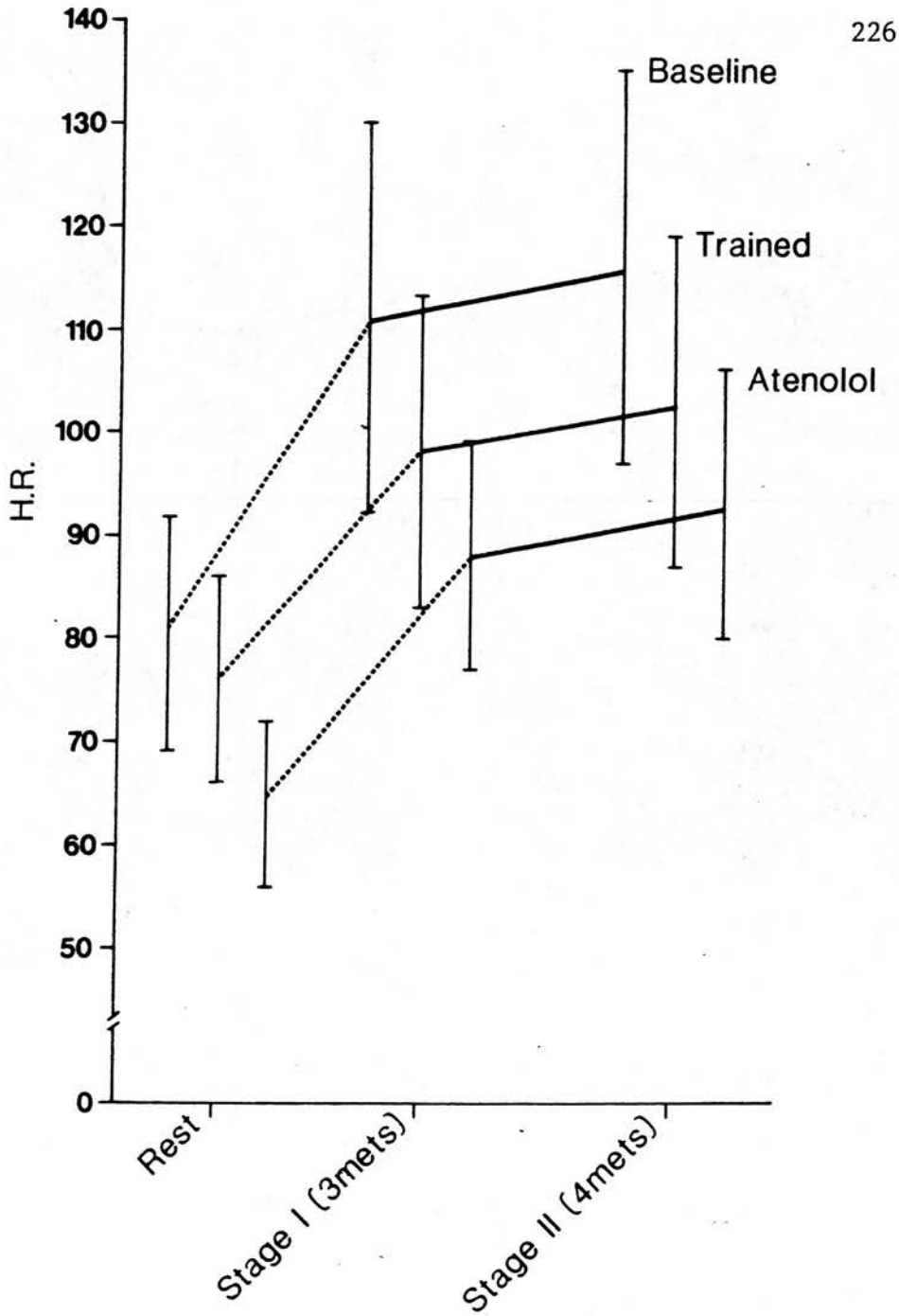


Figure 47 Graph of mean heart rate against treadmill protocol stage for the exercise group at baseline, after beta-blockade and after training

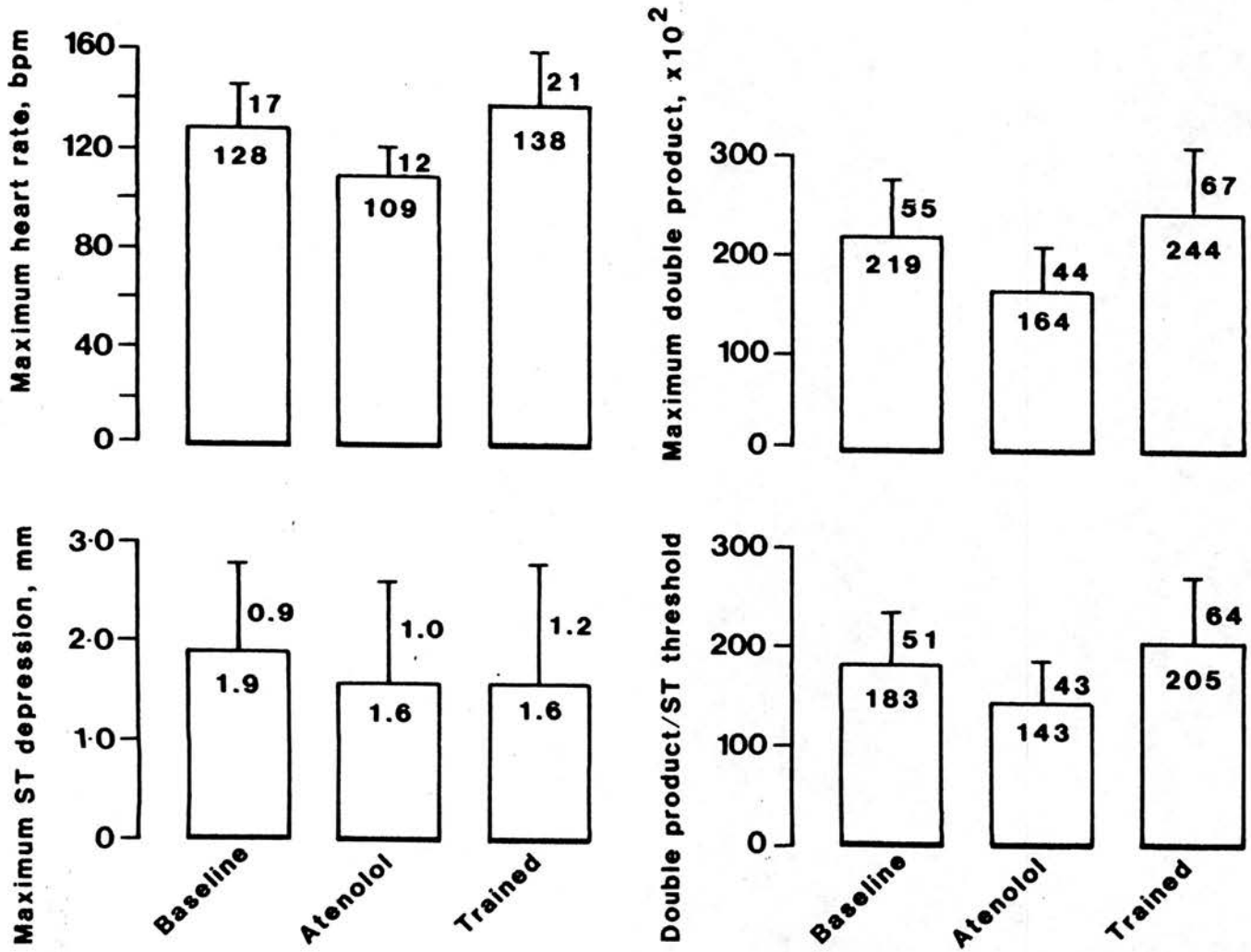


Figure 48 Treadmill parameters of disease severity: Effect of training or atenolol

to 138 ± 21 beats per minute ($p < 0.05$), while with betablockade maximum heart rate was reduced to 109 ± 12 beats per minute ($p < 0.001$). Similarly maximum double product was increased by training from 219 ± 55 to 244 ± 67 ($p < 0.05$) and decreased by atenolol to 164 ± 44 ($p < 0.001$). Likewise the submaximal measure of disease severity, the double product ST threshold, was increased by training from 183 ± 51 to 205 ± 64 but decreased by atenolol to 143 ± 43. Both training and atenolol reduced maximum ST depression by similar amounts (1.9 ± 0.9 at baseline, 1.6 ± 1.0 for atenolol and 1.6 ± 1.2 after training).

The combined parameters of treadmill performance showed that both atenolol and training produced large improvements in time to 1 mm ST depression, treadmill time and treadmill workload. Atenolol increased time to 1 mm ST depression by 100% (374 ± 749 seconds vs 769 ± 439 seconds), but training produced a 136% increase in this parameter to 881 ± 668 seconds. Similarly treadmill time was increased from 741 ± 356 seconds to 974 ± 430 seconds by atenolol (31% increase: $p < 0.001$) but to 1272 ± 514 seconds by training (72% increase: $p < 0.001$). Treadmill workload increased from 5.6 ± 1.9 METS to 7.6 ± 2.2 METS with atenolol to 9.7 ± 2.8 METS with training. Improvements in these parameters achieved by exercise training were significantly better than those achieved by beta blockade (Figure 49).

b) A comparison of betablockade before and after training. Table 37 shows the results for the sub group of patients who tolerated beta blockade after training. Resting heart rate was unchanged by training in this sub group (82.9 ± 9 vs 81 ± 10) and

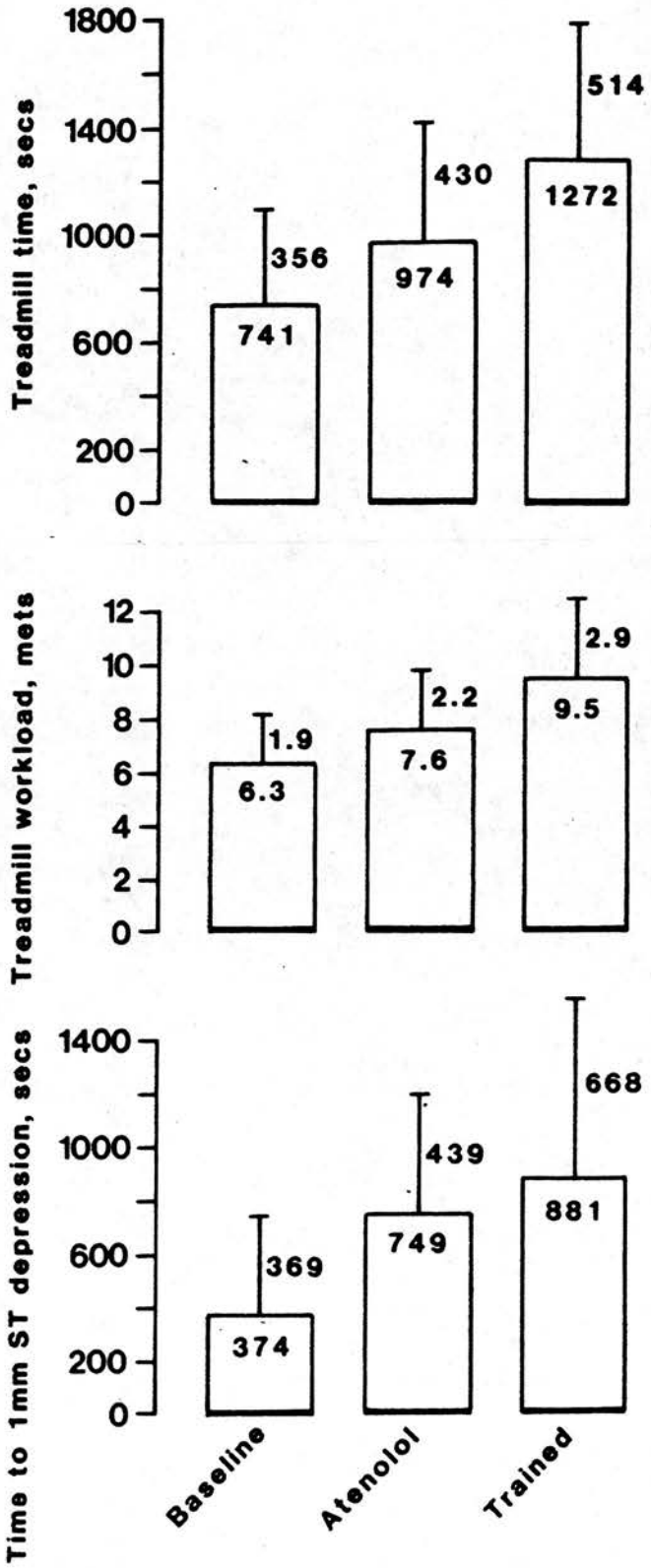


Figure 49 Combined treadmill performance parameters: Effect of training or atenolol

Table 37

Comparative effect of atenolol before and after training on parameters of treadmill performance

	Baseline (mean±SD)	Atenolol 1 (mean±SD)	Trained (Mean±SD)	Atenolol 2 (mean±SD)
Resting HR	82 ± 9	65 ± 10	81 ± 10	65 ± 9
St I HR	108 ± 12	88 ± 12	97 ± 15	79 ± 10
St II HR	114 ± 17	93 ± 13	103 ± 17	82 ± 10
Max HR	125 ± 18	108 ± 12	137 ± 21	108 ± 14
Max DP	205 ± 61	164 ± 50	245 ± 71	167 ± 48
DP/ST threshold	178 ± 62	151 ± 54	222 ± 77	141 ± 43
Max ST depression	1.8 ± 0.9	1.4 ± 1.0	1.5 ± 1.4	1.5 ± 1.1
Time to 1 mm	386 ± 353	830 ± 373	1048 ± 689	1041 ± 463
Tread. time	714 ± 240	971 ± 331	1352 ± 534	1383 ± 475
Workload (METS)	4.4 ± 1.3	5.6 ± 1.6	8.0 ± 2.9	7.6 ± 2.3

fell by similar amounts after betablockade on both occasions (65 ± 10 vs 65 ± 9). Sub maximal heart rate was reduced by betablockade and by training in a similar fashion to that described above for the whole group. Betablockade however produced a further reduction in sub maximal heart rate after training (Figure 50).

Those parameters which reflect disease severity (maximum heart rate, maximum double product and double product ST threshold) all improved by exercise training. However as with the larger group, betablockade produced a worsening of these parameters and despite the improvement with training the results with betablockade on the two occasions were constant. Maximum heart rate was 108 on both occasions, maximum double product was 164 ± 50 initially and 157 ± 48 on the repeat occasion and double product ST threshold was 151 ± 54.2 initially and 141 ± 43 on the second occasion.

Although betablockade was associated with improved treadmill time and workload as well as time to 1 mm ST depression and maximum ST depression before training, there were no such improvements after training.

Discussion

The reduction in submaximal heart rate achieved by exercise training in this study is 57% of that achieved by 100 mg of atenolol. Atenolol was chosen as one of the most commonly used betablockers and one which produces marked reductions in resting and submaximal heart rate at this dose. The degree of

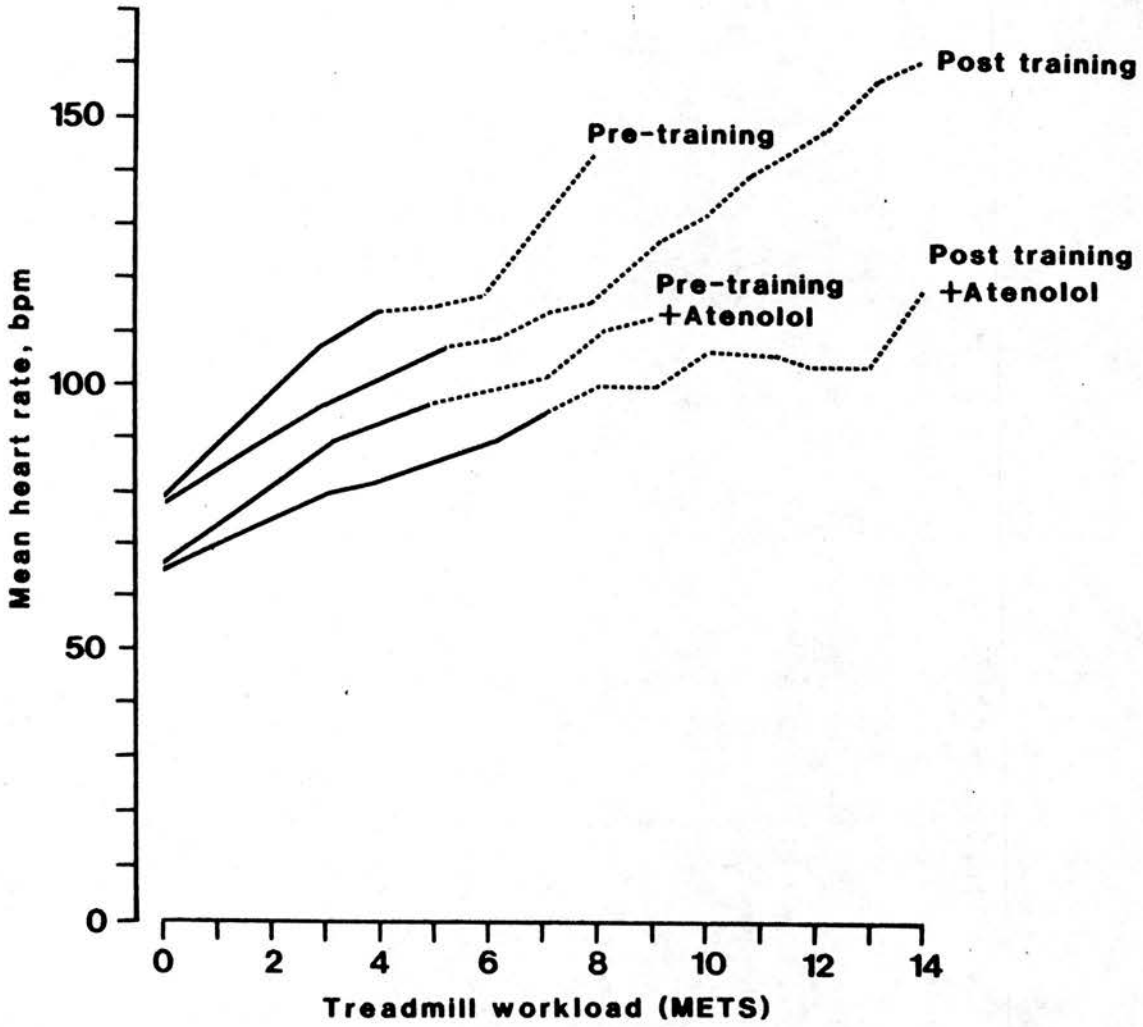


Figure 50 Graph of heart rate against treadmill workload for 10 patients betablocked before and after training

Solid line = level achieved by all 10 patients

bradycardia produced by training would compare favourably with the more modest degrees of betablockade produced by other regimes. In addition to this effect however it is important to look at the effects on maximum heart rate. Previous studies have shown that betablockade resulted in a reduction in angina threshold indicating a deleterious effect on the balance between myocardial oxygen supply and demand.(158,159) Several mechanisms have been postulated including a rise in end diastolic volume leading to increased wall tension, reduced contractility and impaired distal coronary perfusion. Whatever the mechanism, the effect is to impair the improvement in exercise tolerance which would be expected from such a lowering of submaximal heart rate. This study confirms this finding. While training has improved those parameters which indicate disease severity (maximum heart rate, maximum double product and double product ST threshold) betablockade has produced a deterioration in them. As a result of the divergent effects of training and betablockade on these parameters, exercise training has produced a greater improvement in treadmill time, time to 1 mm ST depression and treadmill workload than atenolol, despite the lesser degree of "bradycardia". In this group, the anti anginal effect of exercise training is clearly superior to that of 100 mg of atenolol. Furthermore the sense of wellbeing produced by training contrasts with the side effects reported with atenolol in these young patients even at baseline (tiredness and cold peripheries).

While this study may be criticised for comparing one week's

betablockade with one year's training, it is unlikely that more prolonged betablockade would be more beneficial, since, if anything, down regulation of beta receptors may be expected to decrease the efficacy of betablockade.

The subgroup of patients who were betablocked before and after training have shown interesting results. Firstly it is clear that the effects of atenolol and training on submaximal heart rate are additive. This is not surprising since betablockade works by competitive inhibition of receptor sites. If training decreases sympathetic tone then the level of noradrenaline at the receptor site would be lower and hence the effectiveness of atenolol greater. Secondly it is of interest that this subgroup showed no reduction in resting heart rate after training. This lack of effect, despite a clear reduction in submaximal heart rate, suggests that resting parasympathetic tone, said to be the major determinant of resting heart rate, was not altered in this subgroup. It was however altered in the larger group and clearly the seven patients who did not tolerate betablockade were the individuals with most marked resting bradycardia (mean resting heart rate 74 $\pm$ 9 after training). It is possible that increased resting para sympathetic tone is therefore associated with poor tolerance to betablockade.

Finally the constancy of maximum heart rate, maximum double product and double product ST threshold during betablockade despite the background of improvement in these parameters following training suggests that if improved perfusion is the mechanism behind the increased maximum heart rate, maximum double

product and double product ST threshold after training, then this improvement is not effective in the presence of betablockade. Of the factors discussed above by which betablockade may produce a deterioration in parameters of disease severity, impaired distal perfusion would seem to fit the hypothesis best, since such impaired perfusion may lead to an impairment in collateral function.

In summary therefore this subsection has demonstrated the superiority of exercise training to betablockade when assessed by treadmill performance. Furthermore the use of betablockade before and after training has highlighted the differing roles of para sympathetic and sympathetic tone on resting and submaximal heart rates and their modification by exercise training. Finally it also supports the concept of collateralisation as a means of improved perfusion after training and suggests that beta blockade by its effect on distal coronary perfusion may impair such collateral function.

SECTION IV

GENERAL DISCUSSION

In the preceding section the results of the various studies have been reported and discussed in a logical order to try to answer the central question regarding the effect of exercise training on myocardial perfusion. I have attempted to build up the argument for the hypothesis by showing that each set of results agrees with the preceding set and that each fresh piece of evidence strengthens the case. I believe it is reasonable to say that these investigations support the viewpoint that exercise training can improve regional myocardial perfusion and that enhanced collateral function is a possible mechanism for this improvement. The evidence is however circumstantial and one must be wary of overstressing the case. There have been many difficulties both in designing and in carrying out this work. In Section I and II I have discussed those problems which were anticipated beforehand and which were as far as possible dealt with in the design of this study. In this section I would like again to address some of the problem areas already discussed in the earlier sections and in addition to mention some other problems which were not anticipated. The recognition of these areas inevitably leads to a consideration of how the study might be improved or of areas which merit future investigation. Finally I would also like to touch on the possible implications of these results for the management of patients in the future. Inevitably many of the points raised in this section are based on the authors observations and are anecdotal but where possible they are supported by specific examples.

At the outset it was considered important for the outcome of this study that the most appropriate group of patients should be chosen. The absence of myocardial infarction simplified the study and on theoretical grounds increased the likelihood of success. Despite the common features it is clear however that this group was quite heterogeneous with respect to extent and severity of coronary artery disease and with respect to outcome. Symptomatic improvement was the rule throughout the group but when one looks closely at treadmill performance and change in myocardial perfusion the results are less predictable. It was considered at the outset that if myocardial perfusion was improved then this would be accompanied by improvements in those parameters of treadmill performance which indicate disease severity. As already discussed there was for the group overall only a small improvement in these parameters, yet some patients did show large improvements while others showed no change. Neither of these responses need indicate failure to improve perfusion. The patient who increases his myocardial oxygen consumption may have produced an effective collateral flow to the most ischaemic region. This may be by producing its own intravessel bypass in the form of one or more collaterals around the severe lesions. It may alternatively be by bypassing a lesion via a collateral supplied from another vessel feeding distal to the lesion, or it may be by distal filling of the diseased vessel as is often seen in right to left filling of a diseased LAD. The patient who fails to increase his maximal myocardial oxygen consumption has clearly been unable to effectively supply the most ischaemic

region by an alternative means. He may however have significantly reduced the ischaemic area by collateralising around the periphery of the ischaemic zone. The fact that the Thallium studies have shown a significant improvement in degrees of ischaemia with no apparent change in depth of ischaemia may support this viewpoint. Here again however we have a difficulty. If we are suggesting that depth of ischaemia is the limiting factor on exercise tolerance then it may also be a reproducible end point for a given individual. The patient who improves the blood supply to his most ischaemic area may therefore simply increase his maximal cardiac workload until that area becomes as ischaemic again. Obviously in these circumstances Thallium would show no improvement in depth of ischaemia. Our predilection for an improvement in degrees of ischaemia rather than depth of ischaemia may therefore be an inherent difficulty within the technique of Thallium scintigraphy rather than a genuine finding.

The above discussion perhaps highlights the major limitations in the techniques used in these studies. At the outset I acknowledged the limitations of Thallium scinitigraphy for the study of myocardial perfusion and attempted to overcome some of these limitations by narrowing down the study group. Despite this we are still left with the potential for a large variability in extent and site of initial lesions leading to an even greater number of possible modes of collateralisation. Added to this are the changes in cardiovascular efficiency of peripheral origin and their effects on Thallium handling. It is asking a lot of a very

limited technique to unravel this complex interaction of factors. Nonetheless as the results stand they do suggest that the extent of ischaemia detectible by Thallium scinitigraphy is reduced as a result of exercise training. These changes appear localised in nature and not particularly related to improvements in exercise tolerance. They occur despite evidence of equivalent or greater cardiac work and it is difficult to attribute them to improved peripheral cardiovascular efficiency. The rather complex technique of Thallium scinitigraphy used has, I believe, been justified in that it has come as close to providing an answer to the question as the technique will allow. In addition by demonstrating these varied responses it has suggested further areas of study which should be addressed by future techniques.

The analysis of global and regional left ventricular function, considered to be important at the outset of this study, is even more important bearing in mind the apparent predilection for improvement in the left anterior descending territory. Despite the apparent positive findings of Technetium angiography one's enthusiasm is again tempered by doubts about the techniques used. Perhaps a more sensitive gamma camera and the use of first pass studies would have helped. Certainly the use of the poorly understood technique of cold pressor stress adds to the doubts. Exercise echocardiography too is a difficult technique to quantify.

Ambulatory ECG monitoring has allowed one to study the improvements in exercise tolerance in an every day environment and furthermore has provided an interesting assessment of the effects

of exercise training on silent ischaemia. First consideration suggests that it would be a useful technique for assessment of the individual response to exercise training. One must however bear in mind that there is a natural day to day variability in frequency and extent of ischaemia which limits the value of such assessment. Furthermore one should also appreciate that the current systems allow analysis of two leads and that this may mean that ECG changes are missed. A more prolonged period of ambulatory monitoring, associated perhaps with an attempt to position the leads over the site of maximum ST change, would enhance the use of this technique for individual assessment as well as for a group study of this sort.

The one investigation which was available but not used in this study was coronary angiography. The reasons have already been outlined but it is clear from the comments in this section that, despite those initial views, coronary angiography would have been of interest. Its use to demonstrate collaterals would have been open to criticism as explained, but having put forward a number of complex ways in which Thallium perfusion may have been improved then the argument would have been much more convincing if it were backed up by details of the underlying coronary anatomy and visible collaterals in individual cases. This might have supplied important information also on why some patients improved myocardial perfusion while others did not. Intracoronary xenon has also been used to delineate patterns of myocardial perfusion at rest and during exercise.(160) The use of such a technique in this study, either serially or at the end of the study, would have

been invaluable. Xenon studies have shown that cross perfusion between the right and left coronary arteries may be present both at rest and on exercise, at rest alone, or on exercise alone. In light of the improved stress responses shown in this study the xenon perfusion patterns would not only allow confirmation of collateral flow but would also help to demonstrate whether this improved flow related to denovo creation of collateral channels or to enhanced performance during stress of channels which were already present at rest. With hindsight therefore this study could have been improved by using a combination of exercise Thallium scintigraphy and coronary angiography with xenon perfusion studies. The addition of rapid atrial pacing would have allowed the analysis of left ventricular function and xenon perfusion during stress. Whether one could ethically justify such a study is of course open to debate.

One final difficulty in performing this study requires mention. It is not a study which can easily be carried out in a blinded fashion. Both patient and observer bias inevitably will play their part. This study was carried out almost entirely by the author, assisted by technical and para medical staff. To have one person supervising the exercise training programme and also carrying out the tests is not ideal. It would have been much more preferable, had staffing allowed, if a separate individual could have carried out the investigations. The use of observer independent computerised techniques was in the circumstances the best way round this difficulty. Nonetheless working with this group of patients it is difficult not to be

impressed by the marked improvements in wellbeing which have taken place. It is possible that this may introduce some subtle bias during investigation and clearly it also hinders one's objectivity in interpreting the results. Perhaps it does however allow one to take a more holistic view of such a study and to discuss some of the more general points of interest which have arisen.

Can we draw any conclusions from this group of patients regarding which patients to choose for future exercise training programmes? The group is small and one must beware of drawing too firm conclusions, however it does appear that improvement in myocardial perfusion and function may not be related to initial disease severity. As discussed earlier, it was considered important to the outcome of this study that the most appropriate group of patients should be chosen. In particular the absence of myocardial infarction simplified the study and increased the likelihood of success. It does not of course imply that improvements in myocardial perfusion are impossible in the presence of myocardial infarction but perhaps that the association of reversible ischaemia in conjunction with myocardial infarction is likely to imply more diffuse disease and less opportunity for collateralisation.

Despite the common features it is clear that this group was quite heterogeneous with respect to extent and severity of coronary artery disease. Symptomatic improvement was the rule throughout the group despite this variability and furthermore improvement in myocardial perfusion and function was not related to initial disease severity. Patient E.P. displayed the largest

perfusion defect occupying 80% of the circumference of the anterior view and an average of 56% of all three views. This abnormality traversed the vascular territory of all three major coronary branches and was associated with a fall of 7% in ejection fraction during cold pressor stress and severe hypokinesis on regional wall motion assessment. Furthermore on ambulatory ECG monitoring 13 episodes of ST depression totalling 95 minutes in 24 hours were recorded with the maximum ST depression of 4.6 mm. (Figure 51) This patient was unable to work and required to be accompanied when travelling because of frequent angina. On his second attendance at the exercise class he collapsed with chest pain and marked hypotension while climbing one flight of stairs to the exercise class. Despite this he was asymptomatic at one year, his treadmill exercise duration had increased from 5 mins 21 secs to 26 mins 47 secs (4 METS to 11 METS) and his perfusion defect had decreased by 60%. The only episode of ST depression noted on ambulatory monitoring was during his daily exercise programme. (Figure 52) In this small study therefore disease severity did not seem to be of overriding importance.

Perhaps more disappointingly exercise performance could not be used as a guide to likely improvement. Two members of the exercise group achieved exercise levels greatly in excess of the others. Both became asymptomatic. One of these (E.H.) showed a marked improvement in ambulatory monitoring in association with his improved symptoms. However despite regular exercise at level A + on chart 3 of the exercise programme, his Thallium perfusion at one year was unaltered with evidence of ischaemia infero

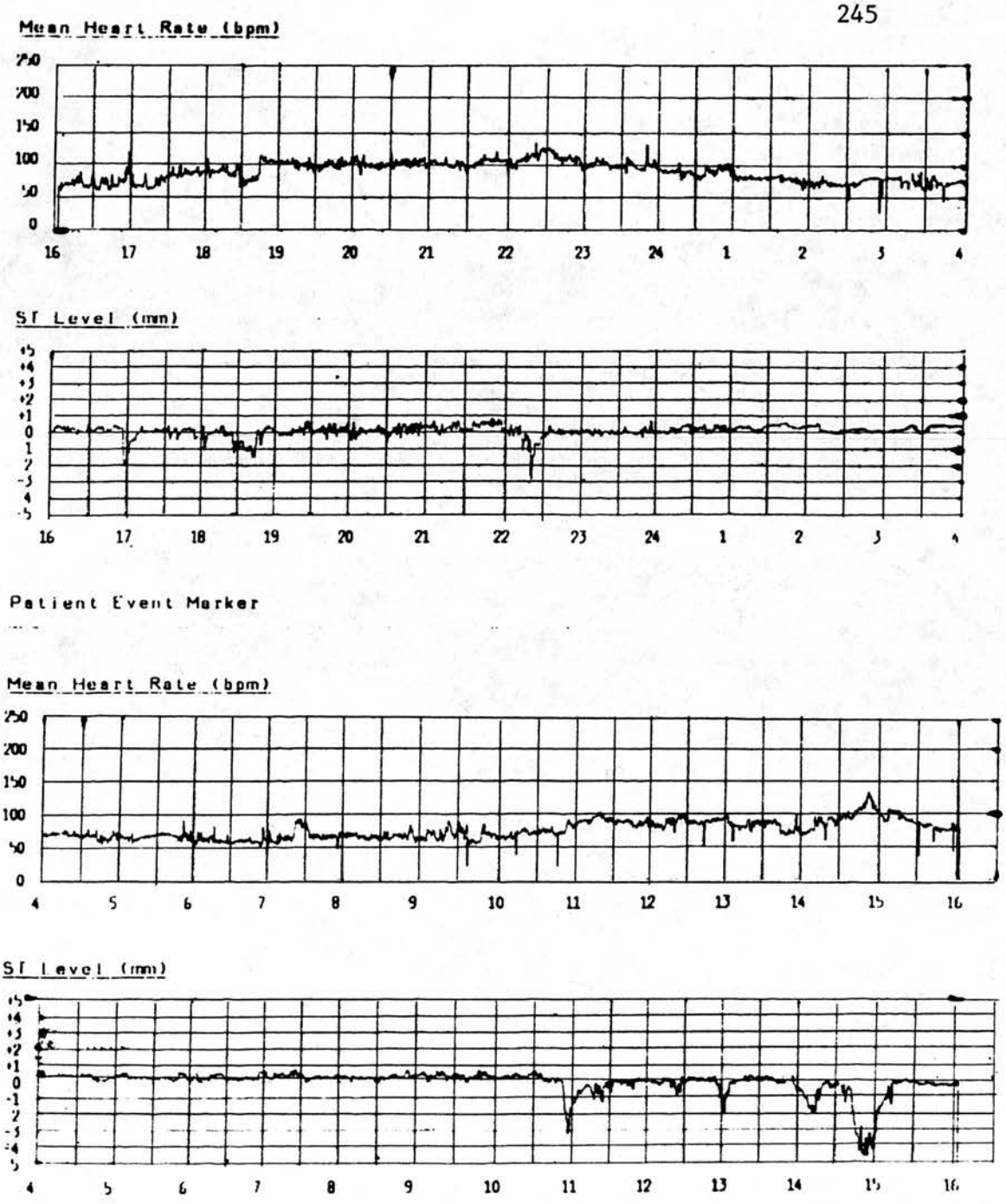


Figure 51 Patient E.P. Graphs of ambulatory heart rate and ST level at baseline

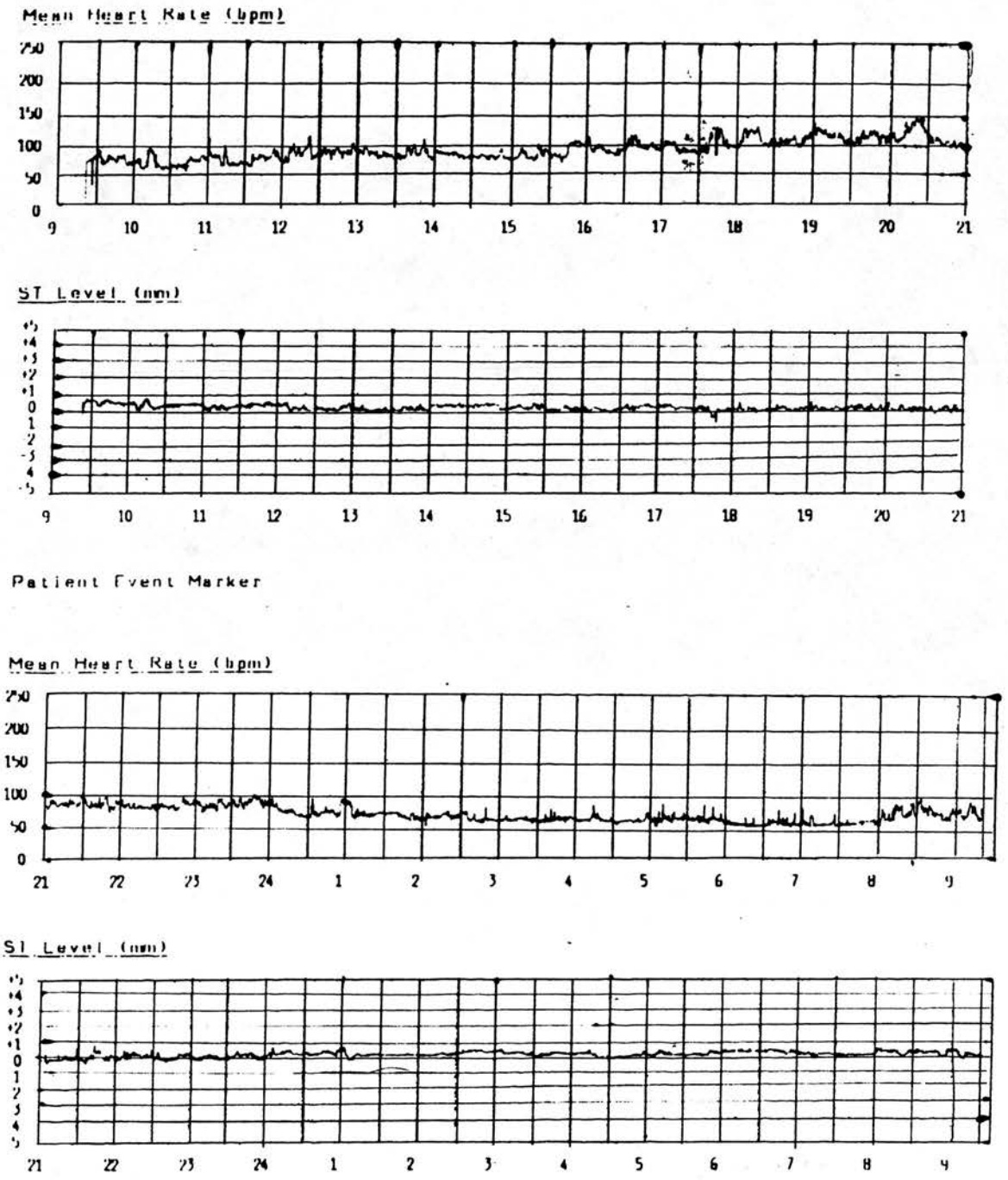


Figure 52 Patient E.P. Graphs of ambulatory heart rate and ST level at one year

apically and septally. Despite the appropriate "recipe" for improved myocardial perfusion this was not produced. One can only assume that local anatomical factors prevented the development of collaterals. The implication of this finding is that it is difficult to predict improved myocardial perfusion on clinical grounds or indeed on symptomatic grounds. If the aim of the exercise programme used is to improve patient wellbeing, then this does not matter, but if the intention is to improve myocardial perfusion then a more direct assessment of this improvement is necessary.

The results of Thallium perfusion scanning suggested that left anterior descending territory ischaemia was most amenable to collateralisation and that on theoretical grounds single vessel disease would be most readily collateralised. However it is clear that the majority of patients in this study had perfusion defects in more than one vascular territory and therefore did not have single vessel disease. No anatomical information is available but the variability of results obtained within this small exercise group suggests that perhaps local anatomical factors are most important in determining the success of exercise therapy in terms of improved myocardial perfusion.

The Canadian Airforce programme was chosen for its ease of application and high level of stimulation. It is clear from the results that it has been successful. It has achieved the desired level of cardiac stimulation. Ambulatory ECG monitoring has shown that it provokes heart rate increases in excess of that achieved on treadmill testing and that it actively provokes ST

depression. Despite this there have been no cardiac events during or following the performance of these exercises. In a group of 20 patients throughout the one year study period one patient developed unstable angina and one patient suffered acute myocardial infarction, the latter developing during a phase of persistent hypertension which proved difficult to control. There were no fatalities during the study in the exercise group. Clearly a much larger study would be required in order to assess the effect of this programme on cardiac events, but the incidence noted here is well within the expected incidence for a group of this sort. Indeed the control group suffered one sudden death and one myocardial infarction during the same period. Compliance was also very high. During the one year study period only one patient of the 20 defaulted. The patient who developed unstable angina was withdrawn from the programme and one other patient who completed the exercise programme was unable to attend for reassessment due to family problems. This compares favourably with other studies (102,161,162) and reflects the ease of application of the training programme. There was no necessity for repeated hospital attendance during the week and indeed weekly attendance was optional. Furthermore the brief nature of the exercise programme in terms of daily time allocated allowed it to be fitted easily into the daily activities of most patients. It is notable that this programme has to date been running for 46 years and is still regularly attended by the original group of patients. While no attempt was made to confirm compliance with the exercises at home, after cessation of the study it was

suggested that fitness could be maintained by reducing the exercises to three or four days per week but this idea was rejected by all patients in the study group. The patients felt that the daily regime became habit forming and could easily be complied with but that the introduction of days without exercises would eventually lead to non compliance.

The point has already been made in this thesis that the intention of using this exercise programme was not necessarily that it alone would provide the stimulus required but that it would form the basis of a modified lifestyle in terms of exercise for the patients. Anecdotally it is clear that this was the case in that many patients took up new sporting activities or resumed former activities as a result of taking part in this programme. In addition dietary habits were altered in some cases. Smoking however was not altered during this study. Many patients were already ex smokers and those who were not continued to smoke despite the study. The conclusion with respect to the exercise programme therefore must be that it is "user friendly" and that it produces the stimulus necessary to provoke improvements in myocardial perfusion, whether directly or indirectly via its effect on the patient's exercise habits. Aside from its ease of use its advantage may well be that it encourages a less fearful attitude to angina pectoris in general and to exercise in particular. The lack of monitoring of exercise levels and heart rate by the patient is in direct contrast to accepted practice for exercise training programmes. It is conceivable that the practice of monitoring ones own heart rate during an exercise

programme is counterproductive in that it encourages the belief that exercise beyond a certain level is dangerous to the patient and may lead to a rather obsessional preoccupation with heart rate.

Some of the points made in this thesis may appear to be critical of drug therapy in angina pectoris. At the outset of this study it was suggested that elimination of myocardial ischaemia by drugs might impair the process of collateralisation and in the final results section it was demonstrated that exercise training could produce improvements in exercise tolerance in excess of that achieved by atenolol, one of the most commonly used pharmacological agents. Furthermore it was suggested that the enhanced collateral function may be impaired by subsequent betablockade. Despite these comments however it would be wrong to adopt a nihilistic approach to drug therapy and to ignore the possible benefits of primary or secondary prevention. Perhaps however these results do suggest that a more studied approach to the effects of drugs is appropriate. In particular the interaction of drugs with myocardial perfusion and collateral function is an area which merits further study. The suggestion already made that betablockade may impair distal coronary perfusion and therefore collateral function is graphically illustrated by one patient from the study group (J.F.) whose case has already been reported in the British Heart Journal.(163) His maximum heart rate ECG tracings are shown in Figure 53. This patient achieved the highest exercise performances of any of the study group. His exercise test was clearly positive at baseline

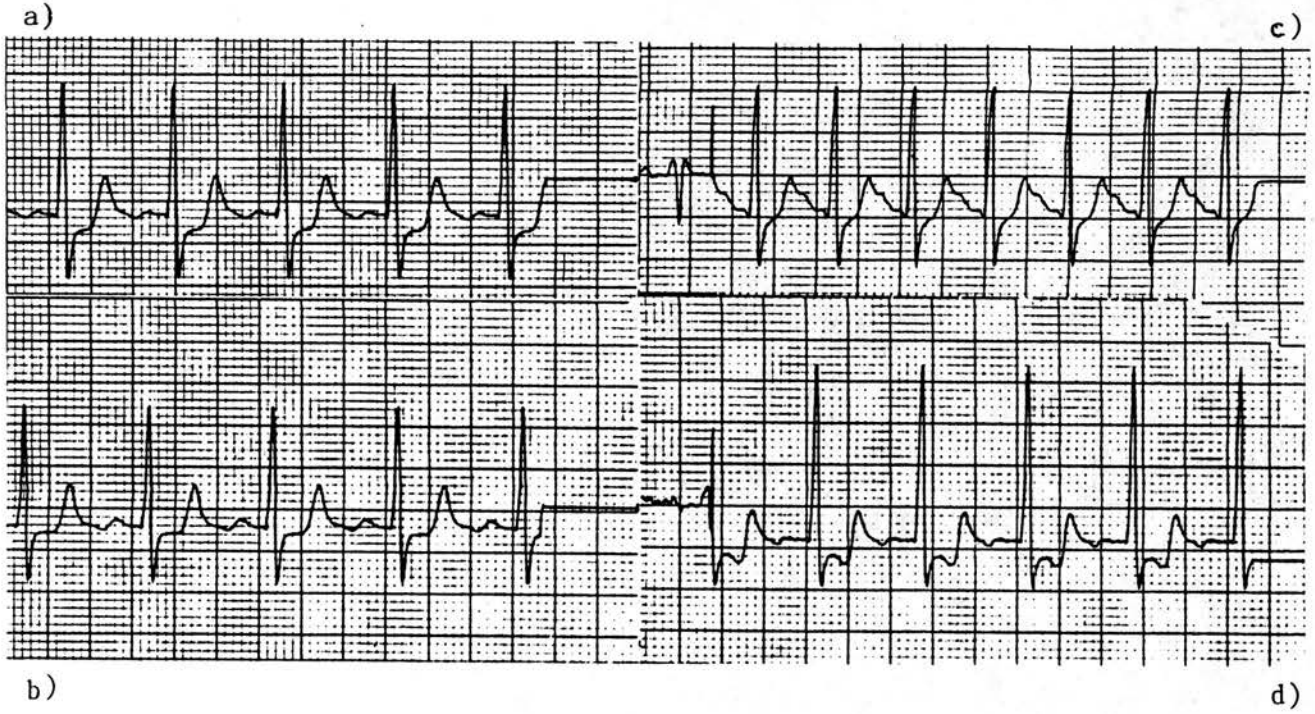


Figure 53 Patient J.F. Treadmill ECG's during maximal exercise at baseline and one year before and after betablockade

a) Initial test on no drugs
b) Initial test on atenolol
c) After training on no drugs
d) After training on atenolol

and became negative after training. He became asymptomatic. Subsequent betablockade resulted in recurrence of ST depression at low heart rate. His initial Thallium scan showed apical ischaemia while his one year scan, in association with a negative exercise test, demonstrated impaired perfusion proximally within the septum. In view of the finding of ST depression precipitated by betablockade, a Thallium scan was carried out during betablockade and this showed recurrence of apical hypoperfusion. Interestingly only two other patients had exercise tests after exercise training which failed to produce diagnostic ST depression and in both cases a greater degree of ST depression was demonstrated during subsequent beta blockade.

This study has challenged established beliefs with regard to the safety of exercise training in angina pectoris and the nature of exercise training programmes themselves. It has furthermore questioned the traditional anti anginal approach of drug therapy. The potential implications are therefore great. It has shown that exercise therapy is a valuable anti anginal agent in this group of patients. It has further suggested than unlike other available agents it may possibly improve myocardial perfusion. At the beginning of this Thesis it was suggested that the true link between extent of disease and prognosis was related to area at risk and indeed it has been suggested that size of perfusion defect can be used to stratify patients according to risk (164) or that the presence of collaterals is associated with improved prognosis While that is not quite the same as saying that changing the size of area at risk in a favourable way will have a

favourable result on prognosis, it does suggest that exercise training may indeed be of prognostic importance. This programme is not only of theoretical value but is clearly clinically applicable. Former exercise programmes have been criticised on financial grounds, in that they require extensive use of hospital facilities, specialised equipment and specialised staff. The programme used here requires none of these. It has been carried out in a disused ward and requires physiotherapy support during the hospital exercise session and one co-ordinator. This role was filled by the author but could equally be filled by a rehabilitation nurse. From the patient's point of view carrying out exercises for 11 minutes daily is no more troublesome than taking daily medication. I believe therefore that this programme could be instituted without difficulty even in the average district general hospital. The small financial cost of this programme is further offset by the reduced drugs bill for anti anginal agents. On these grounds one could justify the widespread use of exercise training programmes at the point of diagnosis of ischaemic heart disease rather than solely as a means of rehabilitation after myocardial infarction or coronary artery surgery. Clearly in many cases anti anginal agents would be of benefit but their use would, I believe, be more restricted than at present. A more extensive use of programmes of this type would then allow the necessary evaluation of their prognostic importance. The long-term effects of such an approach must also be considered however and it is perhaps appropriate to end on a somewhat cautionary note. In the opening section conventional

drug therapy was described as palliative. It is of course true that collateralisation is also a palliative process. This thesis has not sought to question the effect of exercise training on the progress of coronary artery narrowing. If this continues then ultimately collateral function will become impaired in the donor vessel. It may be therefore that this means of therapy results only in temporary improvement in myocardial perfusion and in symptomatic relief. The same criticism may be aimed however at all other current therapeutic approaches and at least exercise therapy addresses those factors in the lifestyle of individuals which may predispose to the development of coronary artery disease in the first place.

It is ironic that this approach which questions many of the established ideas regarding exercise in ischaemic heart disease is in reality as old as the description of the syndrome itself. Sir William Heberden coined the name Angina Pectoris in a presentation to the Royal College of Physicians in 1872.(165) His descriptions of the clinical syndrome and all its variations have not been bettered. He understood little of the pathology and could offer few therapeutic ideas, yet in a more complete account of his presentation published after his death he described the case of a patient "nearly cured" by chopping logs for 30 minutes every day and offered this as a possible means of treatment.(166) The results of this study bear out, at least in part, some of Heberden's early enthusiasm for daily exercise therapy in Angina Pectoris.

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ABBREVIATIONS

ECG	Electrocardiograph
HR	Heart rate
BP	Blood pressure
LAD	Left anterior descending
LAO	Left anterior oblique
RAO	Right anterior oblique
RBC	Red blood cell
RNV	Radionuclide ventriculography
PVC	Premature ventricular contraction