Sequential Effects of Aerobic Exercise Training and Weight Loss on Risk Factors for Coronary Disease in Healthy, Obese Middle-Aged and Older Men

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The relative benefits of weight loss (WL) versus aerobic exercise training (AEX) on cardiac risk factors in obese individuals remain controversial. In this study, we examined the effects of the sequential interventions of 9 months of AEX followed by weight loss with continued AEX (AEX + WL) on cardiac risk factors in 21 obese (body fat, 29.5% ± 0.8%, mean ± SEM) middle-aged and older men. AEX increased the maximal aerobic capacity ([$\dot{V}O_2$max] in liters per minute) of these men by 14% ($P < .001$), with no significant change in weight. AEX did not improve blood pressure (BP) or oral glucose tolerance, and had no significant effect on lipid concentrations. During the AEX + WL intervention, the 21 men lost 8.1 ± 0.6 kg. Despite continued training, there was no further increase in $\dot{V}O_2$max during this intervention. Compared with AEX, AEX + WL decreased glucose and insulin responses during the oral glucose tolerance test (OGTT) by 8% ($P < .05$) and 30% ($P < .01$), respectively. AEX + WL reduced plasma triglyceride (TG) by 17% ($P < .05$) and low-density lipoprotein cholesterol (LDL-C) by 8% ($P < .01$) and increased high-density lipoprotein cholesterol (HDL-C) by 11% (3.7 mg/dL, $P < .01$). The sequential interventions resulted in a 20% decrease in the LDL-C/HDL-C ratio. The results demonstrate that AEX + WL had a more substantial impact than AEX alone on glucose tolerance and lipoprotein concentrations. Physicians should encourage obese patients to become physically active and lose weight to improve their cardiac risk factor profile.

OBESITY AND PHYSICAL INACTIVITY, risk factors for diabetes mellitus and cardiovascular disease (CVD), are prevalent in the adult population.[1,2] Based on the 85th-percentile value for body mass index (BMI) in persons aged 20 to 29 years, approximately one third of the adult US population is overweight.[2] Furthermore, the prevalence of obesity in the United States is increasing.[3] Data from the 1994 Behavioral Risk Factor Surveillance System survey also indicate that greater than one third of overweight men and women are inactive during their leisure time.[1,3] It is also noteworthy that the proportion of inactive overweight individuals increases with increasing age[4] and degree of obesity. As a result, weight loss (WL) and regular physical activity are widely advocated to improve overall health and reduce the risk for heart disease.[1,5-7]

We recently reported the results of a randomized clinical trial comparing the effects of WL versus aerobic exercise training (AEX) on CVD risk factors in healthy, obese middle-aged and older men.[8] In general, WL resulted in more substantial improvements in lipoprotein lipid concentrations, glucose tolerance, and blood pressure (BP) than AEX. It was our intent, using a Latin square design, that upon completion of the first randomly assigned intervention, the men would be enrolled in a second complementary intervention, ie, continued AEX plus WL (AEX + WL) or WL plus AEX. These sequential interventions provide information on the relative contributions of WL and increased maximal aerobic capacity ($\dot{V}O_2$max) to metabolic function in the same subject. Results from the sequential interventions can then be compared with information obtained in the cross-group comparisons involving different subjects. In this report, we present data on the effects of the sequential interventions of AEX and AEX + WL on CVD risk factors in obese middle-aged and older men.

SUBJECTS AND METHODS

Subjects

The study was approved by the University of Maryland and Johns Hopkins Bayview Medical Center Human Studies Institutional Review Boards, and all subjects provided informed consent prior to participation. As previously reported, healthy, nonsmoking, sedentary obese (120% to 160% of ideal body weight) male volunteers aged 46 to 80 years were recruited from the Baltimore-Washington metropolitan area for participation in a randomized clinical trial to compare the effects of WL alone versus AEX not accompanied by WL on cardiac risk factors.[8-11] After a review of their medical histories, nonsmoking men without a history of diabetes, hypertension, hyperlipemia, or coronary artery disease had a physical examination and measurement of the blood chemistry. Additional exclusion criteria included hypertension (BP > 160/95 mm Hg), hyperlipidemia defined as plasma triglyceride (TG) or low-density lipoprotein cholesterol (LDL-C) greater than the 90th percentile for age and gender according to the Lipid Research Clinics criteria,[12] or fasting glucose greater than 140 mg/dL. An exercise treadmill test[13] was also performed to exclude subjects with asymptomatic exercise-induced ischemia.[14] Forty-four of 73 men randomized to WL and 49 of 71 men randomized to AEX completed the intervention. Upon completion of the first intervention, the men were enrolled in the second intervention: continued aerobic training plus weight loss or continued weight loss plus aerobic training. Twenty-two men who completed AEX entered AEX + WL, whereas only five of 44 men who completed WL entered the AEX intervention. There were no significant differences in baseline characteristics of subjects who completed the sequential interventions compared with subjects who did not complete them. In this study, we report data on the 21 men who completed the sequential interventions of AEX followed by AEX + WL.

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Study Protocol

Prior to baseline testing, the men were instructed for 3 months on the principles of an isocaloric American Heart Association (AHA) phase I diet.[15] They were told not to lose weight or change their level of physical activity. Adherence to the AHA diet was monitored by 24-hour recall and analysis of 3- and 7-day food records. To further ensure dietary stability during metabolic testing, subjects were provided a 6-day weight-maintaining AHA phase I diet of composition comparable to their own AHA phase I diet. All participants were weight-stable (±0.5 kg) for 6 days during testing.

After completion of baseline testing, the men entered a 9-month aerobic exercise program. Subjects trained at our facility on treadmills and cycle ergometers for 45 minutes three times per week. The initial exercise intensity was set at 50% to 60% of the subjects' heart rate reserve, and the target heart rate during exercise was monitored by palpation. Exercise intensity was gradually increased to 70% to 80% of the heart rate reserve, and duration to 30 to 45 minutes of continuous exercise. The goal was for the men to increase their $\dot{V}O_2$max by 10% while maintaining their body weight and continuing the AHA phase I diet. By design, to maintain their initial body weight, on average, subjects were instructed to consume an additional 200 to 300 kca/d to compensate for increased energy expenditure during exercise. Attendance was good throughout the study, with greater than 85% of the men exercising three times per week at our facility. After 9 months, subjects were stabilized for 1 month at their new $\dot{V}O_2$max before reevaluation. The men were again provided weight-maintaining AHA phase I diets for 6 days during retesting. Metabolic studies were performed 24 to 36 hours after the last exercise session.

After completion of the post–exercise intervention testing, the men entered a WL intervention in which they attended weekly group WL sessions. The subjects also continued to exercise three times per week at our facility. They were instructed to consume 300 to 500 fewer calories per day (hypocaloric AHA phase I diet). The goal was for the men to decrease their body weight by greater than 10% over a 9-month period. After 9 months, the men were stabilized at their new weight for 1 month before retesting. Food records were reviewed to ensure compliance to the diet. At the time of retesting, the men were again provided weight-maintaining AHA phase I diets for 6 days. Metabolic studies were performed 24 to 36 hours after the last bout of exercise.

Analytical Methods

BMI was calculated as body weight in kilograms divided by the square of the height in meters. Percent body fat was determined by hydrostatic weighing.[16] Fat-free mass was calculated as body weight minus fat mass. The waist circumference and the waist to hip ratio (WHR), measured as the minimal abdominal circumference divided by the circumference at the maximal gluteal protuberance, were used as indices of body fat distribution. Resting BP was determined before the oral glucose tolerance test (OGTT) with the subject seated after 5 minutes of rest. Brachial artery pressure in the right arm was determined indirectly using a standard sphygmomanometer and stethoscope. The first- and fifth-phase Korotkoff sounds were used as the systolic and diastolic BP. Three measurements were made, and reported values are the average of the last two measurements.

$\dot{V}O_2$max was determined using a modified Balke protocol as previously described.[9] The grade was increased every 2 minutes until the subject was exhausted and could not continue. $\dot{V}O_2$max tests fulfilled at least two of the following three criteria: heart rate at maximal exercise greater than 95% of the age-adjusted maximal heart rate (220 − age), respiratory exchange ratio greater than 1.10, and a plateau in oxygen uptake achieved on the basis of a change in $\dot{V}O_2$ of less than 0.2 L/min during the final two oxygen collections. $\dot{V}O_2$max is expressed in liters per minute.

Blood samples were drawn into chilled EDTA (1 mg/mL blood) tubes after a 12- to 14-hour overnight fast on days 4 and 6 of the controlled metabolic diet. On day 4 of the metabolic diet, an OGTT was performed.[17] Samples were drawn every 30 minutes over a 2-hour period for measurement of plasma glucose and insulin levels using the glucose oxidase method and a radioimmunoassay, respectively. Two-hour total glucose and insulin areas were calculated using the trapezoidal method. One of the subjects with a normal fasting glucose level had a diabetic response (2-hour glucose > 200 mg/dL) during the OGTT.

Plasma TG and cholesterol levels were measured enzymatically on an Abbott ABA 200 series bichromatic analyzer (Abbott Laboratories, Irving, TX).[9] High-density lipoprotein cholesterol (HDL-C) levels were measured in the supernatant after precipitation of apolipoprotein B–containing lipoproteins with dextran sulfate.[18] A second precipitation with high–molecular weight dextran sulfate was performed on the supernatant HDL to separate HDL_2-C and HDL_3-C subfractions.[19] The LDL-C level was calculated using the Friedewald equation.[20] Coefficients of variation of internal-standard control samples for separate assays of TG, cholesterol, and HDL-C were 3.1%, 2.8%, and 3.8%, respectively. Reported values are the mean from blood samples drawn on 2 separate days.

Statistical Methods

Insulin levels following glucose ingestion were not normally distributed, and were $\log_{10}$-transformed before parametric analysis. The effect of a given intervention, ie, AEX or AEX + WL, on the outcome variables was examined using paired *t* tests. Repeated-measures ANOVA was also used to compare variables across three time points: baseline, post-AEX, and post-AEX + WL. For variables for which the ANOVA was significant, Scheffe's F test was used to identify significantly different pairs of means. Pearson product-moment correlation coefficients (*r*) were calculated. All results are expressed as the mean ± SEM. Differences with *P* less than .05 were considered significant.

RESULTS

Effects of the AEX Intervention

Baseline values for the 21 men are summarized in Table 1. The men were moderately obese, with a mean BMI of 29.7 ± 0.6 kg/m^2 and 29.5% ± 0.8% body fat. The waist circumference of 104 ± 2 cm and WHR of 0.97 ± 0.01 are indicative of an abdominal distribution of body fat. The mean $\dot{V}O_2$max of 2.64 ± 0.13 L/min is consistent with the subjects' sedentary life-style.

On average, after the intervention of AEX alone, the subjects increased their $\dot{V}O_2$max by 14% (+0.38 ± 0.02 L/min; range, −0.06 to 1.39; $P < .001$; Table 1 and Fig 1). Twelve of the 21 men increased their $\dot{V}O_2$max by greater than 10%. By design, there were no overall changes in weight with exercise training, nor were there significant changes in waist circumference or WHR with training (Table 1). However, there was a small decline in percent body fat and an increase in fat-free mass with exercise training ($P < .05$).

Overall, AEX had little impact on CVD risk factors (Table 2). With AEX, there were no significant changes in systolic or diastolic BP (Fig 2), glucose tolerance (Fig 3), or lipoprotein lipid concentrations (Fig 4).

Effects of the AEX + WL Intervention

On average, the 21 men lost 8.1 ± 0.5 kg. Compared with their baseline values, the range of WL was 3.6 to 14.0 kg, resulting in significant mean decreases in percent body fat, fat mass, waist circumference, and WHR (Table 1 and Fig 1).

Table 1. Physical Characteristics of the Subjects at Baseline and After Intervention (n = 21)

Characteristic	Baseline	AEX	AEX + WL	Difference	
				AEX − Baseline	AEX + WL − AEX
Age (yr)	59 ± 2				
Weight (kg)	90.4 ± 2.3	90.3 ± 2.2	82.2 ± 2.0†	−0.1 ± 0.4	−8.1 ± 0.6‡
BMI (kg/m²)	29.7 ± 0.6	29.7 ± 0.6	27.1 ± 0.5†	0.0 ± 0.1	−2.6 ± 0.1‡
Body fat (%)	29.5 ± 0.8	28.6 ± 0.8*	23.4 ± 0.8†	−0.9 ± 0.4	−5.2 ± 0.6‡
Waist (cm)	103.7 ± 1.6	103.2 ± 1.6	95.3 ± 1.7†	−0.5 ± 0.7	−7.9 ± 0.9‡
WHR	0.97 ± 0.01	0.97 ± 0.01	0.94 ± 0.01†	0.0 ± 0.01	−0.03 ± 0.01‡
$\dot{V}O_2$max (L/min)	2.64 ± 0.13	3.02 ± 0.13†	3.04 ± 0.17	0.38 ± 0.08‡	0.02 ± 0.06
Systolic BP	128 ± 3	126 ± 4	124 ± 4	−2 ± 2	−2 ± 2
Diastolic BP	81 ± 2	80 ± 3	77 ± 2	−1 ± 1	−3 ± 3

NOTE. Data are the mean ± SEM.
*$P < .05$ *v* baseline.
†$P < .01$ *v* AEX.
‡$P < .05$.

Despite their continued training, there was no further increase in $\dot{V}O_2$max. Systolic and diastolic BP did not change with WL (Fig 2).

Although there were no significant changes in either fasting glucose or insulin concentrations, after AEX + WL there were significant reductions in post–glucose load plasma glucose and insulin levels (Table 2 and Fig 3); the 2-hour glucose area decreased by 8% ($P < .05$) and the 2-hour insulin area decreased by 30% ($P < .01$). The 30% change in 2-hour insulin area with AEX + WL was significant ($P < .05$) compared with the nonsignificant change in 2-hour insulin with AEX alone. Compared with the baseline values, the 2-hour insulin area decreased by 38% ($P < .001$). This improvement in glucose and insulin levels is consistent with an increase in insulin sensitivity.

Compared with the AEX values, AEX + WL further reduced plasma TG by 17% ($P < .05$) and LDL-C by 8% ($P < .01$; Table 2 and Fig 4). In response to AEX + WL, plasma HDL-C increased by 11% (3.7 mg/dL, $P < .01$) and HDL_2-C by 59% (1.6 mg/dL, $P < .01$). The changes in total cholesterol and HDL-C concentrations with AEX + WL were significant ($P < .05$) when compared with the nonsignificant changes with AEX alone. Even more substantial improvements in lipoprotein lipid profiles occurred compared with the baseline values: plasma TG decreased by 27% ($P < .001$) and plasma HDL-C increased by 16% (5.3 mg/dL, $P < .001$). Thus, at completion of the sequential interventions, the LDL-C/HDL-C ratio decreased by 20% ($P < .001$), the total cholesterol to HDL-C ratio decreased by 19% ($P < .001$), and the non–HDL-C/HDL-C ratio decreased by 22% ($P < .001$).

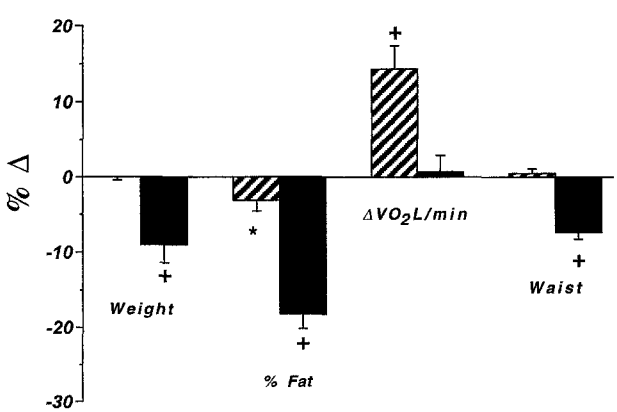

Fig 1. Relative change (% Δ) (post intervention *v* baseline) of the sequential effects of AEX alone (▨) followed by AEX + WL (■) on body composition and $\dot{V}O_2$max. Data are the mean ± SEM. *$P < .05$, †$P < .01$.

Correlational Analyses

In univariate analyses, there were significant relationships between the initial TG concentration and the overall change in TG concentration with the sequential interventions ($r = -.74$, $P < .0001$) such that individuals with the highest baseline TG levels had the largest improvement in TG with intervention. By contrast, there were no significant relationships between the initial values for the other lipoprotein lipids and the overall change in the values. In addition, there were significant relationships between baseline plasma insulin levels ($r = -.63$, $P < .01$) and postload glucose levels ($r = -.70$, $P < .0001$) with the change in those values; individuals with the highest baseline values, demonstrated the greatest improvement with intervention. However, there were no significant relationships between the change in insulin or glucose values and the change in lipoprotein lipids.

The contribution of changes in body composition and $\dot{V}O_2$max to changes in metabolic parameters in response to the sequential interventions was also examined. In univariate analyses, improvements in LDL-C levels correlated with reductions in the waist circumference ($r = .65$, $P < .001$) and WHR ($r = .71$, $P < .001$). The improvement in HDL-C levels was marginally associated with a decrease in WHR ($r = -.41$, $P = .07$). There were no significant relationships between the change in percent body fat or in $\dot{V}O_2$max and changes in any of the metabolic variables.

DISCUSSION

The intent of this study was to determine the sequential effects of improved aerobic fitness and WL on CVD risk factors in obese men. In the first intervention, a 14% increase in $\dot{V}O_2$max not accompanied by a significant change in body weight had a relatively minor impact on metabolic function. By

Table 2. Metabolic Parameters at Baseline and After Intervention (n = 21)

Parameter	Baseline	AEX	AEX + WL	Difference	
				AEX − Baseline	AEX + WL − AEX
Fasting glucose	97.4 ± 3.0	98.5 ± 2.7	97.1 ± 1.8	1.1 ± 1.7	−1.4 ± 2.3
2-h glucose area	17,500 ± 850	18,600 ± 1,000	17,100 ± 650*	1,100 ± 610	−1,500 ± 870
Fasting insulin	11.4 ± 1.1	12.3 ± 1.3	10.0 ± 1.0	0.9 ± 1.0	−2.3 ± 1.3§
2-h insulin area	9,950 ± 1,510	8,600 ± 1,000	6,150 ± 640†	−1,350 ± 900	−2,450 ± 1,110§
TG	124 ± 10	113 ± 8	94 ± 7*	−11 ± 7	−19 ± 7§
Cholesterol	177 ± 7	175 ± 6	166 ± 6†	−2 ± 4	−9 ± 4
HDL-C	33.0 ± 1.3	34.6 ± 1.4	38.3 ± 1.8†	1.6 ± 0.6	2.7 ± 1.3§
HDL_2-C	1.9 ± 0.4	2.7 ± 0.5	4.3 ± 0.8†	0.8 ± 0.3	1.6 ± 0.4§
LDL-C	119 ± 6	119 ± 6	110 ± 6*	0 ± 3	−9 ± 4§
Cholesterol/HDL-C	5.55 ± 0.33	5.22 ± 0.23	4.50 ± 0.24‡	−0.33 ± 16	−0.72 ± 17‖

NOTE. Data are the mean ± SEM. Lipoproteins and fasting glucose are mg/dL, fasting insulin μU/dL, glucose area mg · min/dL, and insulin area μU · min/dL.

*$P < .05$, †$P < .01$, ‡$P < .001$: *v* prior value.

§$P < .05$, ‖$P < .001$: *v* the other intervention.

contrast, in the second intervention, a 9% decline in body weight in combination with continued AEX significantly improved lipoprotein lipid levels and glucose tolerance, but did not change BP. It is noteworthy that the sequential interventions performed in the same individuals and the cross-group comparisons previously reported in the initial phase of the clinical trial[8] provide similar estimates of the relative contributions of increased aerobic fitness and reductions in total and central obesity to improvements in CVD risk factors. In the cross-group comparison, a 10% decrease in body weight was associated with an 18% reduction in TG, a 7% reduction in LDL-C, and a 13% increase in HDL-C, whereas in the current study, a 9% decline in body weight during the WL phase of the current study produced a 17% reduction in TG, an 8% reduction in LDL-C, and an 11% increase in HDL-C. Collectively, these results highlight the importance of reductions in body weight for improving metabolic function and risk factors for CVD.

Després et al[21] have promoted the concept of "metabolic fitness," which they define as "the state of a set of metabolic variables relevant to coronary heart disease risk and affected by the level of physical activity," which must be distinguished from "cardiorespiratory fitness."[21] In their paradigm, low-intensity endurance exercise and the associated loss of weight and body fat can improve CVD risk factors through mechanisms that are independent of exercise-induced changes in cardiorespiratory fitness. Therefore, prolonged low-intensity exercise can result in substantial improvements in metabolic fitness even in the absence of changes in $\dot{V}O_2max$. Indeed, the present study supports this concept. There was a dissociation between changes in cardiovascular fitness induced by AEX and improvements in metabolic risk factors for CVD elicited by WL.

The independent effects of AEX on lipoprotein lipid concentrations remain controversial.[22,23] Some studies show significant increases in HDL-C,[24-26] while others report no significant changes.[27,28] Our finding of a nonsignificant increase of 1.6 mg/dL in HDL-C after exercise training agrees with the results of a meta-analysis of 95 studies that demonstrated no significant changes in HDL-C concentration after training.[22] The lack of uniform results from studies examining the effects of exercise training on lipoprotein lipid concentrations may be due to differences in training intensity and the duration of exercise, as well as to whether there were concomitant changes in body composition and dietary composition.[21-23,29-33] Some investiga-

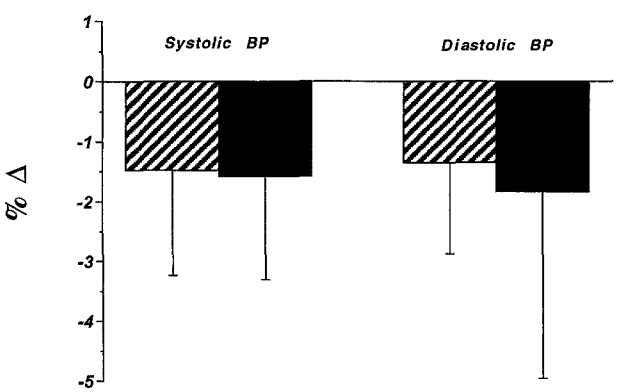

Fig 2. Relative change (% Δ) (postintervention *v* baseline) of the sequential effects of AEX alone (▨) followed by AEX + WL (■) on BP. Data are the mean ± SEM.

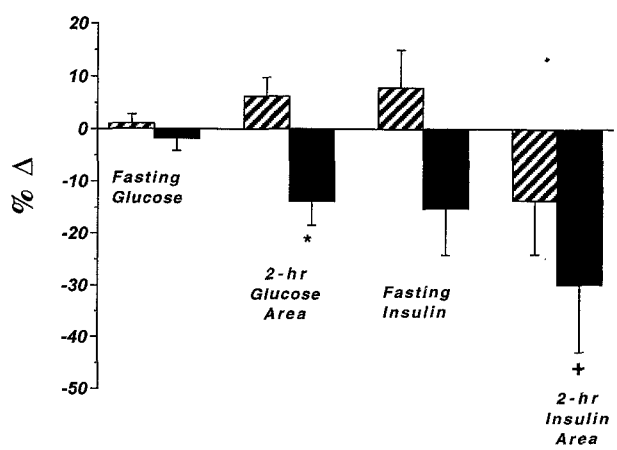

Fig 3. Relative change (% Δ) (postintervention *v* baseline) of the sequential effects of AEX alone (▨) followed by AEX + WL (■) on fasting plasma glucose and insulin concentrations and 2-hour glucose and insulin values during the OGTT. Data are the mean ± SEM. *$P < .05$, †$P < .01$.

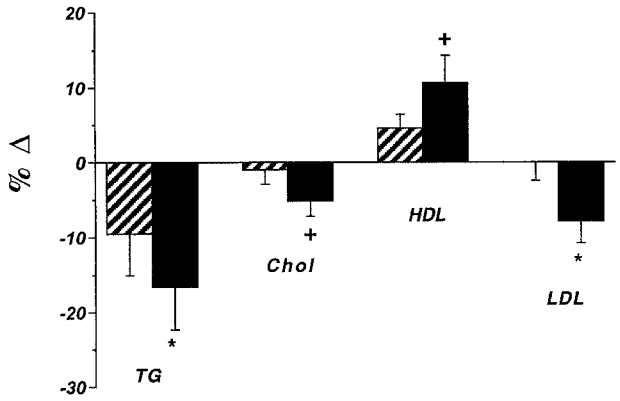

Fig 4. Relative change (% Δ) (postintervention *v* baseline) of the sequential effects of AEX alone (▨) followed by AEX + WL (■) on fasting lipoprotein lipid concentrations. Data are the mean ± SEM. *$P < .05$, †$P < .01$.

tors argue that the effects of AEX on HDL and other lipoprotein lipids are primarily related to the effects of exercise-induced WL. In our study, the improvement in LDL-C concentrations with the sequential interventions correlated with reductions in abdominal adiposity, not $\dot{V}O_2$max. There was also a marginal correlation between improvement in HDL-C levels and a decrease in WHR. The initial degree of obesity and fitness also affects the metabolic response to training. We recently showed that the change in HDL-C and TG levels with AEX is inversely related to the initial degree of obesity,[34] with leaner individuals experiencing greater lipoprotein responses to AEX than obese subjects. Thus, it is likely that our subjects' increased total and central obesity blunted their metabolic response to improved aerobic fitness.

A study by King et al[26] demonstrated that the beneficial effects of AEX on HDL-C concentrations may be delayed in the elderly. In that study, HDL-C concentrations did not increase during the first year of training, whereas after 2 years, the low-intensity home-based exercise program increased HDL-C concentrations by 8%. King et al attributed the changes in HDL-C concentrations that occurred after 2 years of training to exercise-induced changes in body composition. It is therefore possible that some of the benefits that occurred in our study during the AEX + WL intervention were due to the continued AEX, rather than WL per se. Practical constraints prevented us from enrolling a group with only a long-term exercise intervention to directly address this question. However, it is noteworthy that despite their additional 9 months of training, $\dot{V}O_2$max did not increase further in these men. This suggests that the beneficial changes in CVD risk factors that occurred during AEX + WL were due to changes in body composition induced by WL.

Few studies have directly compared the relative efficacy of WL and WL in combination with AEX on cardiac risk factors.[30,31,35] In a study by Wood et al,[30] WL induced either by hypocaloric dieting or by exercise training improved lipoprotein lipid profiles, but there were no significant differences in the lipoprotein lipid changes between the dieters and the exercisers. Prior studies from our laboratory also demonstrate similar effects of WL induced by a hypocaloric diet with and without AEX on lipoprotein lipid concentrations.[35] These two studies suggest that the incremental improvement in lipoprotein profiles attributable to AEX alone in obese subjects losing weight is small. However, there are substantial long-term beneficial effects of AEX on cardiovascular function and of increased caloric expenditure on energy balance.[21] As already noted, overtime, low-intensity endurance exercise and the associated increase in daily energy expenditure can lead to WL that substantially improves metabolic risk factors for CVD, ie, metabolic fitness.[21] Thus, public health recommendations on life-style interventions to reduce the risk for CVD must recognize the importance of exercise training and increased leisure-time physical activity in enabling obese subjects both to successfully lose weight and to maintain the lower body weight.

It is possible that the metabolic benefits of AEX and WL are affected by the order in which the AEX and WL interventions are performed or whether they are performed simultaneously. To address this question, we used a Latin square design in which the order of the WL and AEX intervention was varied. The difficulty in performing these sequential interventions and the time commitment required of the research subjects should be recognized. Enrollment in the first intervention of the randomized clinical trial phase of this research study entailed more than 100 visits to our facility for research testing and exercise training (three times per week for 36 weeks) by each of the participants. It is noteworthy that 22 of 49 men who completed AEX elected to embark on an additional 9 months of visits to our facility as part of the AEX + WL program. By contrast, only five of 44 men who completed the WL intervention elected to enter an AEX intervention. We believe this disparity was due to the overwhelming initial desire of these obese men to lose weight. Men who were originally randomized to the WL group received the intervention that allowed them to pursue this goal, whereas men randomized to AEX did not. If more individuals randomized to WL had entered the AEX intervention, thereby completing the Latin square design, information on whether the order of the WL and AEX intervention affected the incremental benefit of the interventions would be available. Therefore, we cannot definitively answer the question as to whether the order in which the AEX and WL interventions are performed affects the results. The results underscore the challenge of performing long-term life-style intervention studies in humans, where preferences and other psychological factors will affect compliance.

The strengths and limitations of this study warrant discussion. First, we are aware of only one other study, reported in an abstract by Terry et al,[36] that has examined the sequential effects of AEX and WL on lipoprotein lipids. In that study, WL in combination with continued AEX produced additional increases in HDL-C levels compared with the levels in men who continued with AEX alone. Terry et al did not report data on the effects of the sequential intervention on other CVD risk factors. Second, a major strength of this study is the selection of subjects in good health. This minimized the potentially confounding effects of comorbid diseases and medications on metabolic and cardiovascular function. Furthermore, the subjects were instructed on the AHA phase I diet, and the composition of the diets was closely monitored by dietitians, thereby decreasing the effects of dietary heterogeneity on the metabolic responses to intervention. We recognize that the select nature of the

participants limits the generalizability of our results, and conclusions based on their responses to the interventions may not be applicable to other populations. Second, given the inherent limitations in the accuracy of self-reported dietary records, it is possible that there may have been changes in the macronutrient composition of the subjects' diet during the sequential interventions that impacted their metabolic response to the interventions. However, we tried to control for this by carefully monitoring the diets and by providing the subjects with metabolic diets before the study. It is also important to note that since the response to intervention was a function of the initial value, subjects with dyslipidemia, diabetes mellitus, or hypertension might show an even greater response to intervention than the men of this study. Finally, a self-selection bias combined with the high dropout rate could affect the results of the study. However, a post hoc comparison failed to demonstrate any significant differences in baseline characteristics of subjects who completed the sequential interventions compared with subjects who did not.

In summary, these results indicate that the sequential interventions of AEX and WL in combination with continued AEX substantially improve risk factor profiles for CVD in obese men. Based on cardiac risk factor data from the Framingham Heart Study,[37] these changes, if maintained, would decrease their risk for the development of coronary disease by greater than 40%. Longitudinal studies are in progress to determine whether men who completed the sequential interventions of AEX + WL are more successful at maintaining the loss of weight and the favorable risk factor profiles than men who completed only the WL intervention.

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