Effect of exercise training on the total ischaemic burden: an assessment by 24 hour ambulatory electrocardiographic monitoring

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Objective—To examine the effect of prolonged high intensity exercise training on total ischaemic burden in men with chronic stable angina pectoris.

Design—A randomised controlled trial based on 24 hour ambulatory electrocardiographic monitoring of patients on two occasions a year apart.

Setting—Cardiology department of a large general hospital.

Subjects—40 men under 60 years of age with chronic stable angina pectoris and no previous myocardial infarction.

Results—After training the exercise group showed a 30% reduction in frequency of ST segment depression. There were significant reductions in painful episodes of ischaemia and those triggered by changes in heart rate. There was also a trend towards a reduction in silent ischaemia and episodes not triggered by changes in heart rate. The duration of ischaemic episodes was also reduced. No significant change in frequency or severity of dysrhythmia was shown.

Conclusions—Exercise training reduces total ischaemic burden in patients with angina pectoris by reducing the frequency and duration of all types of ischaemic episode.

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In a recent publication we reported the anti-anginal efficacy of exercise training compared with β blockade.¹ A brief daily exercise training regime was shown to compare favourably with daily atenolol when assessed by treadmill exercise tolerance. It is apparent, however, that the assessment of ischaemic heart disease and its treatment is incomplete without some measure of ischaemic activity outside the controlled environment of the exercise laboratory. The development of frequency modulated ambulatory electrocardiographic recording that allows accurate monitoring of ST segment changes has produced information that makes such monitoring vital not only in assessment of the disease but also the treatment.

Several authors have shown that most ischaemic episodes are not associated with pain.¹⁻⁵ Such silent episodes may relate to alterations in the pain threshold or to other as yet unidentified factors. They have the same characteristics as painful episodes and so may

have the same clinical significance.^{3,4} Most episodes of ischaemia on Holter monitoring, whether associated with angina or silent, are not secondary to increases in myocardial oxygen demand.²⁻⁵ It is probable that they are secondary to alterations in myocardial oxygen supply. These facts raise two important aspects of the assessment of any treatment that can be clarified only by ambulatory electrocardiographic monitoring, namely the effect of treatment 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 efficacy of exercise training in reducing angina. Exercise training has been shown to affect exercise induced increases in heart rate by reduction in sympathetic stimulation of the heart. If most episodes of angina are not induced by exercise then what effect can training have on these episodes? Furthermore patients on exercise training programmes report less angina and some become symptom free. Does this mean that they have fewer ischaemic episodes or have we merely changed them from painful to silent by raising their pain threshold or by increasing endogenous opiate production? To answer these questions we undertook a randomised controlled study of exercise training in men with chronic stable angina pectoris by 24 hour ambulatory electrocardiographic monitoring.

Patients and methods

Forty men under 60 years of age with chronic stable angina pectoris of at least six months duration and no previous myocardial infarction were recruited and allocated by a random number generator to exercise training and control groups. All had positive exercise tolerance tests by standard criteria with a treadmill. The demographic data and exercise tolerance results have already been published.⁶ After randomisation the exercise group began the Canadian Airforce PBX plan of daily exercise training for physical fitness.⁷ This programme consists of 11 minutes of daily callisthenic exercise and has already been described in detail.⁶ Exercises were continued for a period of one year.

Holter monitoring was carried out with the Oxford Medilog 4000 (MARS) ambulatory electrocardiographic recorder. This frequency modulated recorder has a frequency response of 0.05-40 Hz and a signal to noise ratio of better than 30 dB. The recorder processes each

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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 used for each recording. Cassette tapes were demagnetised before use. The patient's chest was shaved if necessary and the area of skin prepared by rubbing with abrasive paste to remove the stratum corneum. Electrodes were then applied to the chest over bony sites (fig 1). This produced a recording of leads CM5 and a modified lead II. An impedance meter was used to ensure that the resistance between electrodes was <5 k ohms. The leads were then attached to the patient with surgical tape incorporating stress loops to reduce artefacts. The whole electrode system was further fixed with an elastic vest and the recorder was worn in a pouch on a waist belt. A 1 mv calibration signal was fed into the recorder and an electrocardiographic signal recorded on a conventional machine to ensure adequate quality before starting to record. Two other channels recorded a quartz time signal and a flutter compensation signal during the 24 hours. Recordings were made among the exercise group at the end of the first week of the exercise regime timed in such a way that the patients could carry out their weekly supervised exercise before removal of the monitor. A repeat assessment was carried out one year into the exercise programme.

The control group underwent similar investigations one year apart. In the interim they were reviewed at three monthly intervals. No attempt was made to advise them either to undertake or to avoid exercise. Those patients who asked were told that moderate exercise may be of benefit. Medication for both groups during the study was nifedipine where required and if this was insufficient isosorbide dinitrate was also used. β blockers were not allowed during the study period. To ensure as far as possible that medication was not inadvertently changed, the control group were granted open access to the supervising physician.

The analysis of the completed 24 hour tapes was made up of two phases. Firstly the cassette

was automatically analysed with the Oxford Medilog MARS replay system to produce trend graphs of heart rate, ST segment analysis, and ventricular extrasystoles. Also an hourly summary of maximum and minimum heart rates and arrhythmias was produced. The second phase of the analysis was to use the summary information to select times of ST segment shift or arrhythmia, and by entering these times in the replay system. Print outs of the two lead electrocardiograms were obtained. This manual check meant that all events identified were confirmed as genuine and in no case was the diagnosis of ST segment depression or arrhythmia based solely on software used by the automatic analysis programme. This was particularly important with regard to ST segment analysis as the starting 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 ≥ 1 mV from a baseline occurring 80 ms after the J point and lasting for at least 30 s. Patients with obvious resting ST segment or T wave changes in the monitored lead were excluded from analysis. Ventricular extrasystoles or arrhythmic activity was analysed as the total number of ventricular premature contractions per hour or per 24 hour period and as the maximum Lown grading of ventricular extrasystoles noted on the patient's tape.⁸ Table 1 shows the Lown grading system.

STATISTICAL ANALYSIS

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, and these data were therefore analysed with the Wilcoxon signed rank test as were the data for total ventricular extrasystoles. As both periods of monitoring were carried out after randomisation and the exercise group included periods of exercise, intergroup comparison was inappropriate.

Results

There were no significant differences between the groups at baseline in terms of demographic data or drug treatment. Nifedipine was used for symptomatic control in most cases at the outset. Three patients found it unhelpful and one of these used isosorbide dinitrate instead. At the end of the study most of the exercise group were symptomatically improved such that eight had discontinued medication. Three of

Figure 1 Lead positions for ambulatory electrocardiography. Electrodes 1 and 3 provide OM5 recording and electrodes 2 and 4 record lead I.

Table 1 Lown ventricular extrasystolic grading system⁸

Grade 0	No VPCs
Grade 1A	Occasional isolated VPCs ($<30/h$) $<1/min$
Grade 1B	Occasional isolated VPCs ($>30/h$) $<1/min$
Grade 2	Frequent VPCs ($>30/h$)
Grade 3	Multiform VPCs
Grade 4A	Repetitive VPCs; couplets
Grade 4B	Repetitive VPCs; salvos
Grade 5	Early VPCs (R on T)

VPCs, ventricular premature contractions.

Figure 2 Maximum 24 hour heart rates in the exercise group.

the control group increased the dose of nifedipine and one added oral nitrates.

Compliance among the exercise group was high as assessed by continued attendance at hospital supervised sessions and the ability to perform exercises well. Only one patient in the exercise group defaulted, one other was withdrawn due to unstable angina, and one was not able to attend for repeat assessment. Of the 17 who were restudied all reported increased levels of physical activity in diaries recorded while wearing the tape, including return to work and participation in daily walking or sporting activities. The tape results at one year therefore represent recordings at higher activity levels on fewer antianginal drugs.

By contrast there were no significant changes in activity among the controls. Two patients defaulted from follow up, one died suddenly, one was unable to tolerate the tape on either occasion and two refused repeat taping, leaving 14 completed controls.

Figure 2 shows the hourly maximum heart rate for the exercise group at baseline and one year. For this, as well as for minimum and mean heart rate, there was a trend towards lower heart rates after exercise training. Individual results were, however, variable and the standard deviations large, so the differences were not significant. Table 2 shows the group means for minimum, maximum, mean, and nocturnal heart rate. The mean heart rate was calculated by dividing the total number of beats/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 studied between midnight and 8.00 am that produced the lowest mean heart rate. Again the trend for all four measurements was towards a reduction in heart rate after exercise training. The reductions in minimum 24 hour heart rate and mean 24 hour heart rate were not significant. Maximum heart

rate (mean (SD)) was significantly lower after training at 142 (16.1) compared with 151 (17.8) at baseline ($p < 0.05$). Mean nocturnal heart rate was also significantly lower after training at 63 (4.6) compared with 66 (6.3) before training ($p < 0.04$). All heart rates measured in the control group tended to increase at one year compared with baseline, although none was significant.

Table 3 shows the individual results for maximum ST segment depression, frequency of ST segment depression, and total duration of ST segment depression in addition to group means, standard deviations, and p values (Wilcoxon signed rank test). Maximum ST segment depression in the exercise group at baseline ranged from 0 to 6 mm with a mean maximum ST segment depression of 2.2 mm. This was reduced by 30% after training to 1.5 mm (range 0–3.8 mm, $p = 0.04$). This improvement is reinforced by a reduction in frequency of ST segment depression from 8.3 to 5.2 episodes/patient/24 hours ($p = 0.02$). The total duration of ST segment depression was also reduced from 63.7 to 37.7 min/24 hours ($p = 0.02$). Over the same period the control group showed no significant change in any of these measurements.

Tables 4 and 5 show the characteristics of the episodes of ST depression. The total number of episodes of ST depression in the exercise group was reduced by 37%. Of the initial 141 episodes, 23% were associated with pain as reported by the patients in diaries. At one year only 12% of the 89 episodes was painful. Mean number of painful episodes of ST depression had therefore decreased from 1.9 (1.9) to 0.7 (1.0) ($p = 0.02$). There were 108 silent episodes at baseline and 77 at one year, representing a mean frequency of 6.4 (7.6) episodes/patient at baseline and 4.5 (7.0) at one year. This difference however was not significant. In the control group there were 80 episodes of ST depression at baseline and 88 at one year, 24% were painful initially and this had decreased to 12% at one year. The reduction in painful episodes was accompanied by an increase in silent episodes. There was no significant change in the mean frequency of either painful or silent episodes in the control group.

The episodes can also be subdivided into those with an increase in heart rate of > 6 beats/min during the minute preceding the onset of ST depression (heart rate triggered) and those not so associated. In the exercise group there were 79 heart rate triggered episodes at baseline and 45 at one year, representing a frequency of 4.6 (4.6) at baseline and 2.6 (3.5) at one year ($p = 0.008$). The incidence of events not triggered by heart rate also fell from 3.6 (4.9) (62 events) to 2.6 (3.9) (44 events). This reduction, however, failed to achieve statistical significance. In the control group there was no significant change in mean frequency of either heart rate triggered or non-heart rate triggered episodes. Figure 3 is a frequency histogram of duration of ischaemic episodes showing that at baseline there was a fairly even distribution of frequency of episodes in the four bands up to 30 minutes

Table 2 Mean (SD) group 24 hour heart rates

Heart rate	Exercise group			Control group		
	Baseline	One year	p Value	Baseline	One year	p Value
Minimum	50 (5.3)	48 (4.0)	NS	49 (5.8)	51 (6.4)	NS
Maximum	151 (17.8)	142 (16.1)	< 0.05	137 (14.6)	139 (18)	NS
Mean	81 (8.4)	79 (6.7)	NS	79 (6.8)	80 (7.0)	NS
Nocturnal	66 (6.3)	63 (4.6)	< 0.05	66 (9.1)	69 (7.8)	NS

Table 3 Individual characteristics of ST segment depression

Patient no	Maximum		Frequency		Total duration	
	1	2	1	2	1	2
Exercise group						
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 (SD)	2.2 (1.5)	1.5 (1.2)	8.3 (8.0)	5.2 (7.0)	63.7 (71.2)	37.7 (57.8)
p Value	0.04		0.02		0.02	
Control group						
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 (SD)	1.4 (1.0)	1.2 (1.2)	5.7 (6.2)	6.3 (8.5)	51.6 (82.2)	44.9 (75.4)
p Value	NS		NS		NS	

duration. At one year, however, there was a relative reduction in frequency of episodes over five minutes duration. Therefore not only were there fewer episodes, but those episodes that did occur tended to be shorter. These two facts together account for the reduction in total duration of ischaemic time. Figure 4 is a similar histogram for the control group showing consistency over the one year period.

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

Figures 5 and 6 show the hourly total number of ventricular premature contractions for the two groups; both groups show an increased frequency at one year. Although the total number of ventricular premature contractions 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 6 shows the

Figure 3 Frequency histogram of duration of ischaemic episodes at baseline and at one year in the exercise group.

maximum Lown grading achieved by each patient. At baseline only six of 17 patients in the exercise group had a Lown grading ≥ 2 . At one year seven patients were $\geq$ grade 2. In the control group only two of the 14 patients were $\geq$ grade 2 at baseline and three at one year. Five patients in the exercise group had identical Lown gradings on both occasions, whereas seven had improved grading and five were graded worse at one year. Among the controls 10 patients showed no change, one improved, and three became worse.

Discussion

There are no previous studies on ambulatory monitoring during exercise training with which to compare these results. The technique has, however, been used to assess drug treatment in angina pectoris and one can therefore compare the antianginal efficacy of exercise training with drugs in these studies.⁹⁻¹² The reduction in hourly heart rate is perhaps less than might have been expected after training. It was clear, however, that most patients with angina were, on medical advice, relatively sedentary patients at baseline and by the end of the year this trend had largely been reversed and they were encouraged to be physically active as often as possible. It is likely therefore that the expected reduction in mean heart rate had been offset by an increase in physical activity. The resting bradycardia of the athletic person is evident,

Table 4 Characteristics of episodes of ST segment depression in the exercise group

	Baseline			One year			p Value
	Group total	(%)	Mean (SD)	Group total	(%)	Mean (SD)	
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
HR triggered	79	56	4.6 (4.6)	45	51	2.6 (3.5)	0.008
Non HR triggered	62	44	3.6 (4.9)	44	49	2.6 (3.9)	NS
Mean HR at onset of ST depression	—	—	107 (17)	—	—	106 (14)	NS
Maximum HR during ST depression	—	—	116 (19)	—	—	112 (16)	NS
Mean maximum degree of ST depression	—	—	1.8 (0.9)	—	—	1.6 (0.7)	NS

Table 5 Characteristics of episodes of ST segment depression in the control group (*p* values all non-significant)

	Baseline			One year		
	Group total	(%)	Mean (SD)	Group total	(%)	Mean (SD)
All episodes	80	100	5.7 (6.2)	88	100	6.4 (8.4)
Painful	19	24	1.4 (1.8)	12	14	0.9 (2.0)
Silent	61	76	4.4 (5.8)	79	86	5.4 (8.3)
HR triggered	47	59	3.4 (4.4)	59	67	4.2 (6.2)
Non HR triggered	33	41	2.4 (2.8)	29	33	2.1 (2.9)
Mean HR at onset of ST depression	—	—	101 (11)	—	—	103 (11)
Maximum HR during ST depression	—	—	114 (12)	—	—	114 (14)
Mean maximum episodic ST depression	—	—	1.5 (0.5)	—	—	1.7 (0.7)

however, in a 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 if the heart rates between 2 and 3 pm on the two occasions are compared. This corresponds to the peak heart rate during the exercise class and has been significantly reduced after training despite a much higher level of exercise. Likewise the group maximum heart rate decreased from 151 to 142 bpm despite the overall increase in physical activity. These measurements support the belief that the improvements in response of heart rate to exercise are not confined to treadmill measurements but do genuinely carry over into normal daily activities.

The baseline measurements for the exercise group show a rather higher maximum ST segment depression and higher mean frequency of ST segment depression than the control group. One must remember, however, that this test was carried out after the start of exercise training. Most subjects performed their exercises on two occasions during the 24 hour period (before retiring to bed or on rising from it and at the exercise class). In most cases this represents two deliberate episodes of provoked ischaemia accounting for most of the difference in mean baseline frequency of ST segment depression between the groups (8.3 *v* 5.7). As in many cases maximum ST segment depression occurred during the exercise routine this also partly explains the difference in maximum ST segment depression (2.2 *v* 1.4). These facts aside, however, the change within the exercise group over the one year period is striking, again considering the apparent increase in physical activity. Not only has maximum ST segment depression decreased,

but also the frequency and duration have been reduced; and the frequency histogram also shows that episodes of ST segment depression tend to be of shorter duration. The antianginal effect of the training programme previously shown on the treadmill is also clear during ambulatory monitoring. There are fewer episodes and those that do occur are shorter and less severe so that total ischaemic burden is reduced. The argument that encouraging such physical activity in the presence of ischaemic heart disease may be dangerous by actively provoking myocardial ischaemia is somewhat weakened in this context as 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 means of improving collateral blood flow is true then we have also reached a situation where those in the control groups at the end of one year are being stimulated more than the exercise group. To maintain the stimulus to improve perfusion it may be necessary, therefore to increase exercise duration and intensity further.

The antianginal efficacy of exercise training as measured by ambulatory electrocardiographic monitoring is comparable to that with drug treatment. Quyyumi *et al* studied a group of patients with severe angina pectoris whose baseline measurements of ST depression were similar to the group studied here in terms of frequency, duration, and extent of ST depression and incidence of painful and silent ischaemia.⁹ They were treated with atenolol and pindolol in a double blind crossover study. Pindolol decreased the frequency of ischaemic episodes by 30%, whereas atenolol produced a reduction in frequency of 53%. Duration of ischaemia was reduced by 30% with pindolol and 45% with atenolol, figures not dissimilar to those produced by the exercise group studied here. Studies with calcium antagonists show similar degrees of efficacy,¹⁰⁻¹² although interestingly, nifedipine, the drug used as an antianginal treatment in this study, seemed not to decrease frequency or extent of ST depression in the study of Bala Subramanian *et al*.¹²

One of the major discoveries resulting from the use of ambulatory ST segment monitoring is that the typical painful ischaemic episode of ST segment depression provided by changes in heart rate is very much in the minority, most episodes of ST segment depression being painless.^{4 5 13 14} Also most are not triggered by an increase in heart rate.^{5 13 15} We postulated that exercise training might, by increasing

Figure 4 Frequency histogram of duration of ischaemic episodes at baseline and at one year the control group.

Figure 5 Frequency histogram of hourly ventricular premature contractions in the exercise group.

Figure 6 Frequency histogram of hourly ventricular premature contractions in the control group.

endogenous opiate production, reduce painful episodes and might also, due to its effect on the heart rate response to exercise, decrease episodes that are triggered by heart rate. From the results these two facts seem to be true. Painful episodes were indeed decreased but there was also a reduction of 29% in silent episodes that was not significant. This would suggest that the primary effect on the exercise group was a reduction in ischaemia, and that superimposed on this was the tendency for fewer episodes to be recognised by the patient,

whether due to opiate production or denial. In the control group, on the other hand, whereas painful episodes did decrease, silent episodes increased. Although neither change was significant it is clear that there was no overall decrease in ischaemia but a tendency to report pain less often.

In the exercise group the situation for events triggered by heart rate or non-triggered events was similar. Both were reduced but only the events triggered by heart rate were significantly reduced. Whereas the reduction in episodes triggered by heart rate is to be expected in a trained subject, any reduction in the rate of non-triggered episodes is encouraging and one would like to see this trend studied in a larger group.

Interestingly, despite the improvements outlined above there was no reduction in the mean heart rate at the onset of ST segment depression, mean maximum heart rate during ST segment depression, or mean maximum ST segment depression. There seems, therefore, to be no change in the threshold for ischaemia to suggest an improvement in myocardial perfusion. This contrasts with the treadmill results in this group where maximum heart rate and ST threshold were increased. As usual with ambulatory monitoring, however, the heart rate thresholds are low indicating that increases in heart rate are only part of the equation even in the episodes triggered by heart rate. These figures perhaps reflect the variability of other factors in the ischaemic process and the lack of sensitivity of ambulatory ST segment monitoring compared with treadmill exercise testing.

The monitoring of arrhythmias was always likely to be beyond a study of this sort. Whereas early studies suggested that premature ventricular contractions were important indicators of risk of sudden death,^{16,17} it has been recognised that there is a great variation in the occurrence of arrhythmias during ambulatory monitoring⁸ and that as episodes in Lown class I are common, they are therefore poor discriminators for identifying patients at risk of sudden death.^{18,19} 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.^{18,20} 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.²¹ Training produced no evidence of a reduction in extrasystoles and little change in the more serious arrhythmias with roughly one third improved, one third worse, and one third unchanged. Whether these arrhythmias are more or less likely to be associated with sudden death in the trained patient is perhaps the key question but beyond the scope of this study. In view of concern over the question of the value of exercise training in preventing sudden death this question would merit further study.

In summary, this study has shown a reduction in frequency and duration of angina and ischaemia after training as assessed by ambulatory monitoring. Whereas the changes are significant only for episodes that are painful

Table 6 Lown grading of ventricular extrasystoles at baseline and one year

Lown grade	Exercise group		Control group	
	Baseline (n)	One year (n)	Baseline (n)	One year (n)
0	0	2	1	0
1A	10	7	11	11
1B	1	1	0	0
2	3	3	0	1
3	1	1	0	1
4A	0	1	1	1
4B	1	2	1	10
5	1	0	0	0

or triggered by changes in heart rate, there is a trend towards a reduction in silent ischaemia and that not triggered by heart rate. This trend may have been significant had we studied larger numbers or extended the study period to 48 hours of monitoring, which is now the accepted norm. This aside, daily exercise training in this group at least would seem an effective way of reducing the total ischaemic burden in angina pectoris.

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