The Effect of Weight Loss and Exercise Training on Flow-Mediated Dilatation in Coronary Heart Disease

A Randomized Trial

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Background: More than 80% of patients entering cardiac rehabilitation are overweight, with a high prevalence of associated insulin resistance, diabetes, hypertension, hyperlipidemia, and a prothrombotic state. Because each of these characteristics is associated with abnormalities of endothelial-dependent flow-mediated dilatation (FMD), a predictor of long-term prognosis in patients with coronary heart disease (CHD), we assessed the effect of exercise training and weight reduction on FMD in overweight patients with CHD.

Methods: All patients (N = 38) participated in behavioral weight loss while taking their usual preventive medications. Subjects were randomized to one of two exercise protocols, which differed by caloric expenditure. The primary outcome was extent (%) of brachial artery FMD measured by ultrasonography before and after the 4-month exercise and weight-loss program.

Results: Both study groups experienced an increase in brachial artery FMD after weight loss and exercise. Patients randomized to the higher-caloric exercise condition (longer-distance walking) lost more weight (8.6 ± 4.1 kg vs 2.3 ± 3.3 kg [$P < .001$]) and experienced a greater percentage increase in brachial artery FMD ($3.6\% \pm 4.1\%$ vs $1.3\% \pm 2.1\%$, $P < .05$) than did subjects in the lower-caloric-expenditure exercise group who lost less weight. Both groups increased peak aerobic capacity similarly. Increased FMD correlated with changes in body weight more than with measures of abdominal fat, glucose disposal, lipid measure, BP, or measures of physical activity or cardiorespiratory fitness.

Conclusions: Exercise and weight loss increased FMD in overweight and obese patients with CHD. Greater weight reduction was associated with a greater improvement in FMD; thus, there was a dose effect.

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Abbreviations: CHD = coronary heart disease; CR = cardiac rehabilitation; FMD = flow-mediated dilatation; peak $\dot{V}O_2$ = peak oxygen uptake

Cardiac rehabilitation (CR) results in improved long-term survival rates after an acute coronary event.^{1,2} To date, the best predictor of this improved prognosis has been the improvement in peak oxygen uptake, often termed peak $\dot{V}O_2$.³⁻⁵ However, since the performance of randomized controlled trials of CR in the 1970s, the clinical profile of patients entering CR has changed markedly. More than 80% of patients now entering CR are overweight, and this is associated with high rates of insulin resistance, metabolic

syndrome, type 2 diabetes, hypertension, and hyperlipidemia.⁶⁻⁸ Obesity, insulin resistance, hypertension, and hyperlipidemia are all associated with abnormal

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endothelial-dependent flow-mediated dilatation (FMD),⁹⁻¹³ and weight reduction results in an improvement in FMD in noncoronary populations.^{14,15} Abnormal FMD increases the risk of a coronary event

in patients with established coronary heart disease (CHD).¹⁶⁻¹⁹ The effects of a combined program of weight loss and exercise on FMD have not been studied in overweight patients with established CHD, nor has it been established whether there is a dose effect of weight loss on FMD in overweight patients with CHD who are already taking evidence-based preventive medications. Finally, we also note that the concept of the "obesity paradox" has made some investigators question whether there is a benefit of weight loss in patients with CHD; thus, the determination of biologic data to support a clinical benefit of weight loss in patients with CHD would be of interest.²⁰⁻²²

We reported recently that cardiac patients who participate in a program of high-caloric-expenditure exercise (daily, longer-distance walking) accomplish double the weight loss than is seen with the lower-caloric-expenditure exercise typically prescribed in CR programs.²³ This is associated with a greater improvement in multiple measures of cardiac risk factors compared with a standard CR program of exercise and dietary counseling, and others have shown similar safety and efficacy of weight reduction in CHD.²³⁻²⁷

The goal of this study was to determine whether exercise and behavioral weight loss counseling is associated with improved FMD and whether there is a relationship between the amount of weight reduction and the magnitude of improvement in FMD. Moreover, we examined whether alterations in FMD were related to changes in weight per se, or to other physiologic regulators that are altered by the weight loss/exercise intervention, such as total or regional adiposity, physical activity, aerobic fitness, or insulin levels/sensitivity. Results of this study are directly relevant to patients with CHD entering CR programs, of whom >80% are overweight, >40% are obese, and >50% are characterized by the metabolic/insulin resistance syndrome.⁶⁻⁸ Although exercise training per se has been shown to improve vascular function

in patients with CHD,²⁷ it is not known if there are supplemental vascular benefits of weight reduction.

MATERIALS AND METHODS

Patients

Nonsmoking individuals with established CHD, a BMI of >27 kg/m², and a waist circumference of >102 cm (men) or >88 cm (women) were recruited into a randomized controlled study of exercise and weight loss in overweight/obese individuals with CHD. Initial weight loss and cardiac risk factor results from this study have been published previously.²³ Patients with severe deconditioning (aerobic capacity of <14 mL O₂/kg/min) were excluded from the study because, in a preliminary non-randomized trial, such subjects were unable to sufficiently increase their exercise-related caloric expenditure and, therefore, were less successful at losing weight.²⁸ All subjects had not been hospitalized for ≥3 months. A total of 38 consecutive subjects underwent an assessment of endothelial-dependent and endothelial-independent vasodilatory capacity measured at the brachial artery using a well-established, highly standardized technique,²⁹ and these subjects compose the study population of the present analysis. Cardiac diagnoses of this population included past myocardial infarction (n = 14), coronary bypass surgery (n = 22), percutaneous coronary intervention (n = 21), or chronic stable angina (n = 4) (diagnoses were not mutually exclusive and did not differ by group). This protocol was approved by the University of Vermont Committee on Human Research (Project No. CHRMS, No. 03-049). After informed consent, each patient underwent a clinical review to ascertain that evidence-based pharmacologic therapies were being taken.³⁰ Baseline measures were taken at the University of Vermont General Clinical Research Center. Exercise was restricted for a minimum of 36 h prior to all metabolic testing procedures, and morning medications were withheld.

Experimental Protocol

Exercise and Weight-Loss Programs: After baseline testing, subjects were randomized to either high-caloric-expenditure exercise or standard CR (lower-caloric expenditure) in blocks of four, balancing 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. Preventive medications were maintained throughout the 5-month protocol.

The behavioral weight-loss program assigned to both groups included 16 hourly group-counseling sessions led by a dietician,³¹ emphasizing dietary records, itemization of food and caloric content, and a caloric goal. The daily caloric goal was 500 kcal less than predicted maintenance calories,³¹ independent of the exercise program to which they were assigned. There were no specific recommendations regarding macronutrient intake, with a general orientation toward the nutritional guidelines from the American Heart Association. Meal replacement plans were not used.

The exercise prescription for the high-caloric CR group emphasized longer-duration, lower-intensity, and more-frequent walking (45-60 min vs 25-40 min per session) than that of the standard CR group.³² Walking was the preferred exercise modality to maximize caloric expenditure over weight-supported exercises (cycling or rowing), which burn fewer calories.³³ The high-caloric exercise group had a weekly physical activity expenditure goal of ≥3,000 to 3,500 kcal/wk, attained after 2 to 4 weeks of gradually lengthening exercise bouts. After performing all sessions under supervision at the cardiac rehabilitation center for

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2 weeks, high-caloric exercise subjects performed 2 to 4 sessions/wk in the home environment using a heart rate monitor subsequently downloaded at the CR center. Both groups eventually performed 1 to 3 sessions/wk under supervision at the cardiac rehabilitation center with home exercise logs. The standard CR group exercise protocol included 25 min of treadmill walking and 8 min on two of three ergometers: cycle, rowing, or arm.

Body Composition and Coronary Risk Factors

Body composition measures included body weight, BMI, waist circumference, fat mass, and fat-free mass by dual-energy x-ray absorptiometry, as described previously³⁴ (General Electric Lunar Prodigy; Madison, Wisconsin). Abdominal visceral and subcutaneous fat area was measured by CT scanning (General Electric Medical Systems; Milwaukee, Wisconsin; and Philips Electronics NV; Eindhoven, The Netherlands). Physical activity energy expenditure was measured over 7 days using the doubly labeled water technique.³⁵ Additionally, physical activity was measured over the same 7-day period using a Caltrac accelerometer (Muscle Dynamics; Torrance, California).

Coronary risk factors assessed included insulin-stimulated glucose disposal, insulin, glucose, lipid profiles, resting BP, and high-sensitivity C-reactive protein. BP was measured three times after a 5-min seated rest with a Dinamap automated BP cuff (GE Healthcare; Waukesha, Wisconsin). Insulin-stimulated glucose disposal was determined after an overnight fast, using the euglycemic hyperinsulinemic clamp technique.³⁶ Testing was preceded by 3 days of standardized meals consisting of 200 to 250 g carbohydrate and 12 g fiber per 1,000 kcal/d. Insulin-stimulated glucose uptake, an index of insulin sensitivity, was the average dextrose infusion rate during the final 30 min of the 3-h clamp plus residual endogenous glucose production expressed relative to fat-free mass. High-sensitivity C-reactive protein was measured using a colorimetric enzyme-linked immunosorbent assay. Isolated values of ≥ 10 mg/dL (three of 74 at baseline) were eliminated from analysis unless they were elevated both before and after the 5-month intervention (one of 71). Peak $\dot{V}O_2$ was measured during a symptom-limited treadmill test using a graded modified-Balke protocol until volitional fatigue, cardiovascular symptoms, symptomatic arrhythmias, or ≥ 2 mm ECG ST segment depression. Expired gas was analyzed using a SensorMedics Vmax 29c (Yorba Linda, California) with measurement of peak $\dot{V}O_2$ in mL O_2 /kg/min. Dietary macronutrient intake was assessed using 3-day dietary diaries, as described previously.²³

Vascular Measures

Brachial artery FMD was measured using two-dimensional ultrasonography (General Electric Vivid 7; GE Healthcare; Little Chalfont, England) with a linear 10-MHz high-resolution probe. Measurements were taken with the patient supine for ≥ 10 min in a quiet room, after an overnight fast, and morning medications were not taken. The brachial artery was visualized in a longitudinal section, and baseline B-mode and Doppler images were obtained and diameter measurements made. Subsequently, an adult BP cuff was placed on the upper arm and inflated to 50 mm Hg above the systolic BP for 5 min. After deflation, flow measures were taken at 15 s and diameter measures were taken at 60 s by tracing a still frame of a 1-cm segment of the brachial artery at the R wave, using off-line electronic calipers during reactive hyperemia; these measures were interpreted by a single reader blinded to treatment and study phase. Vasodilatory capacity was expressed as the percentage change in brachial artery diameter from baseline to 60 s post-cuff deflation. After 15 min of rest, repeat baseline measurements were taken. The patient was then

administered 0.4 mg nitroglycerin sublingual spray, and 3 min later flow and diameter measurements were repeated to examine endothelial-independent vasodilatation. All images were digitized and recorded for study measurements, and techniques followed published guidelines.²⁹

Statistical Analysis

Repeated-measure analysis of variance was used to determine overall treatment efficacy and to examine secondary outcomes between the two groups. A two-sided *P* value of $< .05$ indicated statistical significance. Analyses were based on all subjects who remained in the study at the 5-month time point, without imputation of missing values. Regression analysis was used to explore factors associated with change in vasodilatory capacity. Multivariate analysis of variance was conducted to analyze independent effects of physiologic characteristics on change in vasodilatory capacity.

RESULTS

There were no dropouts during the weight loss/exercise rehabilitation intervention among the 38 subjects described in this study. These individuals were the patients numbered 37 to 74 in the initial randomized trial of exercise and weight loss in 74 overweight individuals with CHD.²³ These 74 were chosen from a pool of 116, with 22 excluded for not meeting inclusion criteria, 11 declining to participate, and nine not able to make appropriate time commitments. Subjects were randomized to either high-caloric-expenditure exercise ($n = 23$) or standard CR exercise ($n = 15$), with both groups participating in similar programs of dietary counseling. At baseline, the two study groups had similar BMI, body weight, fat mass, fat-free mass, waist circumference, intraabdominal fat, glucose disposal, insulin levels, baseline diameter of the brachial artery, and % brachial artery vasodilatation after cuff occlusion and release (Table 1). The high-caloric exercise group had higher baseline measures of total cholesterol and triglycerides (Table 2). Medication use did not differ by group. These included aspirin (100%), statins (90%), β -blockers (76%), angiotensin inhibitors/blockers (29%), and clopidogrel (61%).

The high-caloric-exercise expenditure group lost more weight (8.6 ± 4.1 kg vs 2.3 ± 3.3 kg) and exhibited a greater decrease in fat mass, waist circumference, total and intraabdominal fat, triglycerides, cholesterol/high-density lipoprotein cholesterol ratio, and insulin levels than was seen in the standard CR group (Tables 1, 2).²³ Both groups decreased their daily caloric intake by roughly 300 kcal/d from baseline to 4 months, and there was no difference between groups at baseline or at 4 months in percentage of macronutrients taken as carbohydrate, fat, or protein.

Endothelial-dependent vasodilatory capacity, expressed as the extent (%) of change in brachial artery

Table 1—Body Composition Response

	Total Population (N = 38)			High-Caloric Exercise (n = 23)			Standard Cardiac Rehabilitation (n = 15)		
	P Value Within Group			P Value Within Group			P Value Within Group		P Value Between Groups
	Baseline	5 Mo		Baseline	5 Mo		Baseline	5 Mo	
Age, y	64 ± 9	...	...	66 ± 9	...	...	62 ± 9	...	...
Male (female)	30 (8)	...	...	17 (6)	...	...	13 (2)	...	...
Body weight, kg	94.5 ± 14.9	88.4 ± 14.7	< .001	92.3 ± 16.2	83.7 ± 14.6	< .001	97.7 ± 13.9	95.4 ± 14.3	< .001
BMI, kg/m ²	32.3 ± 4.1	30.2 ± 4.2	< .001	32.2 ± 3.7	29.3 ± 3.7	< .001	32.5 ± 4.5	31.7 ± 4.5	< .001
Fat mass, kg	33.0 ± 7.8	28.9 ± 8.1	< .001	33.1 ± 7.6	27.4 ± 8.1	< .001	32.9 ± 4.0	31.2 ± 8.1	< .005
Fat-free mass, kg	58.6 ± 12.4	56.5 ± 11.1	< .002	56.5 ± 13.7	53.6 ± 11.6	< .002	61.8 ± 9.9	60.9 ± 8.9	< .05
Waist circumference, cm	111 ± 25	105 ± 25	< .001	110 ± 25	103 ± 26	< .001	113 ± 28	110 ± 25	< .003
Total abdominal fat, cm ²	584 ± 133	492 ± 138	< .001	599 ± 136	478 ± 137	< .001	562 ± 131	514 ± 139	< .003
Intraabdominal fat, cm ²	248 ± 82	201 ± 75	< .001	260 ± 84	193 ± 74	< .001	230 ± 79	213 ± 76	< .002

Data are presented as mean ± SD unless indicated otherwise.

diameter post cuff deflation, increased in both study groups (each, $P < .05$) but to a greater degree ($P < .05$) in the high-caloric-exercise expenditure group, which lost more weight (Fig 1, Table 3). There was no difference between groups in hyperemic blood flow (Table 3), nor was there a difference between groups in endothelial-independent vasoreactivity, because both groups responded similarly to nitroglycerine (Table 3).

In the combined study population, we found significant univariate correlations between the extent of change in brachial artery diameter and change in body weight, change in fat mass, change in total visceral abdominal fat, change in total abdominal fat (visceral and subcutaneous), change in physical activity (Caltrac), and change in insulin levels (each, $P \leq .05$, Table 4). By using these same variables in a multivariate analysis, the only independent predictor of change in brachial artery diameter was change in body weight, although we acknowledge that the statistical power of the multivariate analysis was limited by the relatively small sample size. Change in FMD by quintiles of weight loss is shown in Figure 2. Because the high-caloric-expenditure exercise group had higher baseline measures of serum triglycerides and low-density lipoprotein cholesterol, we adjusted for these baseline differences, and this did not show a change in any of the relationships described here.

DISCUSSION

The primary finding of this study is that weight loss and exercise in overweight patients with CHD result in a significant improvement in brachial artery FMD in a dose-response fashion. The improvement in FMD in the overall study group (+ 2.7%) was similar in magnitude to that seen with a statin medication in patients with CHD (+ 2.1%).¹³ We also note that the best predictor of the improvement in FMD was weight loss per se, rather than related measures such as changes in fat mass, visceral fat, or waist circumference, or changes in insulin sensitivity, physical activity, or peak VO_2 . We suspect that the reason for this is that weight reduction results in a multiplicity of risk-factor effects and thus, as a multirisk intervention, serves as an integrated determinant of endothelial function and, potentially, long-term clinical outcomes.^{23,32} We note that the goal of the study was not to determine whether it was exercise vs weight loss that was cause of the improvement in vasodilatory capacity; rather, it was to determine if a new strategy of high-caloric-expenditure exercise and behavioral weight loss results in a greater improvement in vasodilatory capacity than does the “old” or “standard” CR strategy of lower-caloric-expenditure exercise and little to no weight loss. Thus, this was

Table 2—Fitness, Physical Activity, and Cardiovascular Risk Factor Response by Group

	Total Population (N = 38)			High-Calorie Exercise (n = 23)			Standard Cardiac Rehabilitation (n = 15)		
	P Value Within Group		P Value Between Groups	P Value Within Group		P Value Between Groups	P Value Within Group		P Value Between Groups
	Baseline	5 Mo		Baseline	5 Mo		Baseline	5 Mo	
Peak oxygen uptake, mL O ₂ /kg/min	21.9 ± 5.7	23.8 ± 7.1	<.006	22.3 ± 6.6	23.5 ± 8.0	.17	21.4 ± 4.1	24.3 ± 5.9	.20
Accelerometer physical activity, kcal/d	291 ± 85	634 ± 232	<.001	291 ± 100	799 ± 132	<.001	289 ± 56	381 ± 50	.001
Doubly labeled H ₂ O total activity, kcal/d	809 ± 513	1347 ± 624	<.001	751 ± 484	1443 ± 674	<.001	895 ± 560	1179 ± 507	.003
High-sensitivity C-reactive protein, ng/mL	3.2 ± 4.4	2.9 ± 3.7	.43	3.4 ± 4.9	2.9 ± 4.2	.44	2.8 ± 3.5	2.8 ± 2.8	.59
Total cholesterol, mg/dL	149 ± 34	146 ± 32	.53	158 ± 37	153 ± 35	.27	134 ± 24	137 ± 24	.68
Triglycerides, mg/dL	125 ± 70	105 ± 60	<.04	149 ± 80	113 ± 67	<.02	90 ± 26	93 ± 47	.71
HDL cholesterol, mg/dL	41 ± 12	45 ± 11	<.001	39 ± 10	45 ± 10	.002	44 ± 15	47 ± 14	.11
LDL cholesterol, mg/dL	83 ± 25	81 ± 22	.48	89 ± 28	85 ± 25	.40	73 ± 16	73 ± 17	.53
Insulin, μIU/mL	18.8 ± 7.5	14.7 ± 7.1	<.001	19.3 ± 7.9	13.1 ± 6.1	<.001	18.1 ± 7.2	17.1 ± 7.9	.50
Glucose, mg/dL	97 ± 11	94 ± 14	.22	94 ± 12	89 ± 9	<.02	101 ± 8	101 ± 18	.96
Glucose disposal, mg/FFM/min	7.0 ± 2.9	8.7 ± 3.5	<.001	6.8 ± 3.0	9.1 ± 3.4	<.001	7.2 ± 2.8	8.2 ± 3.5	.11
Systolic BP	133 ± 18	127 ± 23	<.06	132 ± 18	126 ± 28	.26	135 ± 22	127 ± 15	.06
Diastolic BP	74 ± 9	69 ± 8	<.004	73 ± 10	67 ± 7	.006	75 ± 8	71 ± 9	.25
Mean BP	94 ± 12	88 ± 11	<.003	93 ± 12	87 ± 12	<.006	95 ± 12	90 ± 9	.09

Data are presented as mean ± SD. FFM = fat-free mass; H₂O = water; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

FIGURE 1. Change in FMD by study group ($\pm$ SD). CR = cardiac rehabilitation; Ex = exercise; FMD = flow-mediated dilatation; Mths = months.

also a comparative effectiveness study of a new approach to CR exercise and weight loss.

Endothelial-dependent vasodilatory capacity is a reflection of overall endothelial function and is adversely affected by the development of atherosclerosis. It is also a factor related to plaque progression and to the occurrence of atherosclerotic complications.¹⁶⁻¹⁹ Several studies have shown that endothelial-dependent vasodilatory capacity is a strong predictor of prognosis in individuals with established atherosclerotic vascular disease.¹⁶⁻¹⁹ In subjects without clinical vascular disease, endothelial dysfunction has been shown to occur in the presence of several cardiac risk factors, including diabetes, insulin resistance, hypertension, hyperlipidemia, and obesity.³⁷ Endothelial dysfunction has also been shown to be a reversible disorder following interventions such as cholesterol-lowering, antihypertensive therapy, exercise training, and weight loss.^{12,13,15,38} To our knowledge, our study is the first to demonstrate that weight loss has a dose-response effect on FMD when superimposed on exercise training in overweight patients with CHD. It is notable that our findings were demonstrated with patients taking prescribed preventive medications such as 3-hydroxy-3-methylglutaryl CoA reductase inhibitors, aspirin, and β -adrenergic blocking agents, such that preventive benefits would be expected to supplement the benefits of these medications.

The strengths of this study include the sophisticated methodologies used to measure body composition, body fat distribution, glucose disposal, physical activity, and physical fitness. Additionally, we note that compliance with the study interventions was extremely high, with no study dropouts, and patients were studied while taking their usual medications.

Table 3—Vascular Response by Group

	Total Population			High-Caloric Exercise			Standard Cardiac Rehabilitation			P Value Between Groups
	P Value Within Group			P Value Within Group			P Value Within Group			
	Baseline	5 Mo		Baseline	5 Mo		Baseline	5 Mo		
Baseline diameter, mm	5.34 ± 0.07	5.35 ± 0.07	.79	5.28 ± 0.08	5.28 ± 0.07	.93	5.44 ± 0.06	5.46 ± 0.06	.30	.26
Postinflation FMD, mm	5.51 ± 0.07	5.66 ± 0.07	.001	5.43 ± 0.08	5.62 ± 0.08	.006	5.63 ± 0.07	5.71 ± 0.06	.05	.05
% change FMD	3.2 ± 3.8	5.9 ± 3.7	.001	2.9 ± 3.6	6.5 ± 3.5	.0004	3.6 ± 4.1	4.9 ± 3.8	.04	.05
Hyperemic flow volume, mL/s	105 ± 75	99 ± 46	.79	100 ± 83	112 ± 60	.62	94 ± 39	109 ± 58	.62	.86
Baseline diameter	5.34 ± 0.07	5.4 ± 0.08	.32	5.2 ± 0.08	5.33 ± 0.09	.17	5.54 ± 0.06	5.52 ± 0.06	.77	.16
Postinflation FID	5.72 ± 0.08	5.81 ± 0.08	.22	5.72 ± 0.08	5.73 ± 0.09	.68	5.95 ± 0.07	5.92 ± 0.06	.79	.92
% change FID	7.4 ± 2.7	7.8 ± 3.4	.33	7.3 ± 2.9	7.9 ± 3.7	.29	7.4 ± 2.4	7.6 ± 3.0	.77	.91

Data are presented as mean ± SD. FID = flow-independent dilatation (after administering nitroglycerin); FMD = flow-mediated dilatation.

Table 4—Correlates With Percentage Change (Δ) of Flow-Mediated Dilatation

	R	R ²	P Value
Δ Weight ^a	0.45	0.18	.005
Δ BMI	0.45	0.18	.005
Δ Visceral fat (CT scan)	0.4	0.14	.01
Δ Fat mass (DEXA scan)	0.37	0.11	.02
Δ Physical activity (accelerometer)	0.35	0.10	.04
Δ Total abdominal fat mass (CT scan)	0.33	0.08	.05
Δ Insulin	0.32	0.08	.05
Δ % body fat	0.28	0.05	.09
Δ M value	0.26	0.04	.11
Δ Waist	0.26	0.04	.11
Δ Physical activity (doubly labeled water)	0.26	0.04	.15

DEXA = dual-energy x-ray absorptiometry; M value = insulin-stimulated glucose disposal.

^aBy multivariate analysis, the only independent predictor of change in brachial artery diameter was change in body weight ($R = 0.46$; $R^2 = 0.19$; $P < .005$).

The limitations of this study include the fact that endothelial-dependent vasodilatory capacity was not measured in all patients, but rather in patients 37 to 74 of the 74 total initial study participants.²³ This limits the statistical power to assess correlates of the improvement in FMD but does not negate our primary finding of a dose-response relationship to degree of weight loss. We also note that with only 13 women undergoing the FMD measures, a gender comparison was not possible.

The results from this study suggest that change in body weight should be considered an important clinical outcome in CR programs,³⁻⁵ and substantial efforts should be directed toward maximizing weight reduction for overweight patients with CHD. These should include maximization of exercise-related energy expenditure in CR and adoption of a hypocaloric diet using behavioral techniques.³² We found a dose-response relationship between weight loss and endothelial-dependent flow-mediated vasodilation, a powerful predictor of clinical outcomes in patients

FIGURE 2. FMD by quintiles of weight loss ($\pm$ SD). See Figure 1 legend for expansion of the abbreviation.

with CHD. Currently used approaches to CR exercise and counseling do not result in significant weight reduction and likely need to be altered to optimize long-term outcomes.³²

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Dr Ades: contributed to obtaining funding for the study and the primary writing of the manuscript.

Mr Savage: contributed to the conception of the study design, writing of the manuscript, and as the study coordinator and exercise physiologist.

Dr Lischke: contributed to the writing of the manuscript, literature review, and statistical analyses.

Dr Toth: contributed to the study design, writing of the manuscript, and measurement and interpretation of physiologic variables.

Dr Harvey-Berino: contributed to the behavioral weight loss intervention and writing of the manuscript.

Dr Bunn: contributed to the writing, revision, review, and approval of the manuscript; and statistical analyses and interpretation of data.

Ms Ludlow: contributed to the study dietary intervention, collection of compliance data, and writing of the manuscript.

Dr Schneider: contributed to the study design, writing of the manuscript, and measurement of blood work analyses.

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