High-Calorie-Expenditure Exercise

A New Approach to Cardiac Rehabilitation for Overweight Coronary Patients

Philip A. Ades, MD; Patrick D. Savage, MS; Michael J. Toth, PhD; Jean Harvey-Berino, PhD, RD; David J. Schneider, MD; Janice Y. Bunn, PhD; Marie C. Audelin, MD; Maryann Ludlow, RD

Background—More than 80% of patients entering cardiac rehabilitation (CR) are overweight, and >50% have metabolic syndrome. Current CR exercise protocols result in little weight loss and minimal changes in cardiac risk factors. We sought to design an exercise protocol that would lead to greater weight loss and risk factor change.

Methods and Results—We performed a randomized controlled clinical trial to evaluate the effect of high-calorie-expenditure exercise (3000- to 3500-kcal/wk exercise-related energy expenditure) compared with standard CR exercise (7 to 800 kcal/wk) on weight loss and risk factors in 74 overweight patients with coronary heart disease. Both groups were counseled for weight loss and taking evidence-based preventive medications. High-calorie-expenditure exercise resulted in double the weight loss (8.2±4 versus 3.7±5 kg; $P<0.001$) and fat mass loss (5.9±4 versus 2.8±3 kg; $P<0.001$) and a greater waist reduction (−7±5 versus −5±5 cm; $P=0.02$) than standard CR exercise at 5 months. High-calorie-expenditure exercise reduced insulin resistance, measured with the euglycemic hyperinsulinemic clamp, along with the ratio of total to high-density lipoprotein cholesterol and components of the metabolic syndrome, more than standard CR exercise (each $P<0.01$). Overall, fat mass loss best predicted improved metabolic risk, and the prevalence of metabolic syndrome decreased from 59% to 31%. Changes in cardiac risk factors included decreased insulin resistance, increased high-density lipoprotein cholesterol, and decreased measures of insulin, triglycerides, blood pressure, plasminogen activator inhibitor-1, and the ratio of total to high-density lipoprotein cholesterol (each $P<0.05$). Significant weight loss was maintained at 1 year.

Conclusion—High-calorie-expenditure exercise promotes greater weight loss and more favorable cardiometabolic risk profiles than standard CR for overweight coronary patients. **(*Circulation*. 2009;119:000-000.)**

Key Words: coronary disease ■ exercise ■ metabolic syndrome ■ obesity ■ weight loss

Although cardiac rehabilitation (CR) has been shown to reduce cardiac and total mortality in patients after a coronary event,[1,2] current CR exercise protocols were developed in the 1970s when profound deconditioning after lengthy hospitalizations was common.[3,4] Profiles of contemporary CR patients have changed as the prevalence of obesity has skyrocketed[5,6] and cardiac hospitalizations have shortened.[7] From 1996 to 2006, the mean body mass index (BMI) for patients entering CR increased from 28.5 to 30.1 kg/m^2.[5] Currently, >80% of CR patients are overweight (BMI >25 kg/m^2), the prevalence of obesity (BMI >30 kg/m^2) is >40%, and >50% have insulin resistance manifest as metabolic syndrome.[5,8–10] Additionally, a focus on secondary prevention and risk reduction in CR has emerged.[11,12] Yet, CR exercise protocols have remained largely unchanged.

Editorial see p ●●●
Clinical Perspective on p ●●●

Obesity and metabolic syndrome predict an increased risk of death and recurrent events after myocardial infarction,[13–17] in part because of their association with an adverse risk factor profile even in patients taking evidence-based preventive therapies.[18] Although some epidemiological studies have questioned the link between BMI and coronary events, often called the obesity paradox,[19] recent data have shown an association between obesity and an earlier presentation of acute myocardial infarction with increasing BMI.[20] Mortality from coronary heart disease (CHD) decreased 50% from 1980 to 2000.[21] However, further declines were offset by increases in rates of obesity and type II diabetes.[21] Weight loss in CR has been linked to diminished cardiovascular

Received November 7, 2008; accepted February 25, 2009.

From the Divisions of Cardiology (P.A.A., P.D.S., M.J.T., D.J.S., M.C.A., M.L.), Nutrition and Food Sciences (J.H.-B.), and Biometry (J.Y.B.), University of Vermont College of Medicine, Burlington.

Clinical trial registration information—URL: http://www.ClinicalTrials.Gov. Unique identifier: NCT00628277.

Correspondence to Philip A. Ades, MD, Cardiac Rehabilitation and Prevention, 62 Tilley Dr, S Burlington, VT 05403. E-mail Philip.ades@vtmednet.org

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.108.834184**

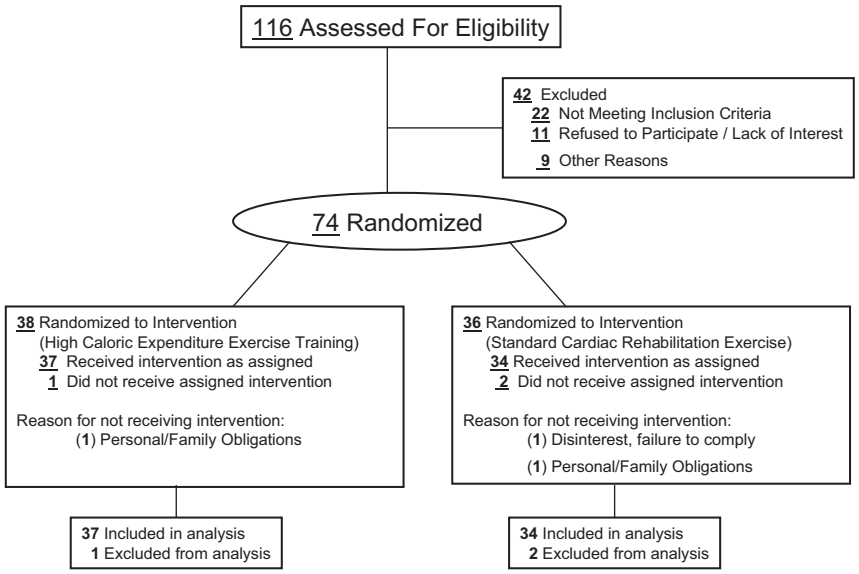

Figure 1. Flow diagram of the recruiting process.

events over 6 years of follow-up.[22] Unfortunately, current CR protocols result in little weight loss or risk factor change,[23,24] in part because of the low CR-related energy expenditure of 7 to 800 kcal/wk.[25–28] Accordingly, we performed a randomized controlled trial in patients with CHD that compared higher-calorie-expenditure CR exercise (longer distance, almost daily walking) with standard CR exercise (shorter distance, 3 times weekly on multiple exercise modalities). Both groups received behavioral weight loss counseling. Primary end points were measures of body composition, insulin sensitivity, and metabolic predictors of cardiovascular risk.

Methods

Subject Selection

Patients with CHD, BMI >27 kg/m^2, and waist circumference >102 cm (men) or >88 cm (women) were eligible for participation. We chose these criteria instead of a BMI >25 kg/m^2 to avoid individuals with borderline excess adiposity with only a minimal need for weight reduction. Patients were enrolled from 2002 to 2006. A flow diagram of the recruiting process is given in Figure 1. We evaluated 114 subjects for eligibility. Subjects with diabetes mellitus were excluded, although 25 patients with a fasting glucose of 100 to 126 mg/dL were enrolled. Patients with severe deconditioning (peak aerobic capacity <14 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) were excluded because in a preliminary nonrandomized trial such subjects were unable to markedly increase their exercise-related calorie expenditure and were less successful at accomplishing weight loss.[28] All subjects were hospitalized ≥3 months previously. The study population ultimately consisted of 74 individuals, 60 men and 14 women. Cardiac diagnoses included past myocardial infarction (n=34), coronary bypass surgery (n=34), percutaneous coronary intervention (n=28), or chronic stable angina (n=6). This protocol was approved by the University of Vermont Committee on Human Research and was registered as a clinical trial (NCT00628277). After providing informed consent, each patient underwent a clinical review to ascertain that evidence-based pharmacological therapies were being taken.[29] Baseline measures were taken at the University of Vermont General Clinical Research Center. Exercise was restricted for a minimum of 36 hours before all metabolic and exercise testing procedures.

Body Composition and Physical Activity

Body composition measures included body weight, BMI, waist circumference, fat mass, and fat-free mass by dual energy x-ray absorptiometry (General Electric Lunar Prodigy, Madison, Wis). Abdominal visceral and subcutaneous fat areas were measured by CT scanning (General Electric Medical Systems, Milwaukee, Wis, and Philips Electronics N.V., Eindhoven, the Netherlands).[30] Physical activity energy expenditure was measured over 7 days with the doubly labeled water technique providing a noninvasive assessment of free-living activity energy expenditure after subtracting resting metabolic rate and thermic effect of food.[31]

Coronary risk factor assessments included insulin-stimulated glucose disposal, insulin, glucose, lipid profiles, resting blood pressure (BP), high sensitivity C-reactive protein, and plasminogen activator inhibitor-1 (PAI-1). Medications were withheld the morning of testing. BP was measured after 5 minutes in the seated position with a Dinamap (GE Medical Systems, Tampa, Fla) automated BP cuff. A mean of 3 measurements constituted the resting BP. Components of the metabolic syndrome were assessed, including waist circumference >102 cm (men) or >88 cm (women), systolic BP ≥135 mm Hg or diastolic BP ≥85 mm Hg, fasting triglycerides >150 mg/dL, high-density lipoprotein (HDL) cholesterol <40 mg/dL (men) or <50 mg/dL (women), and fasting blood glucose >100 mg/dL.[32] The presence of ≥3 components defined the metabolic syndrome.

Insulin-stimulated glucose disposal was determined after an overnight fast with the euglycemic hyperinsulinemic clamp technique.[30,33] Testing was preceded by 3 days of standardized meals consisting of 200 to 250 g carbohydrate and 12 g fiber per 1000 kcal per day. Insulin-stimulated glucose uptake, an index of insulin sensitivity, was the average dextrose infusion rate during the final 30 minutes of the 3-hour clamp plus residual endogenous glucose production[30] expressed relative to fat-free mass.

The concentration of PAI-1 was determined by ELISA (Tintelize, Biopool, Umea, Sweden).[34] High-sensitivity C-reactive protein was measured with a colorimetric ELISA.[35] Isolated values of ≥10 mg/dL (3 of 74 at baseline) were eliminated from analysis unless C-reactive protein was elevated both before and after the 5-month intervention (1 of 71).

Peak aerobic capacity (peak $\dot{V}O_2$) was measured during a symptom-limited treadmill test using a graded modified Balke protocol until volitional fatigue, cardiovascular symptoms, or ≥2-mm ECG ST-segment depression. Expired gas was analyzed with a SensorMedics Vmax 29c (Yorba Linda, Calif) with measurement of peak $\dot{V}O_2$ in milliliters of O_2 per kilogram per minute. Dietary macronutrient intake was estimated at baseline and weeks 15 and 51 with 3-day dietary diaries (Food Intake Analysis System, Houston, Tex).

Study Framework

Subjects were randomized to high-calorie-expenditure exercise or standard CR using a distance function method in sets of 4, balancing

Table 1. Body Composition and Fat Distribution Response by Group

	Total Population			High-Calorie-Expenditure Exercise			Standard CR			
	Baseline	5 mo	*P* Within Group	Baseline	5 mo	*P* Within Group	Baseline	5 mo	*P* Within Group	*P* Between Groups
Age, y	64±9	...	...	64±9	...	...	63±9	...	...	...
Men, n	60	58	...	30	29	...	30	29	...	...
Women, n	14	13	...	8	8	...	6	5	...	...
Body weight, kg	94.7±14.9	88.5±14.7	<0.001	93.5±16.2	85.3±14.6	<0.001	95.4±13.9	91.7±14.3	<0.001	<0.001
BMI, kg/m^2	32.2±4.1	30.1±4.2	<0.001	32.2±3.7	29.4±3.7	<0.001	32.0±4.5	30.7±4.5	<0.001	<0.001
Fat mass, kg	33.8±7.8	29.2±8.1	<0.001	33.4±7.6	27.5±8.1	<0.001	33.7±4.0	30.9±8.1	0.003	<0.001
Fat-free mass, kg	57.9±10.6	56.1±9.6	<0.001	57.1±11.8	54.9±10.2	<0.001	58.7±9.4	57.4±8.8	<0.001	0.13
Waist circumference, cm	110±10	105±10	<0.001	110±10	103±10	<0.001	111±11	106±10	<0.001	0.018
Total abdominal fat, cm^2	579±133	493±138	<0.001	593±136	473±137	<0.001	565±131	513±139	0.004	<0.001
Intraabdominal fat, cm^2	238±82	196±75	<0.001	248±84	185±74	<0.001	231±79	208±76	0.003	<0.001

Results presented as mean±SD.

gender and BMI. After the 4-month intervention, subjects entered a 1-month weight stabilization phase, continuing to exercise but maintaining weight at <1-kg variation from the 4-month weight. We present data measured at 5 months as the primary outcome time point. Subjects underwent testing identical to that at baseline. Subsequently, subjects entered a maintenance phase, performing most but not all of their recommended exercise offsite and keeping exercise records. Each group was instructed to adhere to the exercise protocol established during the 5-month exercise intervention. Monthly onsite reviews of dietary and exercise records were conducted with the dietitian and exercise physiologist, as well as biweekly calls from the dietitian. Data at 1 year also are presented. Preventive medications were kept steady throughout the 12-month protocol.

Behavioral Weight Loss

The behavioral weight loss program included 16 hourly group counseling sessions led by a dietitian[36] emphasizing dietary records, itemization of food, and caloric content. The daily caloric goal was 500 kcal less than predicted maintenance calories,[36] which was independent of the exercise program to which they were assigned. No specific recommendations were provided on macronutrient intake. Meal replacement plans were not used. Features of behavior modification included self-monitoring, stimulus control, problem solving, social assertion, goal setting, feedback, relapse prevention, and family involvement.[36]

Exercise Protocols

The exercise prescription for the high-calorie-expenditure CR group emphasized longer-duration (45 to 60 versus 25 to 40 minutes per session), lower-intensity (50% to 60% versus 65% to 70% peak $\dot{V}O_2$), and more frequent (5 to 7 versus 3 times a week) exercise than the standard CR group. Walking was the preferred exercise modality to maximize caloric expenditure versus weight-supported exercises (cycling or rowing), which burns fewer calories.[37] Simplistically, the high-calorie-expenditure exercise training protocol was to "walk often and walk far." The high-calorie-expenditure group had an exercise expenditure goal of ≥3000 to 3500 kcal/wk, attained after 2 to 4 weeks of gradually lengthening the exercise bouts. After performing all sessions onsite for 2 weeks, high-calorie-expenditure exercise subjects performed 2 to 4 sessions a week in the home environment using a heart rate monitor, subsequently downloaded at the CR center to ascertain duration of exercise. Both groups eventually performed 1 to 3 sessions a week onsite with home exercise logs. Exercise logs were reviewed weekly with the exercise physiologist to estimate caloric expenditure and to ascertain compliance. The standard CR group protocol included 25 minutes of treadmill walking and 8 minutes on 2 of 3 ergometers: cycle, rowing, or arm. After 5 months, subjects transitioned to a primarily home-based exercise program continuing the same exercise prescription. Subjects were allowed to perform up to 1 session a week at the CR facility.

The authors had full access and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Statistical Analyses

Results are presented as mean±SD. Repeated-measures ANOVA was used to determine overall treatment efficacy and to examine secondary outcomes between groups. When results indicated a differential treatment effect, the analysis was followed by an F test for simple effects to examine changes over time in each group separately. A 2-sided value of $P<0.05$ indicated statistical significance. Analyses were based on all subjects who remained in the study at 5 and 12 months, without imputation of missing values. Regression analysis was used to explore factors associated with fat mass loss and metabolic syndrome components during the intervention period, controlling for group assignment. Multivariate ANOVA was conducted on the change from baseline for a panel of cardiometabolic risk factors associated with obesity. The majority of the variables were approximately normally distributed. Log transformations for several variables were considered but did not change the conclusions. Thus, all results presented are based on untransformed data. The presence of the metabolic syndrome and the number of components present were computed both at baseline and at the end of treatment, with a logistic regression used to examine whether the presence of this syndrome changed differentially in each group after treatment. Differences in changes in the number of components of the metabolic syndrome were examined with the Friedman test, and generalized estimating equations were used to examine changes across time in the prevalence of components of the metabolic syndrome. We estimated that a sample size of 34 subjects a group was required to detect a differential group fat mass loss of 1.9 kg, assuming a between-subjects SD for the weight change of 2.5 kg with $\alpha=0.05$ and a power of 80% based on a preliminary study of high-calorie-expenditure exercise.[28]

Results

Baseline Characteristics

The mean age of study participants was 64±9 years (range, 44 to 84 year), mean BMI was 32±4 kg/m^2, (range 27 to 45 kg/m^2), and mean waist circumference was 110±10 cm. Study groups were similar at baseline in terms of age, gender, body weight, and body fat distribution (Table 1). Groups exhibited a similar distribution of cardiac risk factor measures, including BP, glucose disposal, glucose, insulin, and

Table 2. Risk Factor Responses by Group

	Total Population			High-Calorie-Expenditure Exercise			Standard CR			
	Baseline	5 mo	*P* Within Group	Baseline	5 mo	*P* Within Group	Baseline	5 mo	*P* Within Group	*P* Between Groups
Men, n	60	58		30	29		30	29		
Women, n	14	13		8	8		6	5		
Systolic BP, mm Hg	133±18	125±21	0.0001	133±18	125±23	<0.007	134±19	124±19	0.0003	0.73
Diastolic BP, mm Hg	74±9	69±9	0.0001	74±11	67±8	<0.001	75±8	71±10	0.051	0.12
Total cholesterol, mg/dL	155±33	153±32	0.299	162±36*	155±33	0.059	148±27	149±30	0.72	0.11
Triglycerides, mg/dL	132±80	114±62	0.007	149±80*	118±67	0.001	114±28	116±76	0.11	0.07
HDL cholesterol, mg/dL	41±10	44±11	0.001	39±9	42±9	0.001	42±12	44±12	0.11	0.24
Low-density lipoprotein cholesterol, mg/dL	89±24	87±23	0.183	94±27	89±24	0.08	84±20	84±21	0.86	0.26
Total/HDL cholesterol ratio	4.0±1.1	3.6±1.0	0.001	4.3±1.2†	3.8±1.0	<0.001	3.6±0.9	3.5±1.0	0.34	0.01
High-sensitivity C-reactive protein, ng/mL	3.2±3.6	2.7±3.1	0.04	3.3±4.1	3.1±4.7	0.14	3.2±3.0	2.8±2.3	0.11	0.43
Glucose, mg/dL	96±12	92±12	0.007	96±14	89±9	0.003	96±10.0	95±14	0.34	0.14
Insulin, μIU/mL	19±7	14±6	0.001	19±7	13±5	<0.001	19±8	16±6	<0.001	0.17
Glucose disposal, $mg \cdot FFM^{-1} \cdot min^{-1}$	7.1±2.7	8.5±3.2	0.0001	6.9±3.1	8.7±3.5	0.0001	7.2±2.3	8.2±2.4	0.001	0.008
PAI-1, ng/mL	22±9	19±16	0.06	24±11	19±21	0.05	20±8	19±11	0.49	0.37
Peak oxygen uptake, mL $O_2 \cdot kg^{-1} \cdot min^{-1}$	22±5	24±7	0.0002	22±6	24±8	0.004	22±5	24±6	0.01	0.85

Results are presented as mean±SD. For conversion to international units (mmol/L): multiply total cholesterol, low-density lipoprotein cholesterol, and HDL cholesterol by 0.02586; multiply triglycerides by 0.01129; and multiply glucose by 0.05555.

*P=0.05, †P<0.005, baseline comparison between groups; otherwise, P=NS.

cardiorespiratory fitness; however, total cholesterol, triglycerides, and ratio of total to HDL cholesterol were higher in the high-calorie-expenditure exercise group (Table 2). All subjects were taking preventive cardiovascular medications in accordance with evidence-based guidelines.[27] They included aspirin (99%), statins (84%), β-blockers (72%), angiotensin-converting enzyme inhibitors/blockers (36%), and clopidogrel (28%), with no differences in use between study groups. Study subjects had a low level of aerobic fitness comparable to patients entering clinical CR programs (Table 2)[9]; thus, they were not a physically elite subset of CHD patients. A total of 3 subjects dropped out of the study, all during the first month, 1 in the high-calorie-expenditure group and 2 in the standard CR group, with no dropouts from month 5 to 12.

Combined Group Responses

To evaluate the overall effects of exercise and weight loss, we combined study groups (n=71). Mean weight loss was 6.2±5.1 kg; fat mass loss was 4.6±3.9 kg; and peak aerobic capacity increased by 8% from 22±5 to 24±7 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (P=0.0002; Tables 1 and 2). These changes were associated with pronounced favorable effects on cardiac risk factors, including reductions in insulin resistance and fasting concentrations of insulin, glucose, serum triglycerides, ratio of total to HDL cholesterol, high-sensitivity C-reactive-protein, and PAI-1 and an increased HDL cholesterol (all P<0.05; Table 2). The prevalence of metabolic syndrome was reduced from 59% to 31% (P<0.0001). The average number of metabolic syndrome components decreased from 2.76±1.02 to 1.96±1.05 (P<0.001). High-sensitivity C-reactive protein decreased after exercise and weight loss only in patients not taking a statin (n=9) (4.3±3.7 to 2.8±3.5 mg/dL; P=0.002) with no effect in patients taking a statin (3.0±3.5 to 2.7±3.0 mg/dL; P=0.25; n=57; P<0.05 between groups). Fat mass change was the only independent predictor of change in metabolic score (R=0.26, P<0.02, adjusted for group) compared with changes in other anthropometric variables, fitness, physical activity, and dietary intake.

Body Composition by Group Assignment

High-calorie-expenditure exercise training yielded more than double the weight loss (8.2±4 versus 3.7±5 kg; P<0.001) and fat mass loss (5.9±4 versus 2.8±3 kg; P<0.001) and a greater reduction in waist circumference (7±5 versus 5±5 cm; P<0.02) than standard CR exercise (Table 1 and Figure 2). Additionally, high-calorie-expenditure exercise yielded a greater loss of total and intraabdominal fat, measured by computed tomography scan (Table 1). Our goal of increasing exercise energy expenditure was fulfilled, with physical activity energy expenditure increasing 615±427 kcal/d (P<0.001) in the high-calorie-expenditure exercise group versus 169±318 kcal/d (P<0.001) in the standard CR group (P<0.001 between groups; Table 3). The deficit in dietary caloric intake was similar between groups (−312±532 kcal/d in the high-calorie-expenditure group versus −254±424 cal/d in the standard CR group; P<0.01 within groups; P=0.69 between groups). Success with weight reduction did not differ by gender (results not shown). Using multiple

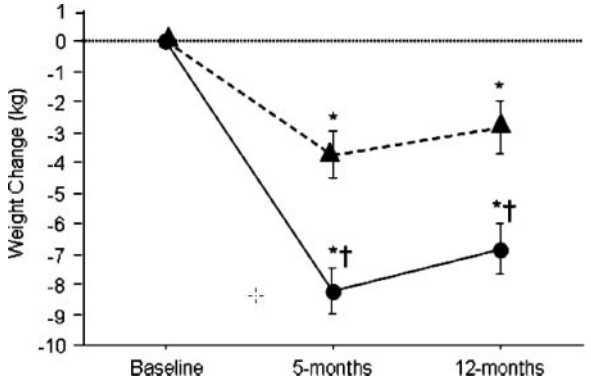

Figure 2. Weight change by group assignment. ▲ Indicate patients in standard CR exercise program; ●, patients in high-calorie-expenditure exercise group. *$P<0.05$ vs preceding time point within group; †$P<0.05$ vs standard CR group at same time point.

regression analysis and controlling for group assignment, we found that exercise compliance ($R=0.54$, $P<0.01$) and physical activity energy expenditure ($R=0.29$, $P=0.02$) were the only independent predictors of fat mass change (cumulative $R^2=0.54$). Adherence to the study interventions was good, with exercise attendance in the high-calorie-expenditure exercise and standard CR groups at 85% and 84%, respectively, and attendance at weight-loss sessions of 77% and 72%, respectively (both P=NS between groups). Five subjects in the high-calorie-expenditure group and 3 in the standard CR group missed ≥1 exercise session (baseline to month 5) because of an exercise-related medical problem ($P=0.76$). These were mostly aggravations of previously existing musculoskeletal conditions in addition to musculoskeletal overuse injuries rather than acute injuries. No exercise-related cardiac events occurred, although 1 individual in the high-calorie-expenditure group and 2 subjects in the standard CR group missed sessions for cardiac hospitalizations. Subjects did not experience greater difficulty accomplishing the high-calorie-expenditure training protocol. This was assessed with a study-specific physical activity satisfaction questionnaire (7-point Likert scale; 1=high level of satisfaction with physical activity, 7=low level of satisfaction with physical activity). Study groups had identical mean baseline scores of 2.7±1.2 with an overall increase in physical activity satisfaction at 5 months (combined group score, 2.3±1.7; $P<0.01$) and no difference in 5-month scores between groups (2.1±1.1 in the high-calorie-expenditure group versus 2.5±1.3 in the standard CR group; P=NS).

Insulin Sensitivity and Cardiac Risk Factors by Group Status

The high-calorie-expenditure exercise group experienced a significantly greater increase in insulin-mediated glucose disposal, reflecting a decrease in insulin resistance, the hallmark of the insulin resistance/metabolic syndrome (Table 2). The high-calorie-expenditure exercise group also experienced a greater reduction in the total-to-HDL-cholesterol atherogenic ratio (Table 2) of −13% versus −3% ($P<0.01$). When effects of study interventions on a panel of cardiac risk factors (insulin sensitivity, waist circumference, systolic and diastolic BPs, plasma glucose, triglycerides, HDL cholesterol, low-density lipoprotein cholesterol, cardiorespiratory fitness, PAI-1, and high-sensitivity C-reactive protein) were entered into a model using a multivariate ANOVA, the high-calorie-expenditure group experienced a significantly greater improvement in overall cardiometabolic risk profile than the standard CR group ($P=0.03$). The high-calorie-expenditure exercise group also experienced a greater reduction in the number of components of the metabolic syndrome compared with patients in the standard CR group: 3.1±1.2 to 1.9±1.1 components versus 2.4±0.7 to 2.0±1.0 components ($P=0.01$ between groups; Figure 3). These differences in weight reduction and cardiac risk factors were related to the differential exercise protocol because group subjects restricted calories similarly. Cardiorespiratory fitness improved similarly by group (each $P<0.01$ within groups; P=NS between groups; Table 2) from an identical baseline of 22 to 24 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$.

One-Year Results

Results at 1 year showed that both groups exhibited a weight regain of 1 kg (1.3 kg for the high-calorie-expenditure group versus 0.9 kg for the standard CR group; each $P<0.05$; P=NS between groups) compared with the 5-month measures, but body weight and body fat remained significantly lower than at baseline (each $P<0.001$) (Figure 2). Favorable alterations in the ratio of total to HDL cholesterol, HDL, peak aerobic capacity, and PAI-1, evident at 5 months in the high-calorie-expenditure exercise group, were maintained at 1 year (results not shown).

Discussion

The primary finding of this study is that high-calorie-expenditure exercise is superior to standard CR exercise in accomplishing weight loss and favorably altering cardiometabolic risk factors, particularly insulin resistance, in overweight patients with CHD. It was not described as being more unpleasant to accomplish and was not associated with an increased rate of exercise-related overuse injuries. Thus, high-calorie-expenditure exercise should be considered the preferred exercise protocol for almost 80% of patients in the United States referred for CR.

Although this is the first randomized study to assess the therapeutic value of high-calorie-expenditure exercise and

Table 3. Physical Activity Energy Expenditure and Daily Dietary Intake

	High-Calorie-Expenditure Exercise			Standard CR			*P*	
	Baseline	5 mo	*P*	Baseline	5 mo	*P*	Time Effect	Between Groups
Physical activity energy expenditure, kcal/d	717±496	1332±650	<0.001	916±624	1185±537	<0.001	<0.001	<0.001
Caloric intake, kcal/d	2080±525	1768±479	<0.001	1881±601	1626±399	<0.001	<0.001	0.61

Results are presented as mean±SD.

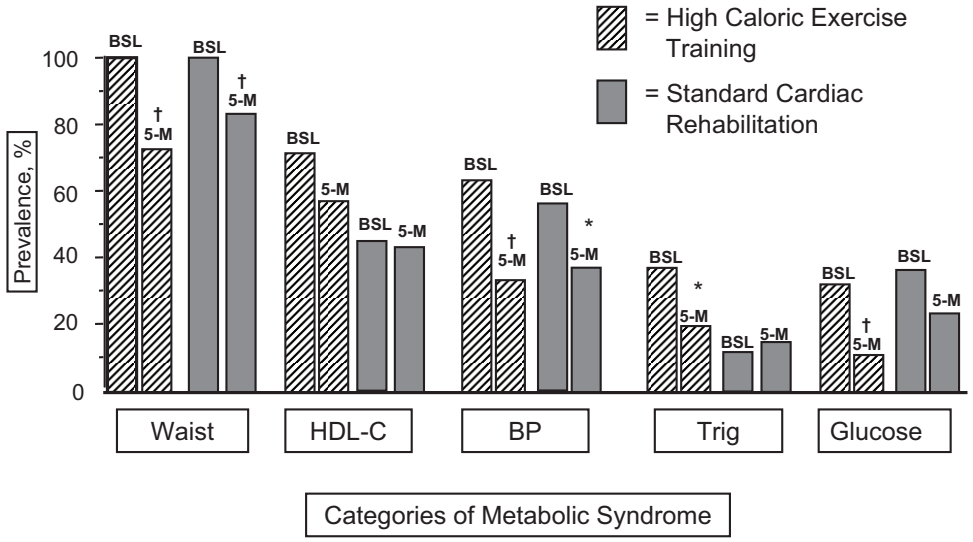

Figure 3. For each paired component of metabolic syndrome, the left bar represents the prevalence of the component at baseline, and the right bar is the prevalence at 5 months. Changes between groups were not statistically significant. Trig indicates triglycerides. *$P<0.05$, †$P<0.01$.

weight loss on cardiometabolic predictors of risk in coronary heart patients, metabolic benefits of exercise and weight loss in healthy overweight adults have been amply demonstrated. Exercise and weight loss prevent type II diabetes[38] and improve insulin sensitivity,[39] clotting parameters,[40] lipid values,[41,42] fasting glucose levels,[41] BP,[41] and systemic inflammation.[43] In patients with established CHD, lipid abnormalities,[44] BP measures,[45] PAI-1 levels,[46] C-reactive protein,[47] and the presence of diabetes[45,48] and insulin resistance syndrome[17] are powerful predictors of prognosis. Thus, it is highly likely, but remains to be demonstrated, that the multiple risk factor benefits of high-calorie-expenditure exercise training and behavioral weight loss would favorably affect long-term clinical outcomes.

Exercise compliance and change in physical activity energy expenditure were the only independent predictors of fat mass loss, which, in turn, was best predicted by improvements in cardiac/metabolic risk. This strongly supports the concept that exercise programs for risk reduction in overweight patients with CHD should focus on enhancing caloric expenditure. Furthermore, because of its lower exercise intensity, the high-calorie-expenditure exercise program may be safer to perform in community-based programs. Finally, the high-calorie-expenditure exercise regimen elicited comparable increases in peak aerobic capacity compared with standard CR exercise, suggesting that this paradigm does not compromise the cardiorespiratory benefits of CR.

We demonstrated lifestyle-induced improvements in cardiometabolic risk factors beyond the effects of preventive medications that most likely can be attributed to improvements in insulin sensitivity, which, in the clinical setting, is usually left untreated. Clinicians should not ignore that insulin resistance is thus a treatable risk factor. Indeed, we have previously shown that insulin sensitivity was the best predictor of the majority of risk factors before induction of the exercise and weight loss program.[18] Although our exercise and weight loss interventions yielded a more modest effect on high-sensitivity C-reactive protein than has been previously demonstrated,[49] this may have been due to higher statin use in the present study. Our 1-year results document that significant weight loss was maintained over a longer-term follow-up period, although some regain occurred. We speculate that if our 5- to 12-month intervention were more intensive than monthly onsite dietary meetings, incorporating more frequent onsite dietary and exercise sessions, this slight weight regain might have been prevented.

Strengths of our study include the state-of-the-art techniques used, including the hyperinsulinemic euglycemic clamp to measure insulin sensitivity, the doubly labeled water technique to measure free-living physical activity, and abdominal computed tomography scanning and dual x-ray absorptiometry to measure abdominal fat and body composition. The randomized controlled format negates the criticism that only highly motivated and selected overweight patients would be able to accomplish the study intervention. Additionally, the high-calorie-expenditure exercise program, a novel approach to CR exercise, was remarkably well accepted by patients. The successful maintenance of weight loss at 1 year provides optimism that weight loss can be maintained if patients are supported in their efforts to continue favorably altering the balance between energy intake and exercise-related caloric expenditure. Finally, the demonstrated benefits of high-calorie-expenditure exercise occurred in the setting of ongoing intensive pharmacological prevention are quite relevant to the care of patients in the clinical setting. We note that comparisons of exercise programs were made in the context of a hypocaloric diet; however, we have previously shown in a less well-controlled study that high-calorie-expenditure exercise in the context of an isocaloric diet also leads to significant weight loss and lower insulin levels.[28]

Because the goal of the study was to compare the effectiveness of high-calorie-expenditure exercise and standard CR exercise, no control group was included that neither exercised or participated in behavioral weight loss. However,

patients with CHD rarely lose weight with usual care. For example in the Gruppo Italiano per lo Studio della Sopravivienza nell'Infarto (GISSI-Prevenzione) trial, only 3.6% of 7027 patients after a recent (<3 months) myocardial infarction and a BMI of >25 kg/m^2 accomplished significant weight loss (>10% body weight) over a 6-month period.[16] A second limitation of the present study was that we did not include patients with diabetes mellitus. This limitation was imposed because of our goal to measure insulin resistance as a primary outcome. The measurement of insulin resistance would be inaccurate in patients taking hypoglycemic medications, particularly if, as expected, medication dose would need to be adjusted after exercise and weight loss. A third limitation is that weight regain follow-up was limited to just 1 year. We also note that the benefits of exercise and weight loss on risk factors might have been amplified if the subjects were not taking medications that influence lipid levels, BP, and C-reactive protein. This, however, would have rendered the results inapplicable to the clinical care of contemporary CHD patients and would not have acknowledged the clear benefits of these medications. Finally, the study population (n=74) was not of a size that was statistically powered to study coronary event rates.

Conclusions

High-calorie-expenditure exercise is substantially more effective than standard CR exercise at inducing weight loss and risk factor change in overweight patients with CHD. These findings do not obviate the established benefits of standard CR (including nonexercise components such as counseling) on mortality and clinical outcomes[1,2,11] but rather optimize the exercise intervention to maximize risk factor benefits. Risk reduction benefits beyond those provided by evidence-based pharmacological treatments alone were accomplished. Considering the negative consequences and increasing prevalence of obesity and metabolic syndrome, high-calorie-expenditure exercise training, combined with a hypocaloric diet, should be considered the exercise approach of choice for overweight patients with CHD. We suspect that the general applicability of the high-calorie-expenditure exercise program in CR programs will be broad, although CR staff and patients alike will need to be comfortable with performing much of a 5- to 6-d/wk exercise program away from the highly monitored CR facility. Some individuals with no exercise experience whatsoever may initially benefit from a standard CR exercise protocol and then gradually evolve to 4 to 6 sessions per week as they improve their fitness. Further research on the value of exercise and weight loss in overweight coronary patients could include refinements of the exercise protocol to add resistance training to minimize loss of muscle mass. Additionally, the effect of exercise and weight loss on long-term coronary events is important to determine.

Sources of Funding

This work was supported by NIH grants RO1-HL72851 (Dr Ades, principal investigator) and the General Clinical Research Center, University of Vermont College of Medicine (RR-109).

Disclosures

None.

References

1. Oldridge NB, Guyatt GH, Fischer ME, Rimm AA. Cardiac rehabilitation after myocardial infarction: combined experience of randomized clinical trials. *JAMA*. 1988;260:945–950.
2. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, Skidmore B, Stone JA, Thompson DR, Oldridge N. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med*. 2004;116:682–692.
3. Dorn J, Naughton J, Imamura D, Trevisan M. Results of a multicenter randomized clinical trial of exercise and long-term survival in myocardial infarction patients: the National Exercise and Heart Disease Project (NEHDP). *Circulation*. 1999;100:1764–1769.
4. Pashkow FJ. Issues in contemporary cardiac rehabilitation: a historical perspective. *J Am Coll Cardiol*. 1993;21:822–834.
5. Audelin MC, Savage PD, Ades PA. Changing clinical profile of patients entering cardiac rehabilitation/secondary prevention programs: 1996 to 2006. *J Cardiopulm Rehabil Prev*. 2008;28:299–306.
6. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960–1994. *Int J Obesity*. 1998;22:39–47.
7. Newby LK, Eisenstein EL, Califf RM, Thompson TD, Nelson CL, Peterson ED, Armstrong PW, Van de Werf F, White HD, Topol EJ, Mark DB. Cost effectiveness of early discharge after uncomplicated acute myocardial infarction. *N Engl J Med*. 2000;342:749–755.
8. Ades PA, Savage PD, Brawner CA, Lyon CE, Ehrman JK, Bunn JY, Keteyian SJ. Aerobic capacity in patients entering cardiac rehabilitation. *Circulation*. 2006;113:2706–2712.
9. Bader DS, Maguire TE, Spahn CM, O'Malley CJ, Balady GJ. Clinical profile and outcomes of obese patients in cardiac rehabilitation stratified according to National Heart, Lung, and Blood Institute criteria. *J Cardiopulm Rehabil*. 2001;21:210–217.
10. Savage PD, Banzer JA, Balady GJ, Ades PA. Prevalence of metabolic syndrome in cardiac rehabilitation/secondary prevention programs. *Am Heart J*. 2005;149:627–631.
11. Ades PA. Cardiac rehabilitation and secondary prevention of coronary heart disease. *N Engl J Med*. 2001;345:892–902.
12. Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Foody JM, Franklin B, Sanderson B, Southard D. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association. *Circulation*. 2007;115:2675–2682.
13. Wolk R, Berger P, Lennon RJ, Brilakis ES, Somers VK. Body mass index: a risk factor for unstable angina and myocardial infarction in patients with angiographically confirmed coronary artery disease. *Circulation*. 2003;108:2206–2211.
14. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med*. 2002;162:1867–1872.
15. Schwartz GG, Olsson AG, Szarek M, Sasiela WJ. Relation of characteristics of metabolic syndrome to short-term prognosis and effects of intensive statin therapy after acute coronary syndrome: an analysis of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial. *Diabetes Care*. 2005;28:2508–2513.
16. Levantesi G, Macchia A, Marfisi R, Franzosi MG, Maggioni AP, Nicolosi GL, Schweiger C, Tavazzi L, Tognoni G, Valagussa F, Marchioli R, for the GISSI-Prevenzione Investigators. Metabolic syndrome and risk of cardiovascular events after myocardial infarction. *J Am Coll Cardiol*. 2005;46:277–283.
17. Daly CA, Hildebrandt P, Bertrand M, Ferrari R, Remme W, Simoons M, Fox KM, for the EUROPA Investigators. Adverse prognosis associated with the metabolic syndrome in established coronary artery disease: data from the EUROPA trial. *Heart*. 2007;93:1406–1411.
18. Ades PA, Savage PD, Toth MJ, Schneider DJ, Audelin MC, Bunn JY, Ludlow M. The influence of obesity and consequent insulin resistance on coronary risk factors in medically treated patients with coronary disease. *Int J Obes (Lond)*. 2008;32:967–974.
19. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, Mookadam F, Lopez-Jimenez F. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet*. 2006;368:666–678.
20. Madala MC, Franklin BA, Chen AY, Berman AD, Roe MT, Peterson ED, Ohman EM, Smith SC Jr, Gibler WB, McCullough PA, for the CRUSADE Investigators. Obesity and age of first non-ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2008;52:979–985.

21. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, Giles WH, Capewell S. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. *N Engl J Med*. 2007;356:2388–2398.
22. Sierra-Johnson J, Romero-Corral A, Somers VK, Lopez-Jiminez F, Thomas RJ, Squires RW, Allison TG. Prognostic importance of weight loss in patients with coronary heart disease regardless of initial body mass index. *Eur J Cardiovasc Prev Rehabil*. 2008;15:336–340.
23. Brochu M, Poehlman ET, Savage P, Fragnoli-Munn K, Ross S, Ades PA. Modest effects of exercise training alone on coronary risk factors and body composition in coronary patients. *J Cardiopulm Rehabil*. 2000;20:180–8.
24. Lavie CJ, Milani RV. Effects of cardiac rehabilitation, exercise training, and weight reduction on exercise capacity, coronary risk factors, behavioral characteristics, and quality of life in obese coronary patients. *Am J Cardiol*. 1997;7:397–401.
25. Savage PD, Brochu M, Scott P, Ades PA. Low caloric expenditure in cardiac rehabilitation. *Am Heart J*. 2000;140:527–533.
26. Schairer JR, Kostelnik T, Proffitt SM, Faitel KI, Windeler S, Rickman LB, Brawner CA, Keteyian SJ. Caloric expenditure during cardiac rehabilitation. *J Cardiopulm Rehabil*. 1998;18:290–294.
27. Mertens DJ, Kavanagh T, Campbell RB, Shephard RJ. Exercise without dietary restriction as a means to long-term fat loss in the obese cardiac patient. *J Sports Med Phys Fitness*. 1998;38:310–316.
28. Savage PD, Brochu M, Poehlman ET, Ades PA. Reduction in obesity and coronary risk factors after high caloric exercise training in overweight coronary patients. *Am Heart J*. 2003;146:317–323.
29. Smith SC Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, Grundy SM, Hiratzka L, Jones D, Krumholz HM, Mosca L, Pasternak RC, Pearson T, Pfeffer MA, Taubert KA, for the AHA/ACC; National Heart, Lung, and Blood Institute. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation*. 2006;113:2363–2372.
30. Toth MJ, Sites CK, Cefalu WT, Matthews DE, Poehlman ET. Determinants of insulin-stimulated glucose disposal in middle-aged, premenopausal women. *Am J Physiol*. 2001;281:E113–E121.
31. Schoeller D, Ravussin E, Schutz Y, Acheson KJ, Baertschi P, Jéquier E. Energy expenditure by doubly labeled water: validation in humans and proposed calculation. *Am J Physiol*. 1986;250:R823–R830.
32. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F, for the American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112:2735–2752.
33. DeFronzo R, Tobin J, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol*. 1979;237:E214–E233.
34. Chmielewska J, Wiman B. Determination of plasminogen activator and its "fast" inhibitor in plasma. *Clin Chem*. 1986;32:482–485.
35. Macy E, Hayes T, Tracy R. Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. *Clin Chem*. 1997;43:52–58.
36. Harvey-Berino J. Weight loss in the clinical setting: applications for cardiac rehabilitation. *Coron Artery Dis*. 1998;9:795–798.
37. Zeni AI, Hoffman MD, Clifford PS. Energy expenditure with indoor exercise machines. *JAMA*. 1996;275:1424–1427.
38. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, for the Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393–403.
39. Ross R, Dagnone D, Jones PJ, Smith H, Paddags A, Hudson R, Janssen I. Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men: a randomized, controlled trial. *Ann Intern Med*. 2000;133:92–103.
40. Calles-Escandon J, Ballor D, Harvey-Berino J, Ades P, Tracy R, Sobel B. Amelioration of the inhibition of fibrinolysis in elderly, obese subjects by moderate energy intake restriction. *Am J Clin Nutr*. 1996;64:7–11.
41. Villareal DT, Miller BV 3rd, Banks M, Fontana L, Sinacore DR, Klein S. Effect of lifestyle intervention on metabolic coronary heart disease risk factors in obese older adults. *Am J Clin Nutr*. 2006;84:1317–1323.
42. Katzel LI, Bleecker ER, Colman EG, Rogus EM, Sorkin JD, Goldberg AP. Effects of weight loss vs aerobic exercise training on risk factors for coronary disease in healthy, obese, middle-aged and older men: a randomized controlled trial. *JAMA*. 1995:27;274:1915–1921.
43. Tchernof A, Nolan A, Sites CK, Ades PA, Poehlman ET. Weight loss reduces C-reactive protein levels in obese postmenopausal women. *Circulation*. 2002;105:564–569.
44. Rossouw JE, Lewis B, Rifkind BM. The value of lowering cholesterol after myocardial infarction. *N Engl J Med*. 1990;323:1112–1119.
45. Wong ND, Cupples LA, Ostfeld AM, Levy D, Kannel WB. Risk factors for long-term coronary prognosis after initial myocardial infarction: the Framingham study. *Am J Epidemiol*. 1989;130:469–480.
46. Malmberg K, Båvenholm P, Hamsten A. Clinical and biochemical factors associated with prognosis after myocardial infarction at a young age. *J Am Coll Cardiol*. 1994;24:592–599.
47. Sabatine MS, Morrow DA, Jablonski KA, Rice MM, Warnica JW, Domanski MJ, Hsia J, Gersh BJ, Rifai N, Ridker PM, Pfeffer MA, Braunwald E, for the PEACE Investigators. Prognostic significance of the Centers for Disease Control/American Heart Association high-sensitivity C-reactive protein cut points for cardiovascular and other outcomes in patients with stable coronary artery disease. *Circulation*. 2007;115:1528–1536.
48. Norhammar A, Malmberg K, Diderholm E, Lagerqvist B, Lindahl B, Rydén L, Wallentin L. Diabetes mellitus: the major risk factor in unstable coronary artery disease even after consideration of the extent of coronary artery disease and benefits of revascularization. *J Am Coll Cardiol*. 2004;43:585–591.
49. Milani RV, Lavie CJ, Mehra MR. Reduction in C-reactive protein through cardiac rehabilitation and exercise training. *J Am Coll Cardiol*. 2004;43:1056–1061.

CLINICAL PERSPECTIVE

More than 80% of patients entering cardiac rehabilitation (CR) are overweight, and >50% have metabolic syndrome. Current CR protocols, however, result in little weight loss and minimal changes in cardiac risk factors. We designed a CR exercise protocol aimed at maximizing exercise-related caloric expenditure and compared its efficacy with standard CR exercise to induce weight loss and favorably affect cardiac risk factors. Both study groups received similar nutritional counseling to reduce caloric intake. The high-calorie-expenditure exercise protocol, consisting of almost daily, longer-distance walking, resulted in double the weight loss and a greater fat mass loss and waist reduction than standard CR exercise. The high-calorie-expenditure exercise protocol resulted in reduced insulin resistance and a reduction in the ratio of total to high-density lipoprotein cholesterol and components of the metabolic syndrome to a greater degree compared with standard CR exercise. When the study groups were combined, the overall prevalence of the metabolic syndrome was reduced from 59% to 31%, and improvements in insulin resistance, lipid parameters, blood pressure, C-reactive protein, and plasminogen activator inhibitor-1 were noted, highlighting the multirisk benefits of exercise and weight loss. These results demonstrate that high-calorie-expenditure exercise should be the exercise modality of choice to maximize weight loss and to reduce cardiac risk predictors for overweight patients in CR programs. Implementation of this approach in CR exercise will require substantial modifications to currently used exercise programs because a large component of the exercise program needs to be accomplished beyond the confines of the usual 3-d/wk, onsite exercise prescription.

High-Calorie-Expenditure Exercise. A New Approach to Cardiac Rehabilitation for Overweight Coronary Patients

Philip A. Ades, Patrick D. Savage, Michael J. Toth, Jean Harvey-Berino, David J. Schneider, Janice Y. Bunn, Marie C. Audelin and Maryann Ludlow

Circulation. published online May 11, 2009;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539