MEDICAL SCIENCE

Can lifestyle changes reverse coronary heart disease?

The Lifestyle Heart Trial

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In a prospective, randomised, controlled trial to determine whether comprehensive lifestyle changes affect coronary atherosclerosis after 1 year, 28 patients were assigned to an experimental group (low-fat vegetarian diet, stopping smoking, stress management training, and moderate exercise) and 20 to a usual-care control group. 195 coronary artery lesions were analysed by quantitative coronary angiography. The average percentage diameter stenosis regressed from 40·0 (SD 16·9)% to 37·8 (16·5)% in the experimental group yet progressed from 42·7 (15·5)% to 46·1 (18·5)% in the control group. When only lesions greater than 50% stenosed were analysed, the average percentage diameter stenosis regressed from 61·1 (8·8)% to 55·8 (11·0)% in the experimental group and progressed from 61·7 (9·5)% to 64·4 (16·3)% in the control group. Overall, 82% of experimental-group patients had an average change towards regression. Comprehensive lifestyle changes may be able to bring about regression of even severe coronary atherosclerosis after only 1 year, without use of lipid-lowering drugs.

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Introduction

The Lifestyle Heart Trial is the first randomised, controlled clinical trial to determine whether patients outside hospital can be motivated to make and sustain comprehensive lifestyle changes and, if so, whether regression of coronary atherosclerosis can occur as a result of lifestyle changes alone. Over twenty clinical trials are being carried out to determine whether the progression of coronary atherosclerosis can be modified; in all of these, cholesterol-lowering drugs, plasmapheresis, or partial ileal bypass surgery are the primary interventions.[1]

We carried out trials in 1977 and 1980 to assess the short-term effects of lifestyle changes on coronary heart disease with non-invasive endpoint measures (improvements in cardiac risk factors, functional status, myocardial perfusion,[2] and left ventricular function[3]). However, the subjects of those studies were not living in the community during the trial, and we did not use angiography to assess changes in coronary atherosclerosis.

Patients and methods

Patients with angiographically documented coronary artery disease were randomly assigned to an experimental group or to a usual-care control group. Experimental-group patients were prescribed a lifestyle programme that included a low-fat vegetarian diet, moderate aerobic exercise, stress management training, stopping smoking, and group support. Control-group patients were not asked to make lifestyle changes, although they were free to do so. Progression or regression of coronary artery lesions was assessed in both groups by quantitative coronary angiography at baseline and after about a year.

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Patients were recruited from Pacific Presbyterian Medical Center (PPMC) and from Moffitt Hospital of the UCSF School of Medicine according to the following criteria: age 35–75 years, male or female; residence in the greater San Francisco area; no other life-threatening illnesses; no myocardial infarction during the preceding 6 weeks, and no history of receiving streptokinase or alteplase; not currently receiving lipid-lowering drugs; one, two, or three vessel coronary artery disease (defined as any measurable coronary atherosclerosis in a non-dilated or non-bypassed coronary artery); left ventricular ejection fraction greater than 25%; not scheduled to have coronary artery bypass grafting; and permission granted by patient's cardiologist and primary care physician. We screened and recruited only patients who were having angiograms for clinical reasons unrelated to this study so that only one additional angiogram was needed for research purposes.

A total of 193 patients who met the first five entry criteria underwent quantitative coronary arteriography at UCSF and PPMC. 94 of these patients (49%) met the remaining entry criteria. Of the 94 eligible patients, 53 were randomly assigned to the experimental group and 43 to the control group; 28 (53%) and 20 (42%), respectively, agreed to take part. All patients who were eligible and volunteered were accepted into the study. These patients represented a cross-section of age, gender, race, ethnic group, socioeconomic status, and educational level. Each gave fully informed written consent and the study was approved by the relevant ethical committees.

Follow-up angiographic data were not available for 7 patients: 1 control-group patient underwent emergency, non-quantitative angiography in another hospital; and of the 6 experimental-group patients, 1 died while greatly exceeding exercise recommendations in an unsupervised gym, 1 could not be tested owing to a large unpaid hospital bill, 1 was a previously undiagnosed alcoholic who dropped out, 1 patient's preintervention angiogram was lost in transit to Houston for quantitative analysis, and 2 patients' angiographic views before and after intervention did not match adequately owing to technical difficulties.

Selective coronary angiography was done by the percutaneous femoral technique. The two laboratories were calibrated at baseline and every 6 months thereafter. Orthogonal views were obtained, and the angle, skew, rotation, table height, and type of catheter were recorded during the baseline angiogram to allow these measurements to be reproduced during angiography about a year (15 [SD 3] months) later. Baseline and follow-up measures were identical in the view angles, their sequence, type of contrast dye, the angiographer, and the cine arteriographic equipment. Catheter tips were saved and used as reference measures for quantitative analyses of films. Cine arteriograms made in San Francisco were sent to the University of Texas Medical School at Houston for quantitative analyses by a protocol described elsewhere in detail.[4]

Blood samples for measurement of serum lipids were drawn (after a 14 h fast) at baseline, after 6 months, and after a year. Total cholesterol, HDL-cholesterol, and triglyceride concentrations were measured by 'Astra' enzymic assays (Beckman Instruments, Brea, California).[5] LDL was calculated as total cholesterol minus HDL-cholesterol plus 0·16 × triglycerides. Apolipoproteins A-I and B were measured by disc gel electrophoresis and by isoelectric focusing.[6]

To check adherence to the programme patients completed a 3-day diet diary at baseline and after a year to assess nutrient intake and dietary adherence.[7] These diaries were analysed by means of the CBORD diet analyser based upon the USDA database (CBORD Group Inc, Ithaca, New York, USA). Patients were asked to complete a questionnaire describing the type, frequency, and duration of exercise and of each stress management technique. Patients who said they had stopped smoking underwent random tests of plasma cotinine.[8] Information from the adherence questionnaires was quantified by a formula determined before the study. A total score of 1 indicated 100% adherence to the recommended lifestyle change programme, and 0 indicated no adherence. Patients who did more than we recommended achieved a score greater than 1.

To reduce the possibility that knowledge of group assignment might bias the outcome measurements, the investigators carrying

TABLE I—BASELINE CHARACTERISTICS OF EXPERIMENTAL AND CONTROL GROUPS

	Mean (SD)	
—	Experimental group (n = 22)	Control group (n = 19)
Male/Female	21/1	15/4
Age (yr)	56·1 (7·5)	59·8 (9·1)
Weight (kg)	91·1 (15·5)	80·4 (22·8)
Body mass index (kg/m²)	28·4 (4·1)	26·5 (5·3)
Education (yr)	15·9 (2·9)	14·2 (3·0)

out all medical tests remained unaware of both patient group assignment and the order of the tests. Different people provided the lifestyle intervention, carried out the tests, analysed the results, and carried out statistical analyses. Coronary arteriograms were analysed without knowledge of sequence or of group assignment.

The intervention began with a week-long residential retreat at a hotel to teach the lifestyle intervention to the experimental-group patients. Patients then attended regular group support meetings (4 h twice a week).

Experimental-group patients were asked to eat a low-fat vegetarian diet for at least a year. The diet included fruits, vegetables, grains, legumes, and soybean products without caloric restriction. Some take-home meals were provided for those who wanted them. No animal products were allowed except egg white and one cup per day of non-fat milk or yoghurt. The diet contained approximately 10% of calories as fat (polyunsaturated/saturated ratio greater than 1), 15–20% protein, and 70–75% predominantly complex carbohydrates. Cholesterol intake was limited to 5 mg/day or less. Salt was restricted only for hypertensive patients. Caffeine was eliminated, and alcohol was limited to no more than 2 units per day (alcohol was excluded for anyone with a history of alcoholism, and no one was encouraged to drink). The diet was nutritionally adequate and met the recommended daily allowances for all nutrients except vitamin B_{12}, which was supplemented.

The stress management techniques included stretching exercises, breathing techniques, meditation, progressive relaxation, and imagery.[3,9-12] The purpose of each technique was to increase the patient's sense of relaxation, concentration, and awareness. Patients were asked to practise these stress management techniques for at least 1 h per day and were given a 1 h audiocassette tape to assist them.

Only 1 patient in the experimental group was smoking at baseline, and she agreed to stop on entry.

Patients were individually prescribed exercise levels (typically walking) according to their baseline treadmill test results. Patients were asked to reach a target training heart rate of 50–80% of the heart rate at which 1 mm ST depression occurred during baseline treadmill testing or, if not ischaemic, to 50–80% of their age-adjusted maximum heart rate based on level of conditioning. Patients were also trained to identify exertional levels by means of the Borg rate of perceived exertion scale.[13] Patients were asked to exercise for a minimum of 3 h per week and to spend a minimum of 30 min per session exercising within their target heart rates. A defibrillator and emergency drugs were available at all times.

The twice-weekly group discussions provided social support to help patients adhere to the lifestyle change programme.[14] The

TABLE II—MEAN LESION CHARACTERISTICS AT BASELINE

	Mean (SEM)	
—	Experimental group (n = 22)	Control group (n = 19)
% diameter reduction	40·0 (1 78)	42·7 (1·95)
Stenosis flow reserve	3·96 (0·12)	3·88 (0·13)
Minimum diameter (mm)	1·67 (0·10)	1·73 (0·10)
Normal diameter (mm)	2·76 (0·14)	2·96 (0·15)

195 lesions: 105 experimental, 90 control.

TABLE III—COMPLIANCE WITH EXERCISE, STRESS MANAGEMENT, AND DIETARY CHANGES

—	Mean (SD) at baseline		Mean (SD) at 12 mo		p (two-sided)
	Experimental (n = 20–22)	Control (n = 17–19)	Experimental (n = 20–22)	Control (n = 17–19)	
Exercise					
Times/day	0·26 (0·37)	0·35 (0·39)	0·69 (0·20)	0·39 (0·37)	0·0008
Min/day	11·0 (17 7)	18·4 (27·7)	38·1 (17·4)	20·6 (27·7)	0·0004
Stress reduction					
Times/day	0·50 (1·21)	0·16 (0·34)	5·94 (2·62)	0·42 (0·74)	<0·0001
Min/day	5·09 (12·7)	1·76 (4·34)	82·1 (36·6)	4·50 (10·2)	<0·0001
Fat intake					
g/day	67·4 (18·6)	58 2 (25·9)	14·0 (8·6)	55·2 (21·1)	<0·0001
% of energy intake	31·5 (7·6)	30·1 (10·7)	6·8 (3·5)	29·5 (8·6)	<0·0001
Dietary cholesterol (mg/day)	213 (111)	205 (127)	12·4 (45·8)	190 (99)	<0·0001
Energy intake (MJ/day)	8·2 (1·8)	7·2 (2·2)	7·6 (2 1)	7 1 (1·9)	0·5082
Total adherence score*	0·55 (0·22)	0·56 (0·30)	1·22 (0·22)	0·62 (0·30)	<0·0001

*Percentage of minimum recommended level of combined lifestyle change; includes all the above plus smoking cessation

TABLE IV—CHANGES IN RISK FACTORS

—	Mean (SD) at baseline		Mean (SD) at 12 mo		p p (two-sided)
	Experimental group (n = 20–22)	Control group (n = 17–19)	Experimental group (n = 20–22)	Control group (n = 17–19)	
Serum lipids (mmol/l)					
Total cholesterol	5·88 (1 29)	6·34 (1·02)	4·45 (1·15)	6·00 (1·55)	0·0192
LDL cholesterol	3·92 (1·25)	4·32 (0·77)	2·46 (1·55)	4·07 (1·17)	0·0072
HDL cholesterol	1 00 (0·26)	1·35 (0·52)	0·97 (0·40)	1·31 (0·38)	0·8316
Triglycerides	2·38 (1·26)	2 45 (2·47)	2·91 (1·47)	2·24 (1 79)	0·2472
Apolipoproteins (mg/dl)					
A-I	133 (21)	156 (36)	135 (26)	166 (47)	0·4612
B	104 (33)	104 (21)	79 (23)	105 (28)	0·0104
Lipid ratios					
Total/HDL cholesterol	6 33 (2 14)	5·32 (1·89)	5·15 (2·23)	4·93 (1·59)	0·1734
LDL/HDL cholesterol	4·18 (1·53)	3·59 (1·37)	2·89 (1·92)	3·33 (1·42)	0·0348
Blood pressure (mm Hg)					
Systolic	134 (13)	140 (26)	127 (13)	131 (20)	0·7550
Diastolic	83 (8)	82 (13)	79 (7)	77 (11)	0·8987
Weight (kg)	91·1 (15 5)	80·4 (22·8)	81·0 (11·4)	81·8 (25·0)	<0·0001

sessions were led by a clinical psychologist who facilitated discussions of strategies for maintaining adherence to the programme, communication skills, and expression of feelings about relationships at work and at home.

Differences in baseline characteristics of the two groups were tested for statistical significance by conventional *t* tests. Comparisons of the two study groups' baseline coronary artery lesion characteristics (measured by quantitative coronary angiography) and changes in lesion characteristics after intervention were examined by a mixed-model analysis of variance.[15] These analyses used lesion-specific data but allowed for the possibility that lesion data in a given subject could be statistically dependent. Mean changes in other endpoint measures were analysed for statistical significance by repeated-measures analysis of variance.

Results

At baseline, there were no significant differences between the experimental and control groups in demographic characteristics (table I), diet and lifestyle characteristics, functional status, cardiac history, or risk factors in the 41 subjects who completed angiography before and after the intervention. The control group had significantly higher levels of HDL-cholesterol (1·33 [SD 0·52] vs 1·02 [0·31] mmol/l; p = 0·029) and apolipoprotein A-I (156 (36) vs 133 (21) mg/dl; p = 0·0155) than the experimental group, but the ratios of total/HDL cholesterol and LDL/HDL cholesterol did not differ significantly between the groups at baseline. The experimental and control groups did not differ significantly in disease severity at baseline. The mean values in table II do not fully reflect the severity of coronary

atherosclerosis in these patients for the following reasons: quantitative analyses of coronary arteriograms tend to assess stenoses as being less severe than do qualitative assessments; we analysed all detectable lesions, including minor ones; and we excluded from analysis 33 lesions that were 100% occluded at baseline.

Adherence to the diet, exercise, and stress management components of the lifestyle programme in the experimental group was excellent (table III). Patients in the control group made more moderate changes in lifestyle consistent with more conventional recommendations.

Table IV summarises changes in risk factors during the intervention period. In the experimental group, total cholesterol fell by 24·3% and LDL-cholesterol by 37·4%. These falls occurred even though patients had already reduced fat consumption to 31·5% of calories and

TABLE V—CHANGES IN ANGINA SYMPTOMS

—	Mean (SD) at baseline		Mean (SD) at 12 mo		p two-sided)
	Experimental group (n = 20)	Control group (n = 17)	Experimental group (n = 20)	Control group (n = 17)	
Chest pain frequency	5·10 (14·1)	2·35 (3·77)	0·45 (0·76)	6·24 (12·9)	0·0578
Chest pain duration (min)	2·73 (4·69)	3·47 (7·95)	1·58 (4·48)	6·97 (14·5)	0 1390
Chest pain severity	2·3 (1·6)	1·8 (1·1)	1·7 (1·2)	2·5 (1·2)	0·0006

*Scale of 1 to 7, 1 least severe.
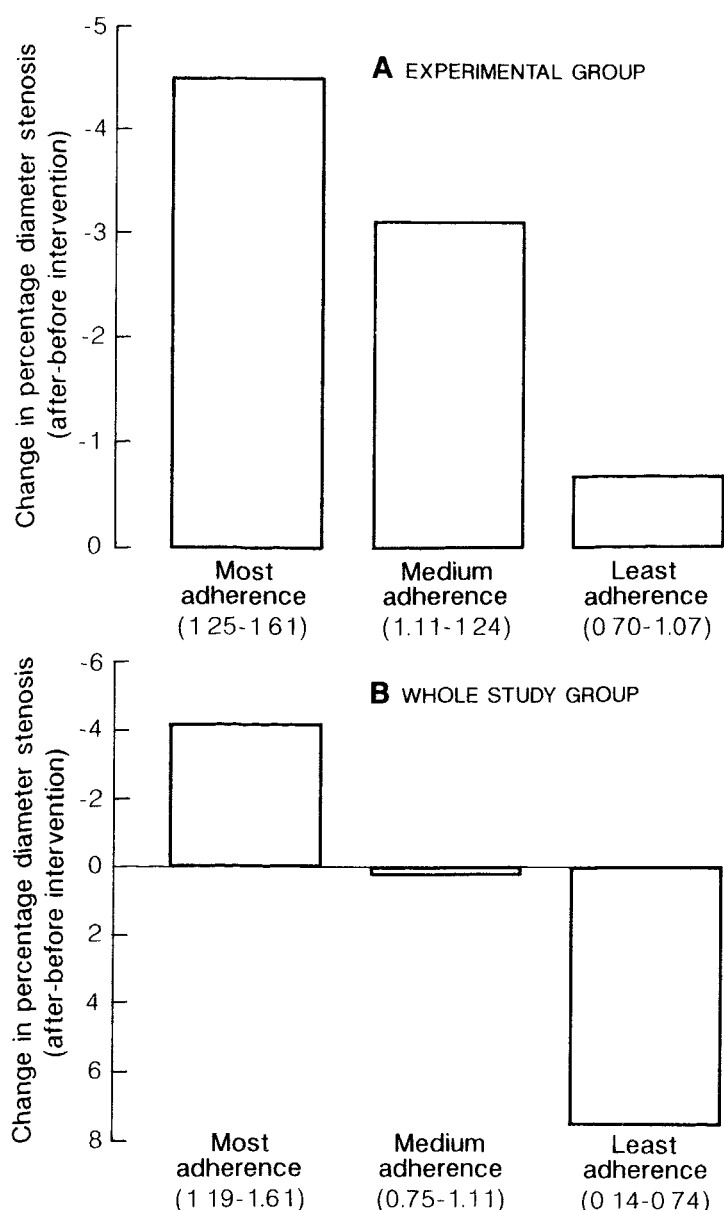
Correlation of overall adherence score and changes in percentage diameter stenosis in experimental group only (A) and in whole study group (B).

A = 7 subjects in each tertile; B = 13, 14, 13.

cholesterol intake to 213 mg/day on average before baseline testing. HDL-cholesterol did not change significantly in either group. Apolipoprotein B fell substantially in the experimental group but it did not change in the control group. Neither group had significant changes in apolipoprotein A-I.

Patients in the experimental group reported a 91% reduction in the frequency of angina, a 42% reduction in duration of angina, and a 28% reduction in the severity of angina. In contrast, control-group patients reported a 165% rise in frequency, a 95% rise in duration, and a 39% rise in severity of angina (table v). In previous studies,[2,3] we found that similar improvements in functional status occurred in only 1 month, which suggests that improvements in angina may precede regression of coronary atherosclerosis, perhaps by changing platelet-endothelial interactions, vasomotor tone, or other dynamic characteristics of stenoses.

All 195 detectable lesions were included in the quantitative analysis. The average percentage diameter stenosis decreased from 40·0 (SD 16·9)% to 37·8 (16·5)% in the experimental group yet progressed from 42·7 (15·5)% to 46·1 (18·5)% in the control group (p = 0·001, two-tailed). When only lesions greater than 50% stenosed were

analysed, the average percentage diameter stenosis regressed from 61·1 (8·8)% to 55·8 (11·0)% in the experimental group but progressed from 61·7 (9·5)% to 64·4 (16·3)% in the control group (p = 0·03, two-tailed).

The average lesion change scores (% diameter stenosis after intervention minus before intervention) in the experimental group were in the direction of regression of coronary atherosclerosis in 18 of the 22 patients (82%) including the 1 woman, in the direction of slight progression in 3 patients, and in the direction of substantial progression in 1 patient with poor adherence. In contrast, in the control group the average lesion change scores were in the direction of progression of coronary atherosclerosis in 10 of 19 (53%), in the direction of regression (including all 4 women) in 8, and 1 showed no change.

In the experimental group and in the whole study group, overall adherence to the lifestyle changes was strongly related to changes in lesions in a "dose-response" manner, suggesting that the relation was causal. The differences in overall adherence are sufficient to explain the observed differences in percentage diameter stenosis. To assess whether programme adherence was related to lesion changes, the experimental group and the combined study group were divided into tertiles based on overall adherence score. Degree of adherence was directly correlated with changes in percentage diameter stenosis (see accompanying figure).

Discussion

This clinical trial has shown that a heterogeneous group of patients with coronary heart disease can be motivated to make comprehensive changes in lifestyle for at least a year outside hospital. The changes in serum lipid levels are similar to those seen with cholesterol-lowering drugs. The lifestyle intervention seems safe and compatible with other treatments of coronary heart disease.

After a year, patients in the experimental group showed significant overall regression of coronary atherosclerosis as measured by quantitative coronary arteriography. Since coronary atherosclerosis occurs over a period of decades, one would not expect to find larger changes in only a year. Perfusion is a fourth-power function of coronary artery diameter, so even a small amount of regression in a critically stenosed artery has a large effect on myocardial perfusion and thus on functional status. In contrast, patients in the usual-care control group who were making less comprehensive changes in lifestyle showed significant overall progression of coronary atherosclerosis. This finding suggests that conventional recommendations for patients with coronary heart disease (such as a 30% fat diet) are not sufficient to bring about regression in many patients.

The strong relation between programme adherence and lesion changes showed that most patients needed to follow the lifestyle programme as prescribed to show regression. Those who made the greatest changes showed the biggest improvement. Since degree of stenosis change was correlated with extent of lifestyle change across its whole range, small changes in lifestyle may slow the progression of atherosclerosis, whereas substantial changes in lifestyle may be required to halt or reverse coronary atherosclerosis.

The 5 women in our study (1 experimental group, 4 control group) were the notable exceptions. All 5 made only moderate lifestyle changes, yet all showed overall regression. All 5 were postmenopausal, and none was taking exogenous oestrogens. The 4 women in the control group showed more

regression than any of the men in that group, even though some men made greater lifestyle changes. Although the numbers are small, these findings suggest the possibility that gender may affect progression and regression of atherosclerosis. Futher studies may determine whether women can reverse coronary atherosclerosis with more moderate lifestyle changes than men.

5 men in the control group showed very slight regression of atherosclerosis. These patients exercised more often, for longer periods, and consumed fewer calories and less cholesterol than the control-group patients who showed progression of atherosclerosis.

We found that the severely stenosed lesions showed the greatest improvement. Although the opposite of what we expected, the finding is important since more severely stenosed lesions are the most important clinically. More work is needed to determine the extent to which the relation between change and initial site of lesions is affected by the phenomenon of regression to the mean.

Increasing evidence supports the roles of diet, exercise, emotional stress, and smoking in the pathogenesis of coronary heart disease,[16-18] but until lately evidence for regression of coronary atherosclerosis was limited or anecdotal. There are case-reports of regression involving femoral[19] and renal arteries,[20] and one case-report of spontaneous regression in a coronary artery.[21] However, several studies have found that regression of coronary atherosclerosis can occur spontaneously in the absence of lifestyle changes or treatment with drugs,[22-24] thereby making it necessary for intervention trials to be controlled. Only two other randomised, controlled trials showing regression of coronary atherosclerosis have been reported,[22,23,25] and both used cholesterol-lowering drugs as the primary interventions.

Some important questions remain unanswered. Can these comprehensive lifestyle changes be sustained in larger populations of patients with coronary heart disease? The point of our study was to determine what is true, not what is practicable. The adherence measures and the angiographic findings suggest that adherence to this lifestyle programme needs to be very good for overall regresion to occur, although more moderate changes have some beneficial effects. Further research will be necessary to determine the relative contribution of each component of the lifestyle programme and the mechanisms of changes in coronary atherosclerosis. It would be interesting to examine the effects of lifestyle changes in a larger sample of postmenopausal women with coronary atherosclerosis. Also, direct comparison of intensive lifestyle changes with pharmacological or surgical interventions would be interesting. Our trial suggests that comprehensive lifestyle changes may begin to reverse coronary atherosclerosis in only a year.

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