Aerobic and Strength Training in Concomitant Metabolic Syndrome and Type 2 Diabetes

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[1]Department for Health, University of Bath, Bath, UNITED KINGDOM; [2]School of Kinesiology, Louisiana State University, Baton Rouge, LA; [3]Department of Kinesiology, East Carolina University, Greenville, NC; [4]Division of Cardiology, Duke University Medical Center, Durham, NC; [5]Universidad Europea and Instituto de Investigación Sanitaria Hospital 12 de Octubre (i+12), Madrid, SPAIN; [6]Division of Preventive Medicine, Pennington Biomedical Research Center, Baton Rouge, LA; and [7]Cardiac Rehabilitation and Prevention, Ochsner Clinical School, University of Queensland School of Medicine, John Ochsner Heart and Vascular Institute, New Orleans, LA

ABSTRACT

EARNEST, C. P., N. M. JOHANNSEN, D. L. SWIFT, F. B. GILLISON, C. R. MIKUS, A. LUCIA, K. KRAMER, C. J. LAVIE, and T. S. CHURCH. Aerobic and Strength Training in Concomitant Metabolic Syndrome and Type 2 Diabetes. *Med. Sci. Sports Exerc.*, Vol. 46, No. 7, pp. 1293–1301, 2014. **Purpose**: Concomitant type 2 diabetes (T2D) and metabolic syndrome exacerbates mortality risk; yet, few studies have examined the effect of combining (AER + RES) aerobic (AER) and resistance (RES) training for individuals with T2D and metabolic syndrome. **Methods**: We examined AER, RES, and AER + RES training (9 months) commensurate with physical activity guidelines in individuals with T2D ($n = 262$; 63% female, 44% black). Primary outcomes were change in, and prevalence of, metabolic syndrome score at follow-up (mean and 95% confidence interval [CI]). Secondary outcomes included maximal cardiorespiratory fitness ($\dot{V}O_{2peak}$) and estimated METs from time-to-exhaustion (TTE) and exercise efficiency calculated as the slope of the line between ventilatory threshold, respiratory compensation, and maximal fitness. General linear models and bootstrapped Spearman correlations were used to examine changes in metabolic syndrome associated with training primary and secondary outcome variables. **Results**: We observed a significant decrease in metabolic syndrome scores (P for trend = 0.003) for AER (-0.59, 95% CI = -1.00 to -0.21) and AER + RES (-0.79, 95% CI = -1.40 to -0.35), both being significant ($P \leq 0.02$) versus control (0.26, 95% CI = -0.58 to 0.40) and RES (-0.13, 95% CI = -1.00 to 0.24). This led to a reduction in metabolic syndrome prevalence for the AER (56% vs 43%) and AER + RES (55% vs 46%) groups between baseline and follow-up. The observed decrease in metabolic syndrome was mediated by significant improvements in exercise efficiency for the AER and AER + RES training groups ($P < 0.05$), which was more strongly related to TTE (25%–30%; $r = -0.38$, 95% CI = -0.55 to -0.19) than $\dot{V}O_{2peak}$ (5%–6%; $r = -0.24$, 95% CI = -0.45 to -0.01). **Conclusions**: AER and AER + RES training significantly improved metabolic syndrome scores and prevalence in patients with T2D. These improvements appear to be associated with improved exercise efficiency and are more strongly related to improved TTE versus $\dot{V}O_{2peak}$. **Key Words**: EXERCISE EFFICIENCY, METABOLIC SYNDROME, METABOLIC EQUIVALENTS (METs), AEROBIC AND RESISTANCE TRAINING

It is well recognized that the metabolic syndrome is an independent risk factor for cardiovascular disease, type 2 diabetes (T2D), cancer, and all-cause mortality (1). Individuals with T2D who present with coexisting metabolic syndrome are not only at a higher risk for respective morbidities but also show additional risks for each accrued metabolic syndrome component feature than those without T2D (17,27). Given the system-wide physiological benefits associated with

exercise training, the continued advocacy for exercise training is of paramount importance for individuals presenting with T2D and metabolic syndrome simultaneously.

Research continues to show that a low percentage of individuals meet recommended physical activity guidelines throughout the world and that these statistics deteriorate as one transitions from childhood through adulthood and aging (24). These statistics worsen in the presence of various disease states (19,24). Fundamental to most recommendation statements is the advocacy for aerobic (AER) and, more recently, resistance (RES) (4). Resistance training is an important addition to health care because the combination of these modalities (AER + RES) may be equally, if not more, beneficial to health in some cases (10,30). In 2007, Sigal et al. (30) demonstrated in the DARE trial that AER + RES proved more beneficial in reducing hemoglobin A1c (HbA$_{1c}$) and some components associated with metabolic syndrome than AER or RES alone. However, the time commitment was

approximately 150 min for the AER and RES training groups, respectively, with AER + RES training in DARE for approximately 270 min·wk^{-1} (30). This latter time commitment may be more than most individuals are willing to adopt given the low rates of exercise participation observed in most countries (7).

We recently reported in the HART-D trial that an exercise intervention using the same treatment strategy as DARE, yet modeled for time commitment according to current physical activity recommendations, also demonstrated a greater reduction in HbA$_{1c}$ and increased peak cardiorespiratory capacity ($\dot{V}O_{2peak}$) associated with AER + RES training (4,10). We also showed that AER + RES training in HART-D trial significantly improved several aspects of skeletal muscle mitochondrial content and substrate oxidation (31). While the primary outcome reports from the DARE and HART-D trials examined various components of metabolic syndrome, neither study has evaluated the effect of exercise training on the prevalence of metabolic syndrome when examined as a composite score of the respective components comprising metabolic syndrome. The analysis of metabolic syndrome is important given a recent report by Bateman et al. (6), demonstrating that, although RES training did not affect metabolic syndrome, AER and AER + RES training decreased metabolic syndrome scores similarly in individuals who were sedentary, overweight, and dyslipidemic. Collectively, the physiologic response to exercise training is of primary importance to patient care for individuals with T2D and concomitant metabolic syndrome. A secondary challenge to these types of investigations is the attempt to reconcile the modest, yet potentially important differences between epidemiologic reports and clinical trial outcomes.

Epidemiology trials examining maximal cardiorespiratory fitness (fitness) often report fitness in terms of metabolic equivalent tasks or METs calculated at time-to-exhaustion (TTE) owing to the inability to measure respiratory gas exchange in large trials. Based on epidemiology findings, it has been estimated that a 1-MET improvement carries with it a 13%–19% reduction in all-cause and CVD mortality risk, respectively (20,21). We have recently demonstrated a dose-dependent decrease in metabolic syndrome associated with fitness from the Aerobics Center Longitudinal Study and, more recently, an improvement in metabolic syndrome in postmenopausal women exercising in accordance with physical activity guidelines (11,14). Despite the protective effects of fitness found in epidemiology, clinical exercise trials show a smaller effect when equating fitness expressed as METs calculated directly from $\dot{V}O_{2peak}$ despite a more pronounced improvement in METs measured from work output at TTE within the same trial (10,11). This disparity is important to consider because the true impact of clinical trials using $\dot{V}O_{2peak}$ as a "gold standard" may not be fully appreciated. While the differences between directly measured and estimated METs can be posited objectively to differences in actual versus estimated METs, it is also conceivable that the difference between changes in $\dot{V}O_{2peak}$ and TTE/estimated METs could be explained by improvements in exercise efficiency. Based on the American College of Sports Medicine's (ACSM) advocacy for "Exercise is Medicine," we used an integrated approach aimed at reconciling laboratory measures with clinical outcomes and further examining their relationships to metabolic syndrome.

The primary aim of this analysis was to examine participants from the HART-D cohort to determine the relationship between AER, RES and AER + RES training and metabolic syndrome in participants with T2D (10). We hypothesized that metabolic syndrome prevalence will improve in a "dose-dependent" manner moving in order of effect from RES, to AER, to AER + RES training. Our secondary aim was to explore the relationship between metabolic syndrome and maximal fitness, whereby we propose that exercise efficiency will explain, at least in part, improvements in metabolic syndrome.

METHODS

The primary aim of the HART-D trial ($N = 262$) was to examine the effect of a 9-month AER, RES, and AER + RES training on HbA$_{1c}$ in participants with T2D (10). Volunteers presented to HART-D as sedentary men and women (30–75 yr) with T2D (HbA$_{1c}$ = 6.5%–11.0%). We defined sedentary behavior as performing AER exercise <20 min on <3 d·wk^{-1} and not participating in RES. Individuals were excluded for the presence of or medical history of stroke, advanced neuropathy or retinopathy, or other serious medical condition contraindicated for exercise or that may prevent adherence to the study protocol. The Pennington Biomedical Research Center institutional review board approved the HART-D study, and written consent was obtained from all participants before study screening. All study procedures were performed in accordance with the Declaration of Helsinki.

Herein we present an ancillary, per-protocol report of 208 participants who completed the HART-D trial and were more than 70% compliant to the exercise protocol. No between-group differences were noted for compliance. As previously reported by Church et al. (10), weekly exercise time did not differ significantly between the AER (140 min), RES (141 min), and AER (110 min) + RES (35 min) groups (total = 145 min). Moreover, no significant differences were noted for changes in body composition changes between groups relative to body fat or lean body mass.

Study Design and Intervention

Volunteers who met inclusion criteria were randomized to AER, RES, or AER + RES or to a nonexercise control group. During the study, we maintained separate intervention and assessments teams, and clinical testing and intervention laboratories were housed in separate buildings. During the course of the trial, participants met with a certified diabetes educator each month to track medication and health history changes, and all exercise sessions were constantly monitored by trained

study staff. The control group was offered weekly stretching and relaxation classes. Participants randomized to the control group were asked to maintain their normal daily physical activity level throughout the intervention. We confirmed physical activity levels outside of exercise training sessions using step counters. The stretching and relaxation classes were optional and considered light-intensity physical activity insufficient to influence fitness or produce significant increases in strength. It should be noted, however, that during the course of the study, data safety monitoring procedures caused us to discontinue the control group after a significant number of participants (~17%) had an increase in $HbA_{1c} > 1.0\%$, resulting in an unequal number of participants in the control group.

The AER and AER + RES groups participated in treadmill walking 3–5 d·wk^{-1} at a moderate to vigorous intensity (65.4% ± 14.6% of $\dot{V}O_{2peak}$, mean ± SD). The exercise dose in the AER group was prescribed at 12 kcal·kg^{-1} body weight per week (KKW), which was estimated to be equivalent to ~150 min·wk^{-1}. Participants were weighed weekly to calculate the prescribed weekly caloric energy expenditure rate estimated from standard equations published by the ACSM (2,4). The time required per session was calculated by dividing the weekly dose by the estimated caloric expenditure rate and the total number of sessions completed that week. The AER dose was lowered to 10 KKW in the AER + RES group to accommodate the RES component and ensure equal time commitment across all exercise groups.

The RES group completed 3 d of strength training exercises per week consisting of two sets of four upper body exercises (bench press, seated row, shoulder press, and lat pull down), three sets of three lower body exercises (leg press, extension, and flexion), and two sets of abdominal crunches and back extensions. Each set consisted of 10–12 repetitions, and the amount of weight lifted was progressively increased once a participant was able to complete 12 repetitions on the final set of an exercise on two consecutive RES sessions. Participants in the AER + RES group completed two sessions of RES each week, each consisting of one set of 10–12 repetitions for all resistance exercises.

Measurements

Metabolic syndrome and cardiorespiratory capacity. The primary outcome for our analysis is metabolic syndrome score as defined by NCEP ATP III guidelines (defined in the statistical methods section) (1). Cardiorespiratory fitness was evaluated using a standardized, ECG-monitored treadmill test while simultaneously collecting respiratory gases sampled from a True Max 2400 Metabolic Measurement Cart (ParvoMedics, Salt Lake City, UT). From this test, we measured METs from peak oxygen consumption ($\dot{V}O_{2peak}$; mL·kg^{-1}·min^{-1} / 3.5) and according to ACSM calculations based on speed and grade obtained at the end of exercise testing (3). Our rationale for examining $\dot{V}O_{2peak}$ and TTE is based on our desire to detail the clinical/physiologic changes surrounding $\dot{V}O_{2peak}$ and

the epidemiological index of TTE, as well as ascertaining exercise efficiency (detailed below).

To examine exercise efficiency, we first calculated the ventilatory threshold (VT) using the V-slope method by plotting $\dot{V}O_2$ and $\dot{V}CO_2$ on the x and y axes, respectively, and visually examining the slope of the relationship for a breakpoint in linearity (33). We also calculated the respiratory compensation point attained during each test as an increase in the ventilatory equivalent of oxygen ($\dot{V}_E/\dot{V}O_2$) and end-tidal partial pressure of oxygen (P_{ETO_2}) with no concomitant increase in the ventilatory equivalent of carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) to confirm these findings (25). Of note, in the literature, VT and RCP are sometimes referred to as ventilatory threshold 1 (VT1) and 2 (VT2), respectively (8). For consistency, we will use the abbreviations VT1 and VT2. To determine exercise efficiency, we calculated the slope of the line between the time of onset of VT1, VT2, and TTE.

Blood chemistries and anthropometric measures. HbA_{1c} was obtained by venipuncture after a 10-h fast and was analyzed with a Beckman Coulter DXC600 Pro (Brea, CA). Weight was measured on a GSE 450 electronic scale (GSE Scale Systems, Novi, MI), and height was measured using a standard stadiometer. Body mass index (BMI) was calculated as follows: body weight (kg) per height (m^2). Waist circumference was measured to the nearest 0.1 cm at the level of the iliac crest while the subject was at minimal expiration. Body composition was measured by dual-energy X-ray absorptiometry using the QDR 4500A whole-body scanner (Hologic, Inc., Bedford, MA).

Statistical methods. The primary outcome for our analysis is metabolic syndrome prevalence and score. Metabolic syndrome is defined as presenting with three of the following features: 1) increased waist circumference (>102 cm [>40 inches] for men, >88 cm [>35 inches] for women), 2) elevated triglycerides (≥150 mg·dL^{-1}), 3) low HDL cholesterol (<40 mg·dL^{-1} in men, <50 mg·dL^{-1} in women), 4) hypertension (systolic blood pressure ≥130 mm Hg and and/or diastolic blood pressure ≥85 mm Hg), 5) impaired fasting glucose (≥110 mg·dL^{-1}).

For secondary outcomes, we examined changes in respective metabolic syndrome component versus changes between the component features of metabolic syndrome and METs calculated from $\dot{V}O_{2peak}$ and estimated from TTE. For exploratory purposes, we also examined the relationship between exercise efficiency and metabolic syndrome.

For our primary and secondary analyses, we used a generalized linear model to analyze the influences of the differing regimens of exercise training on metabolic syndrome (SPSS version 21.0, Somers, NY). Relationships for our tertiary analysis were performed using a Spearman correlation analysis for changes in metabolic syndrome versus changes in cardiorespiratory fitness, metabolic syndrome components, and anthropometry indices as independent variables. For this latter analysis, we performed a bootstrap analysis of our data using 1000 imputations. Bootstrapping was used to improve the

accuracy of confidence intervals (CIs) surrounding various correlations as we reasoned that 1) our cohort continued their medication use during the study and 2) owing to our original report, the participants in our study reduced medication use concurrent with exercise training (10). Subsequently, any change in medication use surrounding metabolic syndrome components would likely influence our analysis, effectively reducing the magnitude of changes in metabolic syndrome.

Based on our primary outcome paper, all of our analyses were covaried for age, ethnicity, duration of T2D, baseline HbA_{1c}, and baseline and follow-up medications used for T2D, blood pressure, and cholesterol. We also included baseline metabolic syndrome score within this analysis. Within-group differences between baseline and follow-up are reported as mean and 95% CI. When we observed significant trends, we further explored our findings using *a priori* comparisons between each exercise training group and the control group via Dunnett-Hsu *post hoc* assessments. All reported *P* values are two-sided ($P < 0.05$), and our analyses accounted for Dunnett-Hsu adjustments when reported. Data are presented as mean ± SD or mean change from baseline and 95% CIs as appropriate.

RESULTS

The demographic characteristics and clinical features of our cohort ($n = 262$) are presented in Table 1. For our exploratory analyses of exercise efficiency, we successfully examined 207 participants who had complete data for each variable examined. No significant differences were observed for maximal fitness characteristics or percentage presenting with metabolic syndrome between the entire cohort and our tertiary assessment so we have presented all fitness characteristics in Table 2. Overall, participants presented with an average age of 56 ± 9 yr and T2D duration of 7.1 ± 5.5 yr and 59% of our cohort presented with metabolic syndrome. Based on BMI ($34.9 ± 5.9$ kg·m^{-2}), participants in our study ranged from class I to class III obese.

Based on $\dot{V}O_{2peak}$ (20.1 ± 4.3 mL·kg^{-1}·min^{-1}), participants in HART-D had low levels of fitness, ranking in the lower 15th percentile for maximal cardiorespiratory capacity achieved during exercise testing (3,28). These $\dot{V}O_{2peak}$ levels correspond to the class I/II fitness levels as defined by the New York Heart Association (15). Fifty-nine percent of our cohort presented with metabolic syndrome at baseline. Sixty-three percent of our cohort were women, 44% were black, 3% were Asian, and 0.5% were Hispanic. Ninety-seven percent of our cohort used diabetes medications, 79% used blood pressure medications, and 64% used cholesterol medications at baseline.

Metabolic syndrome. We presented results for the change in metabolic syndrome score analysis in Figure 1 where we observed a significant trend ($P = 0.003$) for a decrease in metabolic syndrome within the AER (−0.49,

TABLE 1. Baseline characteristics of study participants.

Characteristics	All (*n* = 262)	Control (*n* = 41)	Aerobic (*n* = 72)	Resistance (*n* = 73)	Aerobic + Resistance (*n* = 76)
Age (yr), mean ± SD	56 ± 9	59 ± 8	54 ± 9	57 ± 9	55 ± 8
Sex, *n* (%)					
Male	97 (37%)	13 (5%)	27 (10%)	30 (11%)	27 (10%)
Female	165 (63%)	28 (11%)	45 (17%)	43 (16%)	49 (19%)
Race, *n* (%)					
White	138 (53%)	22 (8%)	39 (15%)	41 (16%)	36 (14%)
Black	114 (44%)	17 (7%)	33 (13%)	30 (12%)	34 (13%)
Hispanic	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Asian	8 (3%)	2 (1%)	0 (0%)	2 (1%)	4 (2%)
Other	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Duration of diabetes (yr)	7.1 ± 5.5	7.2 ± 5.2	7.4 ± 6.0	7.2 ± 5.5	6.7 ± 5.4
Metabolic syndrome					
Metabolic syndrome score, mean ± SD	2.77 ± 0.93	2.63 ± 0.86	2.99 ± 0.91	2.7 ± 0.88	2.72 ± 1.03
Presenting, %	59	56	56	56	55
Follow-up, %	49*	54	43*	53	46*
Anthropometry, mean ± SD					
Height (cm)	167.78 ± 9.2	166.78 ± 9.9	167.89 ± 10.1	168.72 ± 9	167.31 ± 8
BMI (kg·m^{-2})^b	34.86 ± 5.9	34.84 ± 6.2	34.65 ± 6.1	34.07 ± 5.4	35.82 ± 6.2
Weight (kg)	98.18 ± 18.8	97.03 ± 20	97.54 ± 18.6	96.92 ± 16.6	100.61 ± 20.4
Body fat (%)	37.81 ± 7.3	38.48 ± 7	37.12 ± 7.7	37.04 ± 7.6	38.84 ± 6.8
Waist circumference (cm)^a	112.11 ± 13.8	110.56 ± 14.4	111.29 ± 14.2	110.9 ± 12.2	114.89 ± 14.5
Haematology,^{c} mean ± SD					
HbA$_{1c}$ (%)	7.33 ± 1.2	7.71 ± 1.5	7.3 ± 1.2	7.18 ± 1	7.3 ± 1.2
Glucose (mg·dL^{-1})^a	151.02 ± 36.4	158.44 ± 40.7	146.36 ± 30.6	153.77 ± 39.3	148.77 ± 35.9
Insulin (pmol·L^{-1})	21.89 ± 32.5	17.65 ± 14.7	18.46 ± 16.5	20.37 ± 14.7	28.9 ± 54.9
Triglycerides (mg·dL^{-1})^a	147.11 ± 78.2	162.88 ± 86.3	136.25 ± 66.5	152.99 ± 77.6	143.24 ± 83.9
Total cholesterol (mg·dL^{-1})	174.08 ± 34.6	184.71 ± 31.2	168.82 ± 32.2	174.39 ± 34.1	172.96 ± 38.2
HDL (mg·dL^{-1})^a	49.35 ± 11.5	50.39 ± 9.5	48.95 ± 13.4	49.43 ± 12.1	49.07 ± 10
LDL cholesterol (mg·dL^{-1})	95.48 ± 29.4	102.6 ± 25.8	92.45 ± 28.3	94.09 ± 30.4	95.88 ± 31.1
Blood pressure (mm Hg), mean ± SD					
Systolic (mm Hg)^a	126.2 ± 13.1	127.1 ± 13.9	124.4 ± 12.5	124.1 ± 12.5	129.4 ± 13.5
Diastolic (mm Hg)^a	75.6 ± 8.5	76.4 ± 8	75.8 ± 9.4	75.1 ± 8.2	75.34 ± 8.3

^{a}Metabolic syndrome according to NCEP ATP III criteria.
^{b}Calculated as weight in kilograms divided by height in meters squared.
^{c}SI conversions: To convert total, low-density lipoprotein, and high-density lipoprotein cholesterol to mmol·L^{-1}, multiply by 0.0259; triglycerides to mmol·L^{-1}, multiply by 0.0113; and fasting glucose to mmol·L^{-1}, multiply by 0.0555, insulin to μU·mL^{-1}, multiply by 0.144.
*Significantly different from baseline ($P < 0.05$).

	Treatment Group				
	All (n = 207)	Control (n = 33)	Aerobic (n = 54)	Resistance (n = 59)	AER + RES (n = 61)
Ventilatory threshold (VT1)					
Time-of-onset (s)	169.73 ± 75.6	160.50 ± 118.0	165.69 ± 61.3	181.72 ± 70.6	166.89 ± 62.7
Respiratory compensation (VT2)					
Time-of-onset (s)	460.75 ± 134.9	433.85 ± 123.5	465.30 ± 151.0	470.52 ± 130.8	463.56 ± 131.3
Maximal cardiorespiratory fitness					
Maximal oxygen uptake (L·min^{-1})	1.92 ± 0.5	1.88 ± 0.5	2.03 ± 0.5	1.92 ± 0.5	1.81 ± 0.5
Maximal oxygen uptake (mL·kg^{-1}·min^{-1})	20.12 ± 4.3	19.66 ± 3.2	21.18 ± 5.3	20.41 ± 4.5	18.94 ± 3.3
Maximal METs from maximal oxygen uptake*	5.75 ± 1.2	5.62 ± 0.9	6.05 ± 1.5	5.83 ± 1.3	5.41 ± 0.9
Maximal METs from speed and grade	8.57 ± 1.3	8.47 ± 1.2	8.66 ± 1.5	8.62 ± 1.3	8.48 ± 1.3
Time-to-exhaustion (s)	641.42 ± 150.6	638.68 ± 128.4	645.82 ± 166.5	640.34 ± 148.2	639.75 ± 151.1

Calculated METs derived from treadmill speed and grade (reference, ACSM).
*Maximal oxygen uptake (mL·kg^{-1}·min^{-1}) divided by 3.5; significant difference from calculated METs from speed and grade ($P < 0.05$).

95% CI = −0.77 to −0.21) and AER + RES (−0.64, 95% CI = −0.92 to −0.35) groups. Both of these changes were significant ($P \leq 0.02$) versus control (0.03, 95% CI = −0.33 to 0.40) and RES (−0.03, 95% CI = −0.30 to 0.24). These changes led to a significant decrease in the percentage of participants presenting at baseline versus that at follow-up with metabolic syndrome for the AER (56% vs 43%) and AER + RES (55% vs 45%) groups (both, $P < 0.05$; Table 1). For our analysis of metabolic syndrome components, we observed a significant trend ($P = 0.03$) for reduced waist circumference improvement for all treatment groups: RES (−1.91 cm, 95% CI = −3.03 to −0.78), AER (−1.58 cm, 95% CI = −2.76 to −0.39), and AER + RES (−2.80 cm, 95% CI = −3.93 to −1.67), with all treatment groups being significant versus control (0.67 cm, 95% CI = −0.82 to 2.15; $P < 0.05$). We also observed a significant reduction in systolic blood pressure for the AER group (−6.61 mm Hg, 95% CI = −6.00 to −0.22), also significant versus control ($P < 0.05$). No other metabolic syndrome feature changes were found to be statistically significant.

Maximal cardiorespiratory capacity. Participants presented at baseline with an absolute $\dot{V}O_{2peak}$ of 1.92 ± 0.5 L and relative $\dot{V}O_{2peak}$ of 20.1 ± 4.3 mL·kg^{-1}·min^{-1}. This equated to 5.8 ± 1.2 METs. TTE during treadmill testing was 641 ± 151 s or approximately 10.7 ± 2.5 min. This equates to 8.57 ± 1.3 estimated METs. The mean METs measured from $\dot{V}O_{2peak}$ was 5.75 ± 1.2 and was significantly lower than METs estimated from speed and grade at TTE ($P < 0.05$).

After 9 months of exercise training, we observed a 5%–6% increase in METs measured by gas exchange versus a 25%–30% increase in METs estimated from speed and grade. For measured METs, we observed minor, yet significant increases in the AER and AER + RES training (Fig. 2). However, no between-group differences were otherwise noted. For estimated METs, we also observed significant increases in the AER and AER + RES training groups that were (a) significantly different from measured METs and (b) significantly different from respective measured METs ($P < 0.05$; Fig. 2).

Changes in METs obtained directly from $\dot{V}O_{2peak}$ were as follows: control = −0.09, 95% CI = −0.28 to 0.11; RES = 0.00, 95% CI = −0.14 to 0.17; AER = 0.14, 95% CI = 0.02 to 0.28; AER + RES = 0.29, 95% CI = 0.14 to 0.42. Changes in METs calculated from speed and grade were as follows: control = −0.25, 95% CI = −0.66 to 0.15; RES = 0.12, 95% CI = −0.19 to
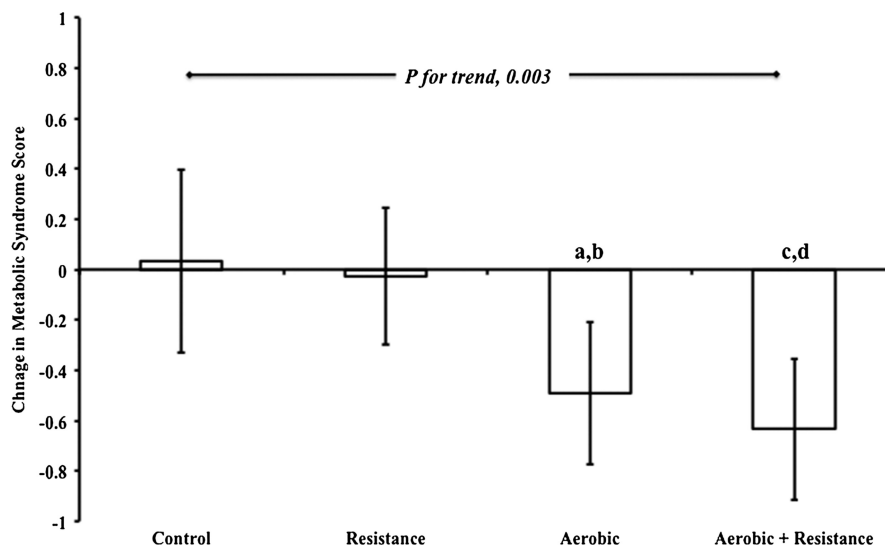

FIGURE 1—Mean change ± 95% confidence interval (CI) in NCEP ATP III–defined metabolic syndrome scores from baseline to follow-up. Statistical notations represent significance as follows: [a]aerobic versus control, $P = 0.028$; [b]aerobic versus resistance, $P = 0.02$; [c]aerobic + resistance versus control, $P = 0.005$; [d]aerobic + resistance versus resistance, $P = 0.003$.
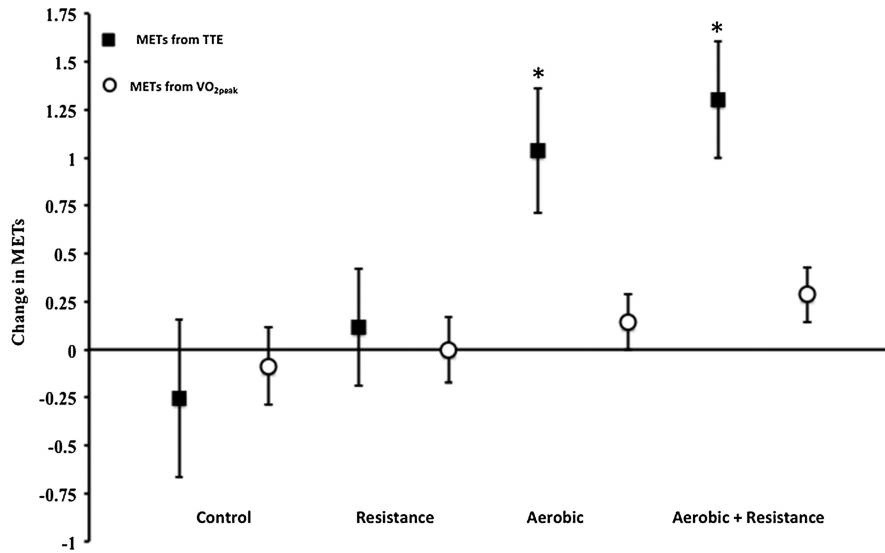
FIGURE 2—Mean change ± 95% confidence interval (CI) in METs measured from $\dot{V}O_{2peak}$ and calculated from speed and grade at time-to-exhaustion during maximal treadmill testing. Statistical notations represent significance versus control: *$P < 0.03$.

0.42; AER = 1.04, 95% CI = 0.71 to 1.36; and AER + RES = 1.30, 95% CI = 1.01 to 1.61, with the AER and AER + RES being significantly greater than control and RES ($P < 0.05$).

TTE after exercise training decreased in the control group (−28 s, 95% CI = −76 to 20) and showed a small increase for the RES (13 s, 95% CI = −23 to 49) training group. Neither of these changes was statistically significant. However, a significant increase in TTE was observed for the AER (119 s, 95% CI = 81 to 157) and AER + RES (154 s, 95% CI = 118 to 189), with both being significant versus control and RES groups ($P < 0.05$; Fig. 3C).

Submaximal cardiorespiratory indices and exercise efficiency. Similar observations to TTE were noted for the time-to-onset of VT1 (Fig. 3B) and VT2 (Fig. 3C). However, while VT1 improved in all treatment groups, VT2 improved only in the AER and AER + RES training groups compared to baseline. Specifically, VT1 (Fig. 3B) did not improve in the control group (9.0 s, 95% CI = −29 to 47) but significantly increased in all treatment groups: RES = 51 s, 95% CI = 5 to 63; AER = 34 s, 95% CI = 22 to 80; AER + RES = 89 s, 95% CI = 61 to 117. For VT2 (Fig. 3C), no significant improvements were noted for the control (6 s, 95% CI = −44 to 56) or RES (28 s, 95% CI = −11 to 68) groups but were significant for the AER (91 s, 95% CI = 50 to 133) and AER + RES (163 s, 95% CI = 123 to 203) groups (Fig. 3B). The net effect of these changes was a significant shift in the slope of the relationship from baseline to follow-up for VT1, VT2, and TTE, whereas no significant improvements were observed for the control group. Lastly, our analysis showed significant associations for changes between metabolic syndrome, TTE ($r = −0.33$, 95% CI = −0.49 to −0.15), $\dot{V}O_{2peak}$ ($r = −0.24$, 95% CI = −0.36 to −0.05), and waist circumference ($r = −0.14$, 95% CI = −0.11 to −0.40). No other significant associations were noted for other indices of body anthropometry.

DISCUSSION

The primary findings from our current study show that AER and AER + RES training reduced metabolic syndrome
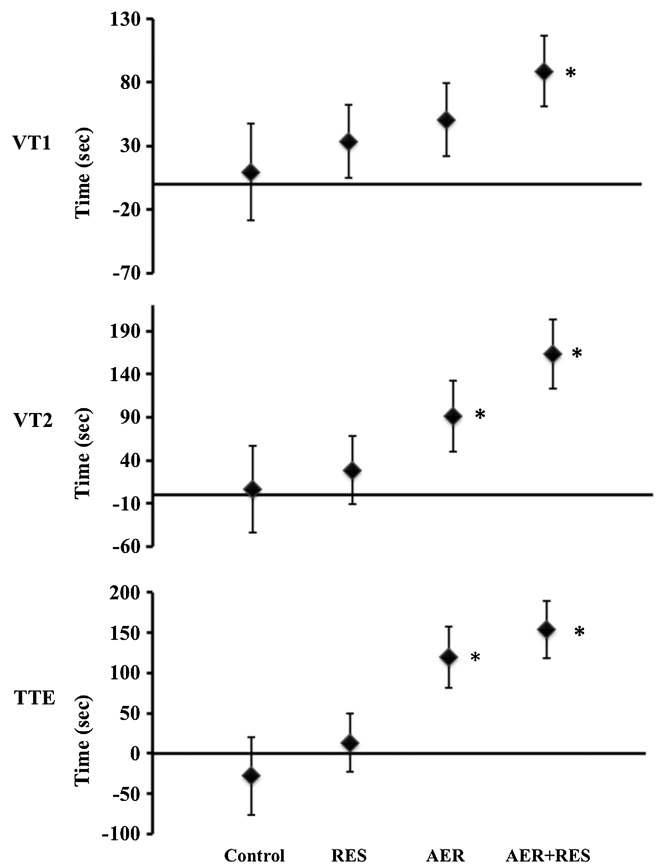

FIGURE 3—Data represent mean ± 95% CI changes VT1 (*top panel*), VT2 (*middle panel*), and time-to-exhaustion (TTE; *bottom panel*). Statistical notations represent significance versus control: *$P < 0.03$.

scores and, subsequently, the prevalence of individuals with concurrent T2D and metabolic syndrome. What is notable is that AER + RES performed in accordance with contemporary exercise guidelines is an effective strategy for reducing metabolic syndrome scores in individuals with T2D and should be considered as a viable treatment as preservation of muscle function becomes increasingly important with age (29). When examined as individual metabolic syndrome component features, we also found that waist circumference was significantly reduced in all exercise groups, while systolic blood pressure was significantly reduced only in the AER group. No other significant component feature reductions were noted for metabolic syndrome. These findings are clinically important to individuals who present with T2D, low cardiorespiratory fitness, and metabolic syndrome simultaneously.

Previous research shows a greater CVD and all-cause mortality risk for individuals who have coexisting metabolic syndrome and T2D (17,27). In 2006, Guzder et al. (17) demonstrated that age, sex, smoking status, total cholesterol, antiplatelet therapy, antihypertensive therapy, and lipid-lowering therapy-adjusted survival curves in patients with conjoint metabolic syndrome and T2D exhibited a hazard ratio (HR) for incident CVD of 2.05 compared to individuals with T2D alone. Under the assumption that the presence of T2D qualified all participants with a minimum of one metabolic syndrome feature, compounding risk was also observed for the accretion of two (HR = 1.93 ± 0.39), three (HR = 2.71 ± 0.18), four (HR = 4.23 ± 0.56), and/or all five (HR = 4.76 ± 0.042) metabolic syndrome component features. Najarian et al. (27) have also shown in data in the Framingham Study that the relative risk of stroke in individuals with T2D and metabolic syndrome is approximately 32%–55% higher compared with those individuals presenting with T2D or metabolic syndrome alone. Previous reports from our group in men show similar findings (12). In a prospective report from the Aerobics Center Longitudinal Study, we found that CVD deaths were higher in individuals with T2D alone (5.5 per 1000 man-years; HR = 2.9, 95% CI = 2.1–4.0) and in combination with metabolic syndrome (6.5 per 1000 man-years; HR = 3.4, 95% CI = 2.8–4.2) versus those in men without T2D or metabolic syndrome (1.9 per 1000 man-years) or metabolic syndrome only (3.3 per 1000 man-years; HR = 1.8, 95% CI = 1.5–2.0) (12).

Epidemiology trials also demonstrated that AER and RES are inversely and independently associated with metabolic syndrome (9,14,18). While clinical exercise intervention trials also support the efficacy of AER or RES training in reducing metabolic syndrome, less is known about combining AER + RES training, especially for those presenting with T2D and metabolic syndrome. A difficulty in interpreting the current literature with regard to the RES and metabolic syndrome is a relative paucity of trials examining RES training on metabolic syndrome versus examining the role of RES on the individual component features of metabolic syndrome. This difficulty is exemplified in a recent systematic and meta-analysis by Strasser et al. (32), who examined 13 trials involving RES and metabolic syndrome. While the authors provided an excellent review of RES training on the component features of metabolic syndrome, they did not account for metabolic syndrome as a composite score. Still fewer reports have examined the effect of AER + RES training in metabolic syndrome.

Similar in nature to HART-D, Sigal et al. (30) reported in the DARE trial significant reductions in HbA_{1c} coinciding with AER, RES, and AER + RES training. Despite the reporting of metabolic syndrome composite features, no further analysis was undertaken to examine metabolic syndrome itself. To date, only the study of Bateman et al. (6) has examined the effects of AER + RES on metabolic syndrome in participants from the STRRIDE study. Although STRRIDE did not examine individuals with T2D, they demonstrated similar effects to our current report in a convenience sample of 84 of 196 individuals presenting with all five NCEP ATP III–defined metabolic syndrome components. Specifically, participants in AER and AER + RES training decreased metabolic syndrome, whereas those undertaking RES and control conditions showed no significant reductions in metabolic syndrome. Overall, the findings of HART-D and STRRIDE demonstrate that AER and AER + RES training are equally effective for reducing metabolic syndrome in individuals with and without T2D, respectively.

The biological effects of exercise training on metabolic syndrome are related to changes in a number of physiologic and cardiovascular adaptations to exercise training and have been thoroughly reviewed elsewhere and are not elaborated on here (16). However, an underlying question we posed when undertaking our current analysis was to examine potential differences between clinical trials that rely on laboratory measures of $\dot{V}O_{2peak}$ and epidemiologic trials that typically use TTE and corresponding estimated MET values. One of the features we observed in some of our trials, inclusive of HART-D, was a disparity between the relative increase in measured $\dot{V}O_{2peak}$ and TTE (10,11). In our current analysis, we observed a significant difference between MET values measured from $\dot{V}O_{2peak}$ or measured METs (5%–6%) and TTE or estimated METs (25%–30%), with the latter showing a stronger relationship with metabolic syndrome. It is easy to rationalize this apparent inequality in terms of the mathematical variance associated with estimating METs from an equation based on speed and grade versus the actual measurement of $\dot{V}O_{2peak}$. This disparity, however, makes it difficult to reconcile epidemiology and clinical trials as data from epidemiology trials suggest a 13% and 15% reduction in all-cause and CVD risk mortality, respectively, for each METs attained during exercise testing (20). Rather than assuming that the difference between the two measures was simply a matter of the mathematical variance introduced with prediction equations, we hypothesized that some of this disparity could be explained by improvements in exercise efficiency.

Our findings showing significant, yet higher correlations for estimated METs compared with $\dot{V}O_{2peak}$ or measured METs are intriguing. Although both measurements detail "maximal cardiorespiratory capacity" *per se* and may covary

to some degree, they also reflect differences in the physiologic response to graded exercise testing. While $\dot{V}O_{2peak}$ reflects changes in measured cardiorespiratory capacity, which, in and of itself, is a reflection of maximal cardiac output and muscle oxygen utilization, TTE may reflect an improvement in submaximal exercise efficiency. Unfortunately, few data exist examining this relationship. Numerous methods have been proposed to measure exercise efficiency in athletic and clinical populations, including mechanical efficiency, gross efficiency, delta efficiency, oxygen uptake efficiency slope, and others (5,13,22,23,26). While all of these methods have their strengths and weaknesses, each measure is largely dependent on a single point of observation or on the slope of the changing relationship between the oxygen uptake of sequential stages and, hence, the workload involved in exercise testing.

We have examined the slope of the relationship between VT1, VT2, and maximal exercise, finding that the slope of this relationship improved in the AER and AER + RES groups and that these changes were more strongly related to TTE than measured $\dot{V}O_{2peak}$. From these data, we conclude that exercise training improves the underlying physiology associated with exercise testing and that these improvements equate to an improvement in TTE and, subsequently, partially explain the difference between estimated METs and those obtained from laboratory-derived $\dot{V}O_{2peak}$.

A primary strength of the HART-D trial is that it was a highly controlled clinical exercise intervention lasting 9 months. Our study is limited in its generalizability to those with T2D. Still, findings from STRRIDE suggest that the findings are similar in those without T2D. It might also be argued that given the medical management (i.e., prescriptive medications) surrounding our cohort could have introduced uncontrollable statistical variance into our reported outcomes.

It may also be argued that the RES stimulus was not sufficient to affect changes in metabolic syndrome components similar to AER regardless of the fact that the study was 9 months in length. Future studies using RES training should therefore consider the training intensity and volume components of RES. From a clinical perspective, we have accounted for changes in medication within our statistical analysis by using baseline and follow-up medication use. This, in turn, strengthens our findings because they are standard measures of clinical care and patient health care management. One of the strongest features of our study is that it was designed to emulate current public guideline statements for exercise. Taken in combination, our results show that AER or AER + RES training plays an important role in the management of individuals with T2D who also present with sufficient qualifying components to also have metabolic syndrome.

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