Effects of Exercise and Stress Management Training on Markers of Cardiovascular Risk in Patients With Ischemic Heart Disease

A Randomized Controlled Trial

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Context Observational studies have shown that psychosocial factors are associated with increased risk for cardiovascular morbidity and mortality, but the effects of behavioral interventions on psychosocial and medical end points remain uncertain.

Objective To determine the effect of 2 behavioral programs, aerobic exercise training and stress management training, with routine medical care on psychosocial functioning and markers of cardiovascular risk.

Design, Setting, and Patients Randomized controlled trial of 134 patients (92 male and 42 female; aged 40-84 years) with stable ischemic heart disease (IHD) and exercise-induced myocardial ischemia. Conducted from January 1999 to February 2003.

Interventions Routine medical care (usual care); usual care plus supervised aerobic exercise training for 35 minutes 3 times per week for 16 weeks; usual care plus weekly 1.5-hour stress management training for 16 weeks.

Main Outcome Measures Self-reported measures of general distress (General Health Questionnaire [GHQ]) and depression (Beck Depression Inventory [BDI]); left ventricular ejection fraction (LVEF) and wall motion abnormalities (WMA); flow-mediated dilation; and cardiac autonomic control (heart rate variability during deep breathing and baroreflex sensitivity).

Results Patients in the exercise and stress management groups had lower mean (SE) BDI scores (exercise: 8.2 [0.6]; stress management: 8.2 [0.6]) vs usual care (10.1 [0.6]; $P = .02$); reduced distress by GHQ scores (exercise: 56.3 [0.9]; stress management: 56.8 [0.9]) vs usual care (53.6 [0.9]; $P = .02$); and smaller reductions in LVEF during mental stress testing (exercise: –0.54% [0.44%]; stress management: –0.34% [0.45%]) vs usual care (–1.69% [0.46%]; $P = .03$). Exercise and stress management were associated with lower mean (SE) WMA rating scores (exercise: 0.20 [0.07]; stress management: 0.10 [0.07]) in a subset of patients with significant stress-induced WMA at baseline vs usual care (0.36 [0.07]; $P = .02$). Patients in the exercise and stress management groups had greater mean (SE) improvements in flow-mediated dilation (exercise: mean [SD], 5.6% [0.45%]; stress management: 5.2% [0.47%]) vs usual care patients (4.1% [0.48%]; $P = .03$). In a subgroup, those receiving stress management showed improved mean (SE) baroreflex sensitivity (8.2 [0.8] ms/mm Hg) vs usual care (5.1 [0.9] ms/mm Hg; $P = .02$) and significant increases in heart rate variability (193.7 [19.6] ms) vs usual care (132.1 [21.5] ms; $P = .04$).

Conclusion For patients with stable IHD, exercise and stress management training reduced emotional distress and improved markers of cardiovascular risk more than usual medical care alone.

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ISCHEMIC HEART DISEASE (IHD) IS the leading cause of death in the United States and is rapidly becoming the leading cause of death in developing countries around the world.[1,2] Traditional biomedical risk factors do not fully account for the development of IHD or for the triggering of adverse cardiac events. Psychosocial factors are now recognized as playing a significant and independent role in the development of IHD and its complications.[3,4] Consequently, efforts to alter psychosocial risk factors, particularly in the setting of cardiac rehabilitation, have received increased attention. However, the value of modifying psychosocial risk factors to reduce adverse cardiac events remains controversial.[5,6] Several large-scale randomized trials failed to demonstrate an advantage for stress management interventions in reducing cardiac morbidity or mortality,[7,8] but these studies also failed to adequately reduce psychosocial risk factors. Because emotional distress was

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not successfully reduced, it was not unexpected that medical end points also were not affected.

Recently we have shown that exercise and stress management training reduced mental stress–induced and exercise-induced ischemia[9] and resulted in fewer adverse cardiac events compared with controls over 5 years of follow-up.[10] However, the study was limited by a quasi-experimental design that used a nonrandom control group. Therefore, the present study was designed to extend our previous work by comparing the impact of 2 behavioral intervention programs, aerobic exercise and stress management training, with routine medical care on psychosocial functioning and select markers of cardiovascular risk in a randomized design. The markers of risk were selected because of their prognostic relationship with adverse cardiac events, including mental stress–induced myocardial ischemia,[11-14] measures of vascular endothelial function,[15-18] and cardiac autonomic control.[19-24]

METHODS

Patients

Participants were recruited via newspaper, television, and radio advertisements, letters sent to local physicians, and fliers posted at clinics, community health fairs, and local shopping centers. The patient sample consisted of 134 patients (92 male and 42 female), aged 40 to 84 years (mean [SD], 63 [10] years), with documented IHD (by prior myocardial infarction, coronary artery bypass graft surgery, coronary angioplasty, and/or >75% stenosis in at least 1 major coronary artery) and evidence of exercise-induced myocardial ischemia within the past year. Patients with cardiomyopathy, valvular heart disease, congestive heart failure, severe cardiac arrhythmias, left bundle-branch block, Wolff-Parkinson-White syndrome, resting systolic blood pressure higher than 200 mm Hg and diastolic blood pressure higher than 120 mm Hg, left ventricular ejection fraction (LVEF) of less than 30%, or left main coronary artery stenosis of 50% or higher were excluded. This study was approved by the institutional review board at Duke University Medical Center (Durham, NC) and written informed consent was obtained from all participants prior to their participation. This study was conducted from January 1999 to February 2003 at a US tertiary care teaching hospital.

Exercise-Induced and Mental Stress–Induced Myocardial Ischemia

Unless medically contraindicated, patients discontinued anti-ischemic medications (eg, β-blockers, calcium channel blockers, and long-acting nitrates) at least 48 hours prior to testing. The medication washout period was at least 5 half-lives of the anti-ischemic drug. Patients restarted their medications following the completion of the assessments (ie, usually ≤3 days of stopping medications). Twenty-eight patients could not safely discontinue their medications and were tested on their usual dosage of anti-ischemic drugs.

After a 40-minute rest, mental stress testing was performed in which patients were presented with 2 mental stress tasks (public speaking and mirror trace) in counterbalanced order. The speech stressor required participants to give a speech on a controversial current events topic after 1 minute of preparation. Sample topics included Do you think cigarette smoking should be made illegal in all public places? What is your position on gun control? Should prayer be allowed in public school? Participants were told that the speech was going to be evaluated by 2 independent judges in which ratings would be based on organization, speech clarity, and content. The mirror trace required participants to outline the shape of a star from its reflection in a mirror. These tasks were used in our previous research[25] and were determined to elicit robust hemodynamic responses and were the most potent triggers of myocardial ischemia relative to other stressors. Each task lasted 5 minutes, with a 10-minute rest between each stressor. At the conclusion of the mental stress testing, and after a subsequent 10-minute rest, patients exercised to exhaustion on a cycle ergometer in the upright position at a beginning level of 25 W. Exercise workload was increased by 25 W every 2 minutes.

To determine the presence of myocardial ischemia, R-wave–synchronized, gated equilibrium radionuclide ventriculography with Paragon PBR software (Medassays Inc, Ann Arbor, Mich) was performed prior to and during each stressor at 20 frames per cardiac cycle using a gamma camera (Siemens Gamma-Sonics Inc, Des Plaines, Ill) equipped with a sodium iodide crystal and an all-purpose collimator. Images were obtained following the labeling of autologous red blood cells with technetium Tc 99m pertechnetate (Amersham Health, Princeton, NJ) using the in vivo technique.[26] Imaging was conducted during the last 2 minutes of the rest period, during the first minute of speech preparation, at 2 and 4 minutes for the speech and mirror trace stressors, and at peak exercise with the camera in the left anterior oblique view. The LVEF was obtained using PBR software. Segmental wall motion of the left ventricle was later assessed visually through the observation of a continuous-loop video display of the images. Wall motion for each of the 4 segments was rated by a consensus of at least 2 experienced physicians blinded to the time of testing (pretreatment or posttreatment) and treatment group. Segmental wall motion abnormalities (WMA) were rated on a scale from 1 (normal) to 7 (severe dyskinesis). A standard 12-lead electrocardiogram was monitored continuously and recorded (Quinton Electronics, Seattle, Wash) at 1-minute intervals during the rest periods, mental stress testing, and exercise testing.

Flow-Mediated Dilation Index of Vascular Endothelial Function

Flow-mediated dilation (FMD) of the brachial artery was assessed following overnight fasting. Longitudinal B-mode ultrasound images of the brachial artery, 4- to 6-cm proximal to the antecubital crease, were obtained using an Aspen ultrasound platform (Acuson, Moun-

tain View, Calif) with an 11-MHz linear array transducer. Images were obtained (1) after 10 minutes of supine relaxation; (2) during reactive hyperemia, which was induced following inflation of a pneumatic occlusion cuff placed around the forearm for 5 minutes until suprasystolic pressure (≈200 mm Hg); and (3) after administration of 400 µg of sublingual glyceryl trinitrate spray. End-diastolic images were stored on a magnetic, optical disk and arterial diameters were measured as the distance between the proximal and distal arterial wall intima-media interfaces using a brachial analyzer (version 4.0, Medical Imaging Applications LLC, Iowa City, Iowa). Peak reactive hyperemic response was assessed from 10- to 120-sec postdeflation of the occlusion cuff; FMD was defined as the maximum percentage change in arterial diameter relative to resting baseline. Glyceryl trinitrate response was defined as peak arterial diameter 3 to 5 minutes following administration and expressed as the percentage change from resting at baseline.

Heart Rate Variability During Deep Breathing and Baroreflex Sensitivity

Beat-by-beat systolic blood pressure and heart rate were collected from patients in the supine position using the Finapres noninvasive blood pressure monitor (model 2300; Ohmeda, Madison, Wis). For the heart rate variability measure during deep breathing (HRV-DB), patients were asked to inhale as deeply as possible for 5 seconds and then to exhale fully for 5 seconds. This was repeated 10 times and only patients with clear changes in R-R interval across at least 3 respiratory cycles were used in the analyses. For each respiratory cycle, the longest R-R interval during expiration and the shortest R-R interval during inspiration were recorded and the mean (SD) changes were calculated for analyses. The change in R-R interval during deep breathing is an established measure in the diagnosis of diabetic autonomic neuropathy.[27] Low levels of HRV-DB are an independent marker of increased mortality risk in IHD patients and in patients with diabetes.[23,24]

Cross-spectral analysis was used to estimate baroreflex sensitivity. Patients breathed spontaneously during recordings used for baroreflex sensitivity estimation. For these analyses, beat-by-beat blood pressure and R-R interval (derived as 60 000 per hour) were edited for artifacts, linearly interpolated, and resampled at a frequency of 4 Hz to generate an equally spaced time series. A fast Fourier transformation was applied to the interpolated data after the detrending process and then a Hanning filtering window was applied. Power spectra were derived for each file using the Welch algorithm, which creates successive periodograms.[28] The baroreflex sensitivity was estimated from the magnitude of the transfer function relating R-R interval oscillations to systolic blood pressure across 0.07 to 0.1299 Hz band. Coherence between systolic blood pressure and R-R interval oscillations was required to be at least 0.5 Hz to be accepted as estimates of baroreflex control. The R-R interval oscillations at this frequency band are mediated by vagal control mechanisms in healthy volunteers in the supine position.[29] All measurements were obtained by experienced personnel blinded to patients' identity, clinical status, and treatment group.

Cardiorespiratory Fitness

After patients restarted their anti-ischemic medications, they underwent a symptom-limited graded exercise treadmill test under continuous electrocardiographic recording to establish their fitness level and develop an exercise prescription. A modified Balke protocol was used, in which workloads were increased at a rate of 1 MET/min.[30] Expired air was collected with a mouthpiece to quantify minute ventilation, oxygen consumption, and carbon dioxide production with a metabolic cart (model 2900; SensorMedics, Yorba Linda, Calif). Samples were collected at 20-second intervals and peak values were determined from an average obtained during the last 60 seconds.

Psychosocial Functioning

Participants completed a battery of psychosocial questionnaires selected because of their known association with IHD. Measures included the 21-item Beck Depression Inventory to assess depressive symptoms,[31] the 50-item Cook-Medley Hostility Scale to assess anger and hostile attitudes,[32] the 20-item Spielberger Trait Anxiety Inventory to assess general anxiety,[33] and the 24-item General Health Questionnaire to assess psychiatric symptoms and general distress.[34]

Interventions

Once patients completed their baseline assessments, they resumed taking anti-ischemic medications. Using block randomization software (Resampling Stats, Arlington, Va), patients were randomly assigned to routine medical care (usual care); usual care plus supervised aerobic exercise training; or usual care plus stress management training.

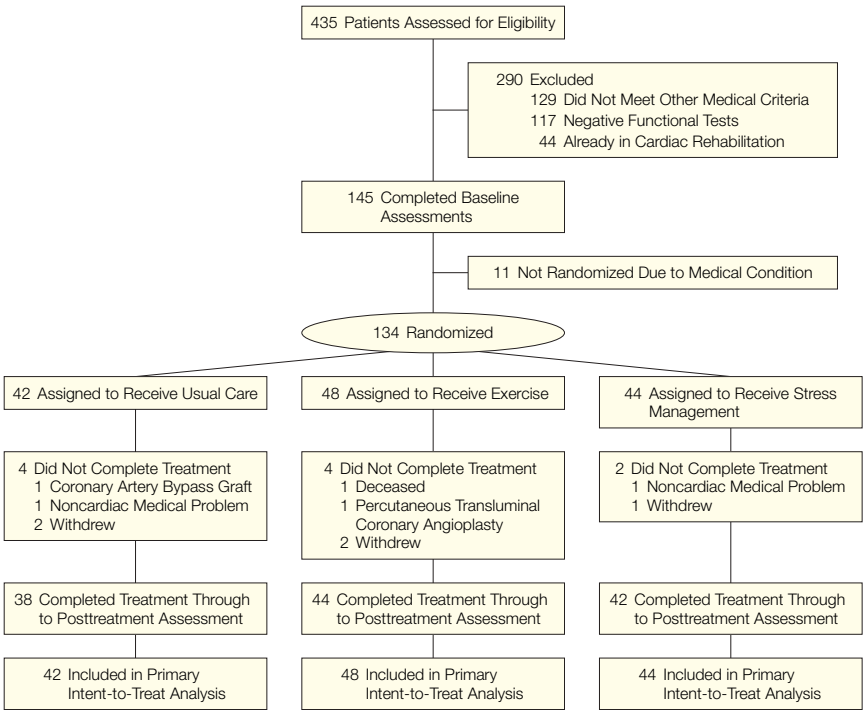
Patients were randomized in blocks of 6 to 8 patients. The randomization occurred in 2 stages. Patients were randomized to either group A or group B in a ratio of 1:2. Group A was usual care plus stress management; patients randomized to group B were randomized to either usual care plus supervised aerobic exercise training or usual care in a ratio of 1:1. This procedure is somewhat unconventional because the size of the block was determined by how many patients were available to be randomized within 1 month of their baseline assessments, which could vary. Because patients' cardiac condition could change over time, we believed that it was important to begin treatment within 4 weeks of completing their baseline evaluations. Patients were provided their group assignment in a sealed envelope; staff performing testing were unaware of the patients' treatment group assignments.

Exercise Training. Patients were assigned to usual care plus supervised aerobic exercise training for 35 minutes 3 times per week for 16 consecutive weeks. Exercise sessions consisted of a 10-minute warm-up involving

stretching and exercise on a stationary bicycle at 50% to 70% of heart rate reserve followed by 35 minutes of walking and jogging at a target intensity of 70% to 85% of heart rate reserve. Patients recorded their heart rates at 10-minute intervals throughout each exercise session, along with ratings of perceived exertion. Each session concluded with 10 minutes of cool-down stretching exercises.

Stress Management Training. Patients were assigned to usual care plus weekly 1.5-hour stress management training for 16 weeks. The stress management training program was based on our prior work,[9] which emphasizes a cognitive-social learning model of behavior. The interaction of the social environment with personality traits that predispose individuals to respond to situations in particular ways was highlighted, and the treatment program was based on the notion that emotion and behavior are largely determined by individuals' cognitive perceptions. The program sessions were conducted in a group setting with approximately 8 patients per group. There were 3 key components. First, an educational component in which participants were provided information about IHD and myocardial ischemia, the structure and function of the heart, traditional risk factors, and emotional stress. Stress was defined as an imbalance between excessive demands and inadequate coping skills. Second, patients underwent skills training, which involved instruction in specific skills to reduce the affective, behavioral, cognitive, and physiological components of stress. Therapeutic techniques included graded task assignments, monitoring irrational automatic thoughts, and generating alternative interpretations of situations or unrealistic thought patterns. Patients were instructed in progressive muscle relaxation and imagery techniques, along with training in assertiveness, problem solving, and time management. Role-playing also was used. Third, social support was considered to be a key aspect of the program. Group interaction and social support were encouraged.

Figure 1. Patient Study Flow



Usual Care. Patients in the usual care group were monitored on a monthly basis to ensure that they had not joined any exercise or stress management training program. Patients maintained their regular medical regimens and saw their local cardiologists as needed. No attempt was made to alter the usual care that these patients received from their personal physicians.

Statistical Analysis

Treatment effects were evaluated using the general linear model with posttreatment measures serving as the dependent variables, treatment group as the between-subject factor, and age, prior myocardial infarction, baseline LVEF, sex, and the corresponding baseline level of the outcome variable as covariates. Separate models were estimated for the psychosocial outcomes, LVEF and WMA change during mental stress, and FMD. For each model, we constructed 2 orthogonal contrasts to compare treatments: exercise and stress management training vs usual care; exercise training vs stress management training. To enhance the reliability of the mental stress assessments and reduce the number of statistical tests, the change in LVEF during mental stress was averaged over the public speaking and mirror trace tasks. Similarly, WMA ratings were averaged over the 2 tasks.

We also conducted an ancillary analysis of the primary outcomes using the propensity score approach.[35] This approach attempts to statistically improve the baseline balance on background characteristics across the groups. These new sets of models included the posttreatment outcome as the response variable, treatment group assignment as a factor, and the propensity score and the pretreatment value of the outcome as covariates. Because the results using propensity scores were essentially the same as our primary models, only the results of the latter analyses are reported.

We also examined the effect of exercise training on aerobic fitness, HRV-DB, and baroreflex sensitivity. In these models, we compared groups by using a

priori contrasts, which compared exercise training with usual care and compared stress management with usual care. We conducted all analyses using the intent-to-treat principle[36]; if the outcome value was missing for a patient, we inserted the baseline value for that outcome (ie, last observation carried forward). The number of patients with available posttreatment data is noted in the results section for each analysis. We also evaluated the extent to which models met assumptions, including additivity, linearity, and distribution of residuals. It should be noted that we estimated the sample size based on estimates from our previous trial.[9] More specifically, the present study was powered to detect the 3 largest treatment effects (≈15% greater improvement in the treatment groups compared with usual care) that we observed previously. Assuming a 2-sided test and a 5% type I error rate, the estimated power for detecting these effects in the sample was 0.87 (exercise training effects in wall motion-defined ischemia during exercise), 0.88 (exercise training effects in wall motion-defined ischemia during mental stress testing), and 0.72 (stress management effects on wall motion-defined ischemia during mental stress testing). $P<.05$ was the level of significance used in this analysis; SAS software (version 9.1, SAS Institute Inc, Cary, NC) was used for statistical analysis.

Table 1. Characteristics at Baseline

	Total Cohort (N = 134)	Usual Care (n = 42)	Exercise (n = 48)	Stress Management (n = 44)
Demographics, No. (%)				
Age, mean (SD), y	63 (10.3)	63 (9.0)	62 (10.5)	63 (11.5)
Annual income >$50 000	64 (48)	21 (50)	30 (63)	13 (30)
At least some college	93 (69)	22 (52)	34 (71)	37 (84)
Married	99 (74)	31 (74)	30 (63)	38 (86)
Female	42 (31)	10 (24)	17 (35)	15 (34)
White	103 (77)	32 (76)	36 (75)	35 (80)
Cardiovascular health				
LVEF at rest, mean (SD), %	57 (10.3)	57 (11.0)	59 (9.5)	56 (10.4)
Prior myocardial infarction, No. (%)	76 (57)	25 (60)	24 (50)	27 (61)
Body mass index, mean (SD)*	29.8 (5.0)	29.8 (4.0)	29.9 (5.7)	29.0 (5.0)
Aerobic fitness				
Peak Vo_2, mean (SD), mL/kg per minute	19.7 (5.7)	20.2 (5.2)	19.1 (6.0)	20.0 (6.0)
Treadmill time, mean (SD), min	7.5 (2.6)	8.1 (2.2)	7.2 (2.6)	7.3 (2.9)
Psychosocial measures, mean (SD)				
General distress (General Health Questionnaire)	54 (8)	53 (9)	55 (8)	54 (7)
Depression (Beck Depression Inventory)	9.4 (7.8)	8.9 (7.9)	9.8 (7.7)	9.5 (8.0)
Score ≥10, No. (%)	49 (37)	13 (31)	19 (40)	17 (39)
Hostility (Cook-Medley Hostility Scale)	11 (5)	12 (5)	11 (5)	11 (5)
Anxiety (Spielberger Trait Anxiety Inventory)	37 (9)	37 (9)	39 (9)	36 (9)
Cardiac changes during stress				
LVEF, change from rest, mean (SD), %	−1.7 (3.2)	−2.3 (3.5)	−1.0 (2.6)	−2.0 (2.5)
Mental stress ischemia				
LVEF reduction >5%, No. (%)	42 (31)	18 (43)	8 (17)	16 (36)
WMA change from rest, mean (SD)	0.20 (0.50)	0.23 (0.60)	0.16 (0.40)	0.21 (0.55)
New WMA, No. (%)	31 (23)	10 (24)	10 (21)	11 (25)
By LVEF or WMA, No. (%)	54 (40)	20 (48)	15 (31)	19 (43)
Exercise stress ischemia, mean (SD)				
LVEF, change from rest, %	−0.57 (8.2)	−0.51 (8.0)	−1.1 (8.6)	−0.06 (8.2)
WMA, change from rest	0.44 (1.7)	0.46 (2.4)	0.63 (1.4)	0.21 (2.4)
Vascular endothelial function, mean (SD), %				
Flow-mediated dilation	4.9 (4.0)	4.9 (3.9)	5.3 (4.4)	4.4 (4.0)
Glyceryl trinitrate	14.9 (7.5)	14.2 (5.2)	14.4 (6.0)	15.7 (10.3)
Cardiac autonomic control, mean (SD)				
Change in R-R interval, ms	135.7 (85.5)	126.0 (49.7)	136.4 (77.0)	143.4 (114.2)
Baroreflex sensitivity, ms/mm Hg	7.1 (4.2)	7.7 (5.1)	7.1 (4.3)	6.6 (3.4)

Abbreviations: LVEF, left ventricular ejection fraction; Vo_2, oxygen consumption per unit of time; WMA, wall motion abnormalities.
*Measured as weight in kilograms divided by the height in meters squared.

RESULTS

Patient Characteristics

FIGURE 1 shows the patient flow from initial recruitment screening to assessment after treatment. A total of 134 patients were eligible for the study and randomized to treatment; 124 (93%) patients completed the study. Demographic characteristics, including age, sex, family history of hypertension, and race, were similar in the 3 groups (TABLE 1). Dropouts did not differ from completers on any background characteristic. In addition, there were no treatment group differences in medication use. Most patients were taking aspirin, and the majority took lipid-lowering drugs or β-blockers. Half of the participants were also taking calcium channel blockers (TABLE 2).

Treatment Adherence

Among the patients in the usual care plus stress management group, 37 (77%) participated in at least 75% of the sessions; the median number of sessions attended was 13 (81% of all possible sessions). The median attendance in exercise training was 43 (89%) of 48 sessions, with 33 (75%) patients attending at least 75% of the training sessions.

Aerobic Fitness

Patients in the usual care plus exercise training group showed a 19% improvement in treadmill duration compared with 9% in the stress management group and 1% in the usual care group. Exercise training participants showed a 6% improvement in peak oxygen consumption per unit time (Vo_2) compared with a 4% improvement in stress

management patients and a 1% decrement in usual care patients. Compared with patients in the usual care group, the general linear model analysis revealed that those patients in the exercise training group showed larger improvements in aerobic fitness as measured by peak VO_2 consumption (1.1 vs –0.2 mL/kg per minute; $P = .002$) and exercise duration on the treadmill (70 vs 2 seconds; $P = .02$).

Psychosocial Outcomes

Patients in the exercise and stress management training groups showed greater reductions in general distress as measured by the General Health Questionnaire ($P = .02$) and in depressive symptoms as measured by the Beck Depression Inventory ($P = .02$) compared with usual care controls (TABLE 3). There were no treatment group differences in hostility (measured by the Cook-Medley Hostility Scale) or anxiety (measured by the Spielberger State-Trait Anxiety Inventory).

LVEF During Laboratory Mental Stress and Exercise Testing

Patients in the usual care group exhibited more ischemia as evidenced by greater postintervention decrements in LVEF during mental stress testing compared with those in the exercise and stress management training groups ($P = .03$; Table 3). No significant treatment group differences were observed between patients in the exercise training and stress management training groups. This pattern was similar with respect to change in LVEF during exercise training, although the contrast between exercise and stress manage-

Table 2. Cardiac Medication History Prior to Treatment

	No. (%)			
	Total Cohort (N = 134)	Usual Care (n = 42)	Exercise (n = 48)	Stress Management (n = 44)
Aspirin	120 (90)	39 (93)	42 (88)	39 (89)
Cholesterol-lowering drugs	105 (78)	35 (83)	37 (77)	33 (75)
β-Blockers	95 (71)	32 (76)	37 (77)	26 (59)
ACE inhibitors or ARBs	75 (56)	26 (62)	23 (48)	26 (59)
Calcium channel blockers	68 (51)	34 (81)	19 (40)	25 (57)
Nitrates	37 (28)	15 (36)	14 (29)	8 (18)
Antidepressants	30 (22)	12 (29)	13 (27)	5 (11)

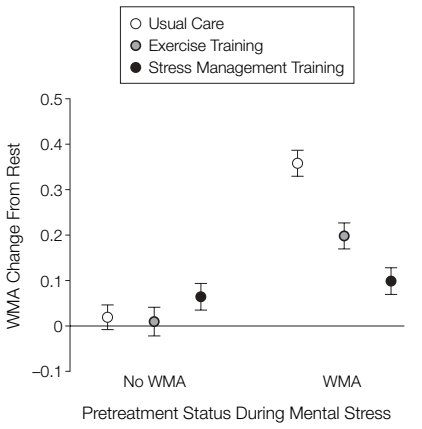
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

Table 3. Outcome Measures After Treatment*

	Treatment Group			*P* Value	
	Usual Care	Exercise	Stress Management	Exercise and Stress Management Groups vs Usual Care	Stress Management vs Exercise
Cardiac changes during stress, %					
Left ventricular ejection fraction					
Mental stress	–1.69 (0.46)	–0.54 (0.44)	–0.34 (0.45)	.03	.75
Exercise	1.66 (0.92)	0.07 (0.86)	2.50 (0.89)	.51	.06
Wall motion abnormalities					
Mental stress	0.09 (0.03)	0.06 (0.03)	0.06 (0.03)	.52	.98
Exercise	0.49 (0.25)	0.68 (0.23)	0.13 (0.23)	.74	.002
Vascular endothelial function, %					
Flow-mediated dilation	4.1 (0.48)	5.6 (0.45)	5.2 (0.47)	.03	.58
Nitroglycerin-induced dilation	13.8 (0.8)	15.9 (0.8)	15.3 (0.8)	.09	.66
				Exercise vs Usual Care	Stress Management vs Usual Care
Cardiac autonomic control					
Change in R-R interval, ms	132.2 (21.5)	131.6 (22.2)	193.7 (19.6)	.99	.04
Baroreflex sensitivity, ms/mm Hg	5.1 (0.9)	7.6 (0.9)	8.2 (0.8)	.63	.02
Aerobic fitness					
Treadmill duration, min	7.5 (0.2)	8.7 (0.2)	8.1 (0.2)	.002	.14
Peak VO_2, mL/kg/min	19.4 (0.5)	21.0 (0.4)	20.3 (0.5)	.02	.19
				Exercise and Stress Management Groups vs Usual Care	Stress Management vs Exercise
Psychosocial outcomes					
General distress (General Health Questionnaire)	53.6 (0.9)	56.3 (0.9)	56.8 (0.9)	.02	.72
Depression (Beck Depression Inventory)	10.1 (0.6)	8.2 (0.6)	8.2 (0.6)	.02	.94
Hostility (Cook-Medley Hostility Scale)	11.8 (0.5)	10.8 (0.5)	11.3 (0.5)	.23	.47
Anxiety (Spielberger Trait Anxiety Inventory)	37.0 (0.8)	35.2 (0.8)	36.4 (0.8)	.22	.28

Abbreviation: VO_2, oxygen consumption per unit of time.
*Values are expressed as fitted mean (SE) and are adjusted for age, sex, prior myocardial infarction, pretreatment resting left ventricular ejection fraction, and pretreatment level of the corresponding outcome variable.

Figure 2. WMA Response to Mental Stress Testing



Effect of treatment was concentrated among patients who exhibited wall motion abnormalities (WMA) during mental stress testing prior to treatment. Among patients with abnormal responses prior to treatment, patients in the exercise and stress management training groups had better WMA rating scores at the end of the trial compared with usual care controls ($P = .02$). Values were adjusted for age, sex, prior myocardial infarction, pretreatment resting left ventricular ejection fraction, and pretreatment levels of change in WMA. Missing or unusable posttreatment assessment values (n = 14) were replaced with pretreatment values. Error bars indicate standard error.

ment training and usual care was not significant ($P = .06$; Table 3).

WMA During Mental Stress and Exercise Testing

There were no differences among any of the groups on WMA scores during mental stress testing (Table 3). However, during exercise testing, patients in the stress management group exhibited fewer new WMA compared with those in the exercise training or usual care groups ($P = .002$; Table 3). While testing model assumptions, we observed that for WMA during mental stress testing, there was a significant treatment-by-baseline interaction ($P<.001$), indicating that the treatment effect on WMA scores depended on the level of WMA prior to treatment. FIGURE 2 shows the fitted means from this interaction model. We examined the contrasts among the exercise and stress management training groups compared with the usual care group and exercise training compared with stress management training within each category of pretreatment WMA status. These analyses indicated that among patients who showed significant stress-induced WMA before treatment, patients in the exercise and stress management training groups had lower WMA scores after treatment compared with the usual care controls ($P = .02$).

Flow-Mediated Dilation

Patients in the exercise and stress management training groups showed postintervention improvements in FMD compared with those in the usual care group ($P = .03$), while patients in the exercise and stress management training groups did not differ from one another ($P = .58$; Table 3). Although there was a trend for patients in both exercise and stress management training groups to exhibit improved glyceryl trinitrate–mediated dilation compared with usual care controls, the results did not reach statistical significance ($P = .09$; Table 3).

HRV and Baroreflex Sensitivity

Because the HRV-DB assessments were initiated after the trial began, data were available for only 47 patients (15 in usual care, 14 in exercise training, and 18 in stress management). Given the small sample and reduced statistical power, we adjusted only for baseline level of the outcome variable and age in these models. The linear model revealed that stress management was associated with improved HRV-DB. Thus, following stress management training, patients showed greater changes in R-R interval during forced deep breathing when compared with patients who were in the usual care group ($P = .04$; Table 3). Patients in the stress management training group also showed significant improvements in baroreflex sensitivity compared with usual care patients ($P = .02$; Table 3).

COMMENT

Results of this randomized controlled trial demonstrate that behavioral treatments provide added benefits to routine medical management in patients with stable IHD. Patients who underwent 4 months of either aerobic exercise training or stress management training exhibited greater improvements in psychosocial functioning, including less emotional distress and lower levels of depression compared with usual care controls. This may be particularly noteworthy insofar as both distress measured by the General Health Questionnaire and depression measured by the Beck Depression Inventory are independently associated with worse prognosis among patients with IHD.[37-39] Participants in the present study were not preselected on the basis of psychosocial functioning, and it is possible that patients with higher levels of emotional distress could have benefited even more from treatment.

Despite the association of depressive symptoms and emotional distress with adverse cardiovascular events, improvements in psychosocial functioning are not necessarily associated with improved clinical outcomes. For example, in the recently completed Enhancing Recovery in Heart Disease (ENRICHD) trial,[40] cognitive-behavioral treatment of depressed or socially isolated patients after acute myocardial infarction led to modest improvements in psychosocial risk factors, but not to greater reductions in all-cause mortality or nonfatal cardiac events compared with usual care controls. In addition, subsequent post hoc analyses revealed that mortality differences between depressed patients and nondepressed controls did not emerge until 9 to 12 months following acute myocardial infarction.[41] Treating patients with chronic IHD may be more effective than treating patients with acute coronary syndromes.

Although the present study was not powered to examine the effects of the interventions on hard clinical end points, we examined the impact of the interventions on several cardiovascular risk markers. Patients who underwent either exercise training or stress management training exhibited smaller reductions in LVEF during mental stress testing and tended to show

smaller reductions in LVEF during exercise testing compared with usual care controls. For patients who exhibited WMAs during mental stress testing, stress management also resulted in reduced WMAs compared with patients in the exercise training group or usual care controls. Although the magnitude of these differences is relatively small, it is not necessarily clinically insignificant. Previous studies have reported that mental stress–induced ischemia is associated with increased risk for adverse events compared with exercise-induced ischemia.[11-14] A mental stress–induced decrease in LVEF of only 1% has been associated with an 8% increase in risk.[14] Although patients in the present study exhibited less ischemia than in our earlier work,[25] the present findings are consistent with the pattern of results that we observed in our previous, nonrandomized trial,[9] and therefore represent a partial replication of our earlier findings.

In the present study, patients who received either exercise or stress management training exhibited more than a 25% improvement in FMD compared with usual care controls. Several smaller studies have suggested that exercise interventions may result in improved vascular endothelial function in IHD patients.[42-44] In a recent article by Hambrecht et al,[45] improved endothelial function after 4 weeks of exercise training in patients awaiting coronary artery bypass graft surgery was closely related to increased phosphorylation of endothelial nitric oxide synthase. Increased bioavailability of nitric oxide is therefore a likely mechanism accounting for improved FMD following the exercise intervention in our study.

The mechanism for improved endothelial function associated with stress management training is not known. However, evidence that FMD is impaired following brief exposure to standardized laboratory mental stressors[46,47] is consistent with the notion that mental stress may promote atherogenesis.[3] The utility of endothelial function assessment as a pathophysiological marker of disease is supported by findings from prospective studies demonstrating that endothelial dysfunction predicts adverse cardiovascular events in patients with IHD.[15-18] Moreover, results from a recent hypertension intervention trial suggest that improved FMD in response to treatment is associated with reduced incidence of adverse cardiovascular events.[48] To our knowledge, our finding that FMD improved following a stress management intervention is the first to suggest that stress reduction might reduce cardiovascular risk in patients with IHD in part through favorable effects on vascular endothelial function.

Patients who received either exercise or stress management training also exhibited an improvement in baroreflex sensitivity compared with usual care controls. This finding is important because abnormally low baroreflex sensitivity has been shown to be associated with worse prognosis in patients with IHD[20-22] and may contribute to the risk associated with depression.[49] In contrast, the change in R-R interval during deep breathing did not show an overall improvement when the 2 active treatment groups were compared with the usual care group. This appeared to be due to the lack of improvement in HRV-DB in the exercise training group; the HRV-DB measure improved by approximately 40% in the stress management group. The magnitude of the change in R-R interval during deep breathing has been known to be predictive of autonomic dysfunction in diabetes,[27] and recent studies have demonstrated that low levels of HRV-DB predict increased mortality in patients with IHD[23] and in patients with diabetes.[24] Our findings suggest that stress management training improves HRV associated with maximal inspiration-expiration.

Our study is limited by its relatively small sample and absence of follow-up to determine the long-term clinical significance of improved ischemic activity, autonomic regulation, and endothelial function that we observed among patients who underwent exercise or stress management training. Although measures of HRV-DB and baroreflex sensitivity were only obtained on a subset of participants, results revealed statistically significant improvements in HRV-DB among patients receiving stress management training. Increased baroreflex sensitivity was found among patients receiving stress management training compared with usual care alone. The exercise and stress management training groups also exhibited improved psychosocial functioning after 4 months of treatment. Because emotional distress and even mild elevations of depressive symptoms measured by the Beck Depression Inventory have been associated with adverse outcomes,[50] these findings raise the possibility that the health benefits of improved psychosocial functioning observed in our prior work[9] may be mediated by improved endothelial function and autonomic control of the heart.

This small randomized clinical trial was not powered to detect differences in hard clinical end points, and improvement in cardiovascular markers may not result in reduced clinical events. Caution should be exercised in interpreting the clinical significance of improvements in intermediate end points.[51] In the absence of clinical standards for these measures, the clinical significance of these changes is uncertain. Ultimately, the long-term effects of exercise training or stress management will need to be evaluated prospectively in a larger sample of patients with IHD. However, the present study provides insight into potential mechanisms by which exercise or stress management training may be of benefit. Our results suggest that exercise and stress management training offer considerable promise to patients with stable IHD through improvement in psychosocial adjustment and by modification of disease risk markers that may translate into improved clinical outcomes.

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