The effect of a 6-month cardiac rehabilitation programme on serum lipoproteins and apoproteins A1 and B and lipoprotein a

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Abstract One hundred and forty-two cardiac rehabilitation patients were followed up over a period of 6 months and the percentage change over time was recorded for various lipid fractions including apoprotein AI (apo AI), apoprotein B (apo B) and lipoprotein a (Lp(a)). Data were analysed to see if improvement in peak oxygen consumption (Vo_2) or changes in body weight were related to any of the above. A significant percentage change was found for peak Vo_2, ventilatory threshold, high-density lipoprotein cholesterol (HDLC) and triglyceride levels, total cholesterol (TC)/HDL ratio, apo AI, apo A/apo B ratio and Lp(a). Multiple regression analysis showed that alterations in the lipid fractions were not related to changes in physical fitness except in the case of TC levels which dropped independently of other measures.

On multivariate analysis, Lp(a) correlated positively with both the Broca index and the use of drugs of the fibrate series.

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Epidemiological, genetic and experimental pathological studies have produced evidence for a cause-and-effect relationship between high cholesterol levels and coronary artery disease (CAD).[1] Two recent studies using meta-analysis have shown that supervised exercise and risk factor modification cardiac rehabilitation programmes significantly decrease mortality rates.[2,3]

The effects of exercise on serum lipoproteins have been extensively documented in respect of apoproteins AI, AII and B.[4-7] We found only one reference to alterations in lipoprotein a (Lp(a)) levels after exercise, and this was in a short-term study involving 16 obviously fit skiers.[8]

In an earlier study we found a significant reduction in the total cholesterol (TC)/high-density lipoprotein (HDL) ratio in patients who complied well with an exercise training rehabilitation programme in Johannesburg.[9]

Apo AI has been found to have a higher discriminant value in CAD than HDL cholesterol (HDLC) alone[10] and a decrease in apo AI in subjects with CAD has been demonstrated.[11,12] The apo AI/apo B ratio is apparently more strongly related to CAD than their respective lipoprotein cholesterol fractions,[13,14] although this has recently been disputed.[15]

Lp(a) is still not generally accepted as an independent risk factor for CAD, although there is agreement that it is a biochemical marker.[16]

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The aim of this study was to examine the effect of an exercise cardiac rehabilitation programme on serum lipid levels with special reference to apo AI, apo B and Lp(a).

Patients and methods

One hundred and forty-two patients referred to the Cardiac Rehabilitation Centre between July 1989 and July 1990 were enrolled into the study. There were 129 men and 13 women, with a mean age of 57,2 years (range 31 - 79 years). Whites accounted for 126 (88,7%), 5 were Asians, 1 patient was coloured and 1 black. Coronary heart disease is rare among blacks in South Africa. The conditions for which the patients were referred to us were angina pectoris (2,8%), percutaneous transluminal coronary angioplasty (PTCA) as the final procedure (16,9%), myocardial infarction (MI) (33,8%), coronary artery bypass grafting (CABG) as the final procedure (41,6%), and miscellaneous (4,9%) (risk factors, ventricular fibrillation, valve replacement). Seventy-seven per cent of patients reached us between 2 and 17 weeks after their MI, CABG or PTCA.

Most patients reached us more than 12 weeks after MI or CABG, so a recent episode was unlikely to have affected the lipogram we performed. Those who presented after a shorter interval had either stable angina or had had a recent PTCA.

After a full medical evaluation the patients gradually progressed through an 18-month rehabilitation programme which included aerobic exercise sessions 3 times a week and weekly discussions about lifestyle modification.[9] The effects of the first 6 months of exercise on lipid values were considered in this study. The intensity of the exercise was set between 70% and 85% of the maximal heart rate achieved at the initial exercise test. The patients' compliance in terms of attendance and exercise prescription was monitored on a daily basis and details were recorded on a computer.

The few patients who still smoked were urged not to do so and counselling sessions were available to those who wished them. Those who were overweight were enrolled on a weight-loss programme and the same basic dietary advice was given to all patients both verbally and in writing.

The lack of structured dietary evaluation is a recognised weakness of this study with regard to TC, low-density lipoprotein cholesterol (LDLC) and possibly the TC/HDLC ratio, but it is unlikely to have affected Lp(a) values.

No patient had been on any formal exercise programme before being referred to our unit, but self-prescribed exercise is known to confound studies of this sort.

The examinations and procedures performed on our patients on admission to the programme were as follows: medical and surgical histories were taken, together with the family history and details of smoking habits and medication. A general physical examination was done. Details of height and weight were recorded and the Broca index calculated, as body weight/height-100, × 100. A resting electrocardiogram was done and pul-

monary function was assessed by means of a flow-volume loop. Symptom-limited stress testing was done on a treadmill according to the Chung protocol.[17] Gas analysis was done by means of the Jaeger Sprint metabolic cart. Oxygen uptake was measured at peak (peak Vo_2) and at the ventilatory threshold (VT). The VT was defined as the first deviation in linearity of the minute volume plotted against the oxygen consumption.

A fasting blood sample was drawn and analysed for TC by the standard enzymatic method, HDLC by phosphotungstate precipitation, triglycerides (TGs) by standard enzymatic assay and apo AI, apo B100 and Lp(a) by radio-immunoassay according to the protocols supplied by the manufacturer (Pharmacia Diagnostics, Uppsala). LDLC was calculated by means of Friedewald's formula. The coefficients of variation for the various assays that comprised our 'lipogram' are as follows: TC – 1,2% at a level of 4,75 mmol/l; HDLC – 6,7% at a level of 1 mmol/l; TGs – 2,6% at a level of 0,97 mmol/l; apo AI – 4,6% at a level of 1,1 g/l; apo B – 4,5% at a level of 0,99 g/l; and Lp(a) – 6,6% at a level of 390 U/l. Haemoglobin, haematocrit, potassium and glucose levels were also measured according to standard procedures. After 6 months each patient went through exactly the same procedure again.

The effects of pharmacological preparations were carefully considered, both for possible influence on Lp(a) and because of the known effects of some of them on other lipid fractions. Sixty-nine patients were taking no drug known to affect serum lipids (group 1). Twenty-five patients were on β-blockers but neither the dosage nor the type of drug were changed during the 6-month period (group 2). Fourteen patients were on antilipid therapy with fibrates; they remained on the same drug throughout (group 3).

All patients taking 3-hydroxymethylglutaryl co-enzyme A (HMG-CoA) reductase inhibitors were excluded. The remaining patients on antilipid therapy were only on fibrates. The other exclusions were because the patient was on either a β-blocker or an antilipid drug for one test only.

The final results were calculated for the 108 patients who remained after exclusion because of incomplete data or undesirable medication or because they failed to complete the 6-month trial period. All these patients attended more than 60% of the possible sessions.

The percentage change between admission and 6 months was calculated for the Broca index, peak Vo_2, VT and all lipogram variables; significance was evaluated by means of Student's t-test for dependent samples. Multiple regression analysis was performed with all lipogram measurements as dependent variables and age, the Broca index, peak Vo_2, VT and the effect of different medications (groups 1, 2 and 3) as explanatory variables. Quantitative explanatory variables were interpreted in the light of estimated partial regression coefficients. Least square means (LSMs) were calculated for the three medication groups and compared by means of Fisher's least significant difference (LSD) tests.

Results

The mean percentage change over time for the variables is shown in Table I. A statistically significant change was found for seven of them: (*i*) peak VO_2 increased over the 6 month training period by 14,89% ($P = 0,0001$); (*ii*) the ventilatory threshold showed a similar increase of 13,80% ($P = 0,0001$); (*iii*) HDLC increased by 7,34% ($P = 0,0002$); (*iv*) apo AI rose by 2,73% ($P = 0,0198$); and (*v*) Lp(a) was 2,23% higher ($P = 0,0353$). The clinically important TC/HDLC ratio fell by 9,24% ($P = 0,0203$) and the ratio of apo AI to apo B rose by 9,37% ($P = 0,0049$).

TABLE I.

Variables on admission and after 6 months of cardiac rehabilitation

Variable	Admission (mean ± SD)	6 mo. (mean ± SD)	% change	P-value
Broca	108,39 (14,30)	107,35 (14,21)	-0,96	0,1205
Peak Vo_2	25,78 (7,18)	29,62 (7,72)	14,89	0,0001
VT	17,32 (4,01)	19,71 (4,83)	13,80	0,0001
TC	5,86 (0,95)	5,71 (1,03)	-2,56	0,3739
LDL	4,05 (0,92)	3,88 (0,94)	-4,20	0,7613
HDL	1,09 (0,25)	1,17 (0,28)	7,34	0,0002
Tg	1,64 (0,83)	1,55 (0,80)	-5,49	0,3092
Apo A	1,10 (0,20)	1,13 (0,22)	2,73	0,0198
Apo B	1,19 (0,22)	1,13 (0,23)	5,31	0,2369
Lp(a)	418,73 (423,73)	428,06 (455,51)	2,23	0,0353
TC/HDL	5,63 (1,49)	5,11 (1,62)	-9,24	0,0203
Apo A/Apo B	0,96 (0,27)	1,05 (0,32)	9,37	0,0049
Apo B/LDL	0,30 (0,08)	0,30 (0,05)	—	0,5135
Apo A/HDL	1,03 (0,19)	1,00 (0,21)	-2,91	0,2353

The results of the multiple regression analysis are shown in Table II. The percentage change in TC tended to decrease with increased fitness ($P = 0,0494$). For every ml/kg/min increase in peak Vo_2 it is estimated that the percentage change in TC decreases by 0,95%.

There was an association between Lp(a) and the Broca index which did not reach the 5% significance level. For every unit increase in Broca index, Lp(a) tended to increase by 0,58 U/l.

TABLE II.

Multiple regression analysis of 108 patients after 6 months of cardiac rehabilitation

Dependent variables (% change)	Explanatory variables (P-values)				
	Age (yrs)	Broca index	Peak Vo_2 (ml/kg/min)	VT (ml/kg/min)	Drugs
TC	—	—	0,0494	—	—
Lp(a)	—	0,0659	—	—	0,0273
TC/HDL	0,0505	—	—	—	—
Apo A/HDL	0,0170	—	—	—	—

A significant association was found between Lp(a) and medication. Patients on antilipid therapy that consisted of fibrates showed a significant increase in Lp(a) after 6 months compared with patients on no drug or on β-blockers (Fig. 1). A negative association was noted between TC/HDL and apo AI/HDL ratios and age. The TC/HDL and apo AI/HDL ratios tended to decrease by 0,93% and 1,1% respectively each year.
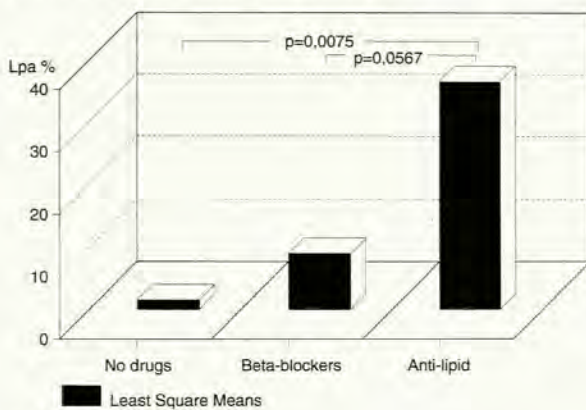

FIG. 1.
Lp(a) changes after 6 months of cardiac rehabilitation with medication.

Discussion

The increase in peak Vo₂ and VT confirms our earlier finding and that of other cardiac rehabilitation programmes that a course of supervised physical exercise can be expected to increase a patient's functional capacity after a myocardial infarction or CABG by an average of 15 - 25%.[7,9]

The Broca index did not alter appreciably over the 6-month period. Many patients were inducted into the programme fairly soon after a MI or CABG operation, after a period of inactivity and probable loss of muscle tissue. It may be that in the ensuing months they actually lost fat and regained muscle, which resulted in no net change in the index. It has been shown[6] that as the percentage of body fat decreases the TC/HDLC ratio improves and body fat composition is probably not reflected by the Broca index, or any other height-weight formula. We did not study body fat composition but we did document a favourable change with exercise in the TC/HDLC ratio, which suggests that there may have been a drop in the percentage of body fat.

TC, LDLC and apo B all behaved similarly, showing no significant change over the period of the study. This is not surprising, since most, if not all, of our patients only reached us 2 - 3 months after their MI or CABG and were already on low-fat diets prescribed elsewhere. Those on medication had already been on it for a similar period before they enrolled. In addition no attempt was made to influence blood lipid levels by therapeutic manipulation. All treatment changes were effected by the patients' own practitioners and those which occurred during the study period resulted in the subjects' exclusion from the study, so further changes in TC levels would not have been expected.

In our study physical exercise was found to reduce TC independently of other measures. This, we believe, has not been demonstrated in other studies.

LDLC and apo B are known only to respond to diet and medication and did not show any association with peak Vo₂.

At the highest levels of significance we found meaningful percentage changes in HDLC, apo AI and in the two key ratios, TC/HDLC and apo AI/apo B. If this status is maintained it will indicate a better prognosis for patients.

Aerobically our patients became much fitter, but oddly this appears not to be related to the changes in HDLC or apo AI. What then determines the increases that we found in the latter two values? HDL is produced at three sites, the liver, the small intestine and the muscles.[18,19] In the latter case, it depends on the action of muscular lipoprotein lipase (mLPL) on triglyceride-rich lipoprotein, which produces HDL and HDL2 from HDL3. The mLPL is found on the intima of the muscle capillaries and as exercise increases capillary density, more mLPL becomes available to make HDL2. The absence of a correlation between peak Vo₂ and HDLC supports the fact that in fit men who exercise regularly it is possible, with further training, to raise HDLC even further without any increase in peak Vo₂.[19] This is further proof that local factors are important in the production of HDL. The supply of apo AI to the working muscle is fixed and it is presumably the amount of cholesterol in the HDL particle which varies.

Ruys *et al.*[18] proposed that nascent and immature HDL particles are produced locally in the muscle, but their electron microscopic studies failed to show this. HDLC rises more with exercise when the subject is on a high-fat, low-carbohydrate diet, which is quite the opposite of the usual 'coronary' diet our patients consumed.

There is still controversy as to exactly how much exercise is necessary to have a meaningful effect on HDLC. One recent publication suggests that at least 56 km per week of running is necessary. However Hardman *et al.*[20] noted a progressive increase in HDLC levels in previously sedentary women walking briskly three times a week for 1 year. Our patients were exercising (stationary cycle, walk/jog) three times a week for up to 40 minutes at 70 - 80% of maximum heart rate. Diet is unlikely to have raised HDLC; when LDLC is lowered by diet, HDLC usually drops as well. In a very few cases, cessation of smoking may have helped to raise the HDLC level but any effect on the final figures would have been minimal. We conclude that the exercise we prescribed was sufficient significantly to raise the HDLC level.

The TC/HDL ratio is thought to be the best single predictor of future coronary events.[21] Again this seemed not to be related to the level of fitness as evidenced by improvements in Vo₂ or VT.

The older patients had a more favourable TC/HDLC ratio than did the younger ones. One interpretation of this is that those with unfavourable ratios acquired their disease at an earlier age than those with more favourable ratios.

The ratio of apo AI/apo B is of major importance as a predictor of angiographically shown coronary artery disease. The apoprotein measurements do not require a fasting blood sample and they also avoid the pitfalls of calculating LDLC levels on the basis of HDLC measurements. They are, however, bedevilled by methodological differences[22] and for this reason studies may not be comparable.

The ratio apo AI/HDLC reflects a physical change in the particle and we believe that this change relative to the patient's age has not been documented before. These particles become larger and less dense and may be functionally different. The reason for the formation of these particles is speculative. Assuming the supply of apo AI to be constant it may be that the changing ratio is dependent upon age-related changes in the cholesterol-scavenging mechanism.

The Broca index showed a modest positive correlation with Lp(a). This relationship at present defies explanation as so little is known about the factors which

affect Lp(a) levels. Of significance is the positive associa-
tion between Lp(a) and antilipid therapy. The effects of
medication are known to a certain degree, but they are
not well characterised and insufficient studies have been
done to date. The significance of any drug-induced rise
in Lp(a) is also not known at present. We know of no
study of the effects of β-blockers on serum levels of
Lp(a), and the effects of various antilipid agents are not
well documented. A rise in Lp(a) has been shown in
patients on HMG-CoA reductase inhibitors. All those
patients were excluded from our series. Our patients
were taking fibric acid derivatives, mainly bezafibrate.
No patient was on nicotinic acid or neomycin.

Changes in diet are said to be without significant
effect, with one exception. Rainwater *et al.*[23] found that
enriching the diet with cholesterol and saturated fat
caused a small but significant rise in Lp(a) values in
baboons. However, the rise was only 11%, compared
with a rise of 97% in TC. Most drugs do not alter Lp(a)
values, with the exception of neomycin, niacin and
stanozolol, an androgenic steroid.[24]

A recent publication claims significant reductions in
Lp(a) from the administration of bezafibrate.[25] Our own
figures thus far do not support this finding and further
studies should be done before this is generally accepted.
In addition, there is no evidence to date that reduction
of Lp(a) levels will decrease the risk of CAD or cerebro-
vascular disease.

The prevention of Lp(a) oxidation might be more
important than the lowering of Lp(a) levels. This would
prevent incorporation of apolipoprotein into the scaven-
ger pathway which is atherogenic.

Substantially raised Lp(a) levels have been reported
in patients taking HMG-CoA reductase inhibitors.[26]
This may be of less significance than it would seem
because of the concomitant fall in LDLC. We have no
reliable information on the influence of other coronary
risk factors on Lp(a) levels.

Conclusion

A cardiac rehabilitation programme is capable of
inducing favourable changes in a patient's lipid profile,
and no adverse effects were observed. In particular the
two important ratios, TC/HDLC and apo AI/apo B,
were improved. Both these have anti-atherogenic
implications.

The implications for exercise as both a therapeutic
and a preventive tool are far-reaching. It is a cost-effec-
tive therapeutic tool with few and minor side-effects.

Serum Lp(a) levels are not lowered but raised after a
6-month period of graded physical exercise. Lp(a) levels
do not affect physical fitness as expressed by peak Vo_2,
but they correlate with changes in the Broca index and
antilipid therapy other than HMG-CoA reductase
inhibitors.

The level of HDLC was raised by exercise but this
was not related to peak Vo_2; a purely peripheral mecha-
nism must therefore be invoked to explain it.

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