Improved Arterial–Ventricular Coupling in Metabolic Syndrome after Exercise Training: A Pilot Study

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ABSTRACT

FOURNIER, S. B., D. A. DONLEY, D. E. BONNER, E. DEVALLANCE, I. M. OLFERT, and P. D. CHANTLER. Improved Arterial–Ventricular Coupling in Metabolic Syndrome after Exercise Training: A Pilot Study. *Med. Sci. Sports Exerc.*, Vol. 47, No. 1, pp. 2–11, 2015. **Purpose**: The metabolic syndrome (MetS) is associated with threefold increased risk of cardiovascular (CV) morbidity and mortality, which is partly due to a blunted CV reserve capacity, reflected by a reduced peak exercise left ventricular (LV) contractility and aerobic capacity and a blunted peak arterial–ventricular coupling. To date, no study has examined whether aerobic exercise training in MetS can reverse peak exercise CV dysfunction. Furthermore, examining how exercise training alters CV function in a group of individuals with MetS before the development of diabetes and/or overt CV disease can provide insights into whether some of the pathophysiological CV changes can be delayed/reversed, lowering their CV risk. The objective of this study was to examine the effects of 8 wk of aerobic exercise training in individuals with MetS on resting and peak exercise CV function. **Methods**: Twenty participants with MetS underwent either 8 wk of aerobic exercise training (MetS-ExT, $n = 10$) or remained sedentary (MetS-NonT, $n = 10$) during this period. Resting and peak exercise CV function was characterized using Doppler echocardiography and gas exchange. **Results**: Exercise training did not alter resting LV diastolic or systolic function and arterial–ventricular coupling in MetS. In contrast, at peak exercise, an increase in LV contractility (40%, $P < 0.01$), cardiac output (28%, $P < 0.05$), and aerobic capacity (20%, $P < 0.01$), but a reduction in vascular resistance (30%, $P < 0.05$) and arterial–ventricular coupling (27%, $P < 0.01$), were noted in the MetS-ExT but not in the MetS-NonT group. Furthermore, an improvement in lifetime risk score was also noted in the MetS-ExT group. **Conclusions**: These findings have clinical importance because they provide insight that some of the pathophysiological changes associated with MetS can be improved and can lower the risk of CV disease. **Key Words:** CARDIOVASCULAR DISEASE, CARDIAC FUNCTION, ARTERIAL FUNCTION, OBESITY

The metabolic syndrome (MetS) is a cluster of metabolic risk factors (abdominal obesity, elevated blood pressure (BP) and glucose, and dyslipidemia) that exerts threefold increased risk of cardiovascular (CV) disease (CVD) mortality compared with individuals without MetS (26). Alarmingly, the prevalence of MetS in US adults is 34% and is on the rise because of the rising rates of obesity (29). MetS has become a leading health concern because of its strong association with future myocardial/cerebral vascular events and CVD mortality (26).

The MetS-associated pathophysiological changes to the CV system contribute to the increased CVD risk. Such changes include an increase in arterial dysfunction (increased arterial stiffness and endothelial dysfunction), left ventricular (LV) hypertrophy (LVH), and impaired CV reserve capacity (15,33,35). In particular, individuals with MetS demonstrate impaired coupling between the heart and arterial system (15). This interaction, termed arterial–ventricular coupling (Ea/Ees), is an important determinant of net CV performance (9) and cardiac energetics (10). Ea/Ees is indexed by the ratio of effective arterial elastance (Ea, a measure of the net arterial load

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Submitted for publication February 2014.
Accepted for publication May 2014.

0195-9131/15/4701-0002/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0000000000000388

imposed on the left ventricle) to LV end-systolic elastance (Ees, measure of LV chamber performance) (9). Impaired Ea/Ees is most readily evident when the CV system is under stress and/or with increasing age (31). For example, in MetS, the ability to reduce the Ea/Ees ratio is blunted during aerobic exercise (15). Furthermore, this impaired coupling response coincides with reduced peak aerobic capacity in those with MetS (15), which has been proposed to be an independent predictor of mortality relative to other risk factors (30).

In healthy older individuals, exercise training has been shown to increase aerobic capacity, improve peak LV performance (smaller end-systolic volume (ESV) and increased stroke volume (SV)), and increase LV contractility (13,37). In patients with CAD, Ea/Ees during handgrip isometric exercise was improved after exercise training. It is unknown whether exercise training in people with MetS (before the development of diabetes or overt CVD) can improve peak exercise LV–arterial coupling and CV function. An improvement in Ea/Ees and CV function in those with MetS would likely reflect lower CVD risk. Thus, the objective of this study was to examine the effects of 8 wk of exercise training on peak exercise arterial–ventricular coupling in clinically defined patients with MetS without diabetes or clinical indications of CVD. We hypothesized that aerobic exercise training would improve peak Ea/Ees in those with MetS because of an improvement in peak exercise LV contractility.

METHODS

Study Population

Twenty subjects with MetS free from overt CVD and diabetes as determined by a detailed medical history, physical examination, and a normal resting and exercise ECG participated in this study. MetS was defined according to the updated National Cholesterol Education Program: Adult Treatment Panel III composed of three of the following five components: 1) obesity (waist in men, >102 cm; women, >88 cm), 2) low HDL cholesterol (men, <40 $mg \cdot dL^{-1}$; women, <50 $mg \cdot dL^{-1}$), 3) hypertriglyceridemia (≥150 $mg \cdot dL^{-1}$), 4) elevated glucose (≥100 $mg \cdot dL^{-1}$ and <126 $mg \cdot dL^{-1}$), and 5) elevated BP (130/85 mm Hg or use of medications for hypertension).

Exclusion criteria included diabetes mellitus (hemoglobin A1C (HbA1C), ≥6.5% or use of diabetic medications), pulmonary disease, angina, atrial fibrillation, aortic stenosis, anemia, myocardial infarction, stroke, or coronary revascularization as assessed by a detailed medical history physical examination and a resting and exercise ECG. Subjects who participated in regular exercise, defined as >30 min for three times per week, were excluded. All subjects provided a written informed consent to participate, and this study was approved by the West Virginia University institutional review board.

Study Design

Physiological assessments were performed between 7:00 and 10:00 a.m. in a quiet temperature-controlled room after a 12-h fast and abstinence from alcohol, caffeine, and vitamins. CV medications were withheld 24 h before assessments. After a minimum of 15 min of quiet rest, subjects underwent resting noninvasive assessments of arterial and cardiac structure and function.

Exercise performance. After assessment of resting CV measurement, subjects exercised to exhaustion on a modified cycle ergometer (Monark 827; Sweden) equipped with a car seat to allow semirecumbent exercise in a seated upright position at approximately 130°. This upright position is necessary and important to allow acquisition of optimal echocardiographic images during exercise. Throughout exercise, the echo images were acquired approximately 60–90 s into each 3-min exercise workload. If all images were not acquired within the time frame, the duration of the exercise stage was extended to acquire those images. Pedal speed was maintained at 50 rpm, and workloads were increased by 25 W every 3 min until exhaustion. Oxygen consumed ($\dot{V}O_2$), carbon dioxide produced ($\dot{V}CO_2$), RER (RER = $\dot{V}CO_2/\dot{V}O_2$), ventilation ($\dot{V}_E$), ventilatory threshold, and the ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}CO_2$) were measured throughout exercise using a metabolic cart (TrueOne 2400; ParvoMedics, Sandy, UT). Subjective symptoms of fatigue (Borg score, 6–20) and BP (sphygmomanometry) were recorded at the end of each workload.

Rest and exercise echocardiography. Echocardiograms were obtained using a GE Vivid i (GE Healthcare, Chalfont St. Giles, United Kingdom) portable ultrasound imaging system with a 5S-RS (2.0–5.0 MHz) wideband phased array transducer. All echochardiograms were performed by experienced, registered, diagnostic cardiac sonographers. At rest, standard two-dimensional images were obtained in the following acoustic views: parasternal long axis and apical four-chamber views. Pulsed wave Doppler tracings of the mitral valve inflow velocity (recorded at the leaflet's tips) were recorded in the apical four-chamber view. Continuous/pulsed wave Doppler tracings of the LV outflow track velocity were obtained in the apical five-chamber view positioned 5 mm proximal to the aortic valve. Spectral tissue Doppler imaging was performed in the apical four-chamber view, with the gate sample positioned in the lateral corner and septal side of the mitral annulus. During exercise, the sonographer quickly acquired a two-dimensional image of the parasternal long axis view to obtain the size of the LV outflow tract diameter (base of the aortic leaflets). The sonographer then focused on capturing the following: four-chamber views to obtain cardiac volumes and mitral flow velocities and five-chamber views to obtain pulsed and continuous wave Doppler flow from the LV outflow track.

LV geometry and remodeling. In the supine position, LV dimensions, wall thickness, and chamber volumes were determined in triplicate from two-dimensional, M-mode, and spectral Doppler echocardiography using standard methods (25). Sex-specific LVH and geometric patterns based on LV mass index and relative wall thickness were defined as LV mass index >95 $g \cdot m^{-2}$ for women or >115 $g \cdot m^{-2}$ for men,

and LV geometry was classified as normal, concentric remodeling, concentric LVH, or eccentric LVH (25).

Arterial–ventricular measurements. In the upright seated rest position and during exercise, LV end-diastolic volume (EDV) and ESV, along with ejection fraction (EF), were determined from Simpson's biplane method (25). Cardiac volumes were normalized to body surface area (BSA). Cardiac index (Ci) was determined from the product of HR and SV index (SVi). Peak arteriovenous oxygen extraction was calculated from the Fick equation ($\dot{V}O_{2peak}$/cardiac output). Systemic vascular resistance index (SVRi) was calculated as mean arterial pressure × 80/Ci. The indexes of arterial and ventricular elastance were calculated as follows: 1) Ea, a measure of the net arterial load, was calculated as end-systolic pressure (ESP)/SV, where ESP is approximated as 0.9 × systolic BP (SBP) (9). Of note, ESP calculated as 0.9 SBP has previously been shown to closely approximate central ESP (21); 2) LV Ees (calculated from BP, SV, EF, and preejection and systolic ejection time intervals from LV outflow Doppler) was determined by the validated single-beat technique (12); and 3) arterial ventricular coupling ratio was determined from Ea/Ees (9). Of note, Ea/Ees is mathematically related to EF via the formula Ea/Ees = (1/EF) − 1. Reserve was defined as the difference in these variables between seated rest and peak exercise.

Diastolic function. In the supine position, the medial mitral annular early diastolic velocity (e') was determined by spectral tissue Doppler imaging (GE Vivid i) using standard methods. Early (E-wave) and late (A-wave) transmitral flow velocities, the isovolumetric relaxation time (IVRT), and the deceleration time of early filling velocity (Dec T) were measured by pulsed wave Doppler (GE Vivid i). End-diastolic pressure (EDP) was estimated as EDP = 11.96 + 0.596 E/e' (32). Because of the high incidence of fusion of the E-wave and A-wave during moderate- or high-intensity exercise, with the A-wave dominating, we are not able to measure Dec T or E-wave. Therefore, we were limited to measuring peak exercise IVRT and A-wave.

Body anthropometry. Height, weight, and waist and hip circumference were measured using standard laboratory procedures. Fat distribution was assessed by measuring the waist circumference at the site of the smallest circumference between the rib cage and the iliac crest with subjects in a standing position. Hip circumference was measured at the site of the largest circumference between the waist and thighs. Lean body mass and fat mass were measured using air displacement plethysmography (BOD POD; COSMED, Inc.). During assessment of body composition, subjects wore close-fitting bathing suits and a swim cap. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Blood analyses. Venous blood sampling was obtained in the morning after a 12-h overnight fast. Posttraining venous samples were collected at least 48 h after the last exercise session. Plasma obtained from blood sampling was analyzed at West Virginia University Hospital's central laboratory in Morgantown, WV. Total cholesterol, HDL cholesterol, triglycerides, and glucose were determined in plasma (lithium heparin, Becton Dickenson plasma separator tubes) using Beckman Coulter (Brea, CA) DxC automated chemistry analyzers. Total cholesterol was measured using a cholesterol esterase/cholesterol oxidase- or peroxidase-driven, timed end point method (coefficient of variation, <7%). HDL cholesterol was measured using a cholesterol esterase/cholesterol oxidase- or peroxidase-driven, timed end point assay with automated initial homogeneous solubilization step (coefficient of variation, <7%). Triglycerides were measured using a lipase/glycerol kinase/glycerophosphate oxidase/horseradish peroxidase-driven, timed end point method (coefficient of variation, 5%–7%). Glucose was measured electrochemically using a glucose oxidase-/catalase-/molybdate-driven oxygen rate method (coefficient of variation, <5%). Glycated hemoglobin (A1C fraction) was measured in whole blood (K_2-EDTA; Becton Dickenson) using a Bio-Rad (Hercules, CA) Variant II Turbo high-performance liquid chromatography system (coefficient of variation, <2%). Insulin was measured in serum (untreated/red top tube; Becton Dickenson) on an Immulite 2000 immunochemistry system (Siemens) (coefficient of variation, <10%). Homeostasis model assessment of insulin resistance (HOMA-IR) was estimated with the following formula: insulin resistance = fasting plasma insulin ($\mu U \cdot mL^{-1}$) × fasting plasma glucose (mM)/22.5.

Training intervention. Participants with MetS were assigned into either an 8-wk aerobic exercise intervention group (MetS-ExT) or an 8-wk nonexercise control (MetS-NonT) group. Group assignments were made using a pseudorandom balance approach to ensure that equal numbers were enrolled in each group. The MetS-NonT exercise group (n = 10, 50% female) was asked to maintain their normal sedentary lifestyle. The MetS-ExT group (n = 10, 70% female) performed 8 wk of supervised aerobic exercise in the human performance laboratory at West Virginia University School of Medicine three times per week for 60 min at fixed exercise intensity. The intensity of the prescribed exercise was based on individual results of maximal cardiopulmonary exercise tests. We used a ramp exercise protocol, whereby exercise training intensity started at 60% of HR reserve (HR range was determined during exercise stress test) and increased every 2 wk by 10%; from weeks 6 to 8, HR reserve was set at 85%. Adherence to the exercise prescription was documented through the use of wristwatch-style HR monitors (E600; Polar Electro Oy, Oulu, Finland) and physical activity logs. Approved modalities included treadmills, elliptical machines, and cycle ergometers. All participants were instructed to maintain current eating behaviors for the duration of the 8-wk intervention. All posttraining measurements were performed 24–48 h after the last exercise training session to avoid the immediate effects of a single bout of exercise. Measurements made before and after exercise training were obtained at the same time of the day for each subject.

Lifetime risk score for CVD. The lifetime risk score is a strong predictive capacity for future CV mortality and is

TABLE 1. Effects of exercise training on body composition and metabolic biomarkers in those with MetS.

	MetS-NonT (n = 10)		MetS-ExT (n = 10)	
	Before	After	Before	After
Age (yr)	43 ± 3		48 ± 3	
Sex, female (%)	60		70	
Height (cm)	171 ± 3		168 ± 3	
Weight (kg)	99 ± 7	99 ± 7	105 ± 6	105 ± 6
Lean mass (kg)	64 ± 4	64 ± 4	59 ± 5	59 ± 2
% body fat	35 ± 2	35 ± 3	43 ± 3*	43 ± 2*
BSA (m^2)	2.10 ± 0.08	2.10 ± 0.09	2.13 ± 0.07	2.12 ± 0.07
BMI ($kg \cdot m^{-2}$)	34 ± 2	34 ± 2	37 ± 2	37 ± 2
Waist circumference (cm)	104 ± 3	103 ± 5	124 ± 10	122 ± 10
Triglycerides ($mg \cdot dL^{-1}$)	149 ± 21	169 ± 20	116 ± 17	140 ± 24
HDL ($mg \cdot dL^{-1}$)	41 ± 4	40 ± 2	47 ± 5	45 ± 4
Glucose ($mg \cdot dL^{-1}$)	98 ± 2	97 ± 3	99 ± 3	97 ± 3
HbA1C (%)	5.7 ± 0.1	5.5 ± 0.1	5.7 ± 0.1	5.6 ± 0.1
Insulin ($\mu U \cdot mL^{-1}$)	10.4 ± 2.4	10.7 ± 2.2	9.0 ± 1.5	9.0 ± 1.8
HOMA-IR	1.34 ± 0.30	1.27 ± 0.30	1.23 ± 0.19	1.45 ± 0.34
Hypertension (>140/90 mm Hg) (%)	70		60	
Diabetes mellitus (%)	0		0	
Medications (%)				
Hypertension	20		30	
Cholesterol	0		10	

Values are mean ± SEM.
No significant differences were found upon comparing pre- and postintervention values within a group.
*$P < 0.05$ vs MetS-NonT at specific visit (i.e., before or after).
BSA, body surface area; BMI, body mass index; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance.

based on an algorithm that incorporates sex (male/female), age (yr), SBP (mm Hg), diabetes mellitus (yes/no), total cholesterol ($mg \cdot dL^{-1}$), smoking (yes/no), BMI ($kg \cdot m^{-2}$), and physical fitness (1 MET = 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) (3,4). Calculation of the score is available using a Web-based interface (www.lifetimerisk.org).

Statistical analysis. Measurements of CV function were performed offline by a single investigator who was blinded to group allocation. The intraclass correlation coefficient (ICC) and coefficient of variations for all echocardiographic variables were derived in a subset of subjects (n = 8). At rest, the ICC and the coefficient of variation for all variables, collected on two separate days, were >0.80 and between 7% and 12%, respectively. Similar results were obtained for echocardiographic variables evaluated during peak exercise, with all variables having an ICC >0.80 and coefficient of variation between 7% and 12%, with the exception of the arterial–ventricular coupling ratio (ICC, 0.63).

Normality was evaluated by the Kolmogorov–Smirnov test. Continuous variables were log-transformed as necessary. To evaluate the effects of exercise training, paired t-tests and two-way repeated-measures ANOVA were used. We also ran a mixed effects model with a time-varying covariate to examine whether the change (before vs after the training intervention) in CV parameters were due to changes in other CV parameters. All analyses were performed with the statistical package SPSS version 21 (SPSS, Inc., Chicago, IL). Values shown in the tables represent

TABLE 2. Effects of exercise training on supine LV geometry and diastolic function in those with MetS.

	MetS-NonT (n = 10)		MetS-ExT (n = 10)	
	Before	After	Before	After
LV geometry				
Septal wall thickness (cm)	0.95 ± 0.05	0.96 ± 0.06	0.92 ± 0.06	0.92 ± 0.05
Posterior wall thickness (cm)	0.87 ± 0.06	0.89 ± 0.06	0.86 ± 0.07	0.93 ± 0.06
LV internal dimension (cm)	4.41 ± 0.13	4.38 ± 0.16	4.73 ± 0.16	4.67 ± 0.12
LV mass (g)	161 ± 8	164 ± 11	181 ± 21	187 ± 16
LV mass index ($g \cdot m^{-2}$)	77 ± 3	78 ± 3	84 ± 9	88 ± 6
Relative wall thickness	0.40 ± 0.03	0.42 ± 0.04	0.36 ± 0.03	0.40 ± 0.02
LV diastolic function				
E ($m \cdot s^{-1}$)	0.75 ± 0.03	0.75 ± 0.04	0.88 ± 0.05	0.92 ± 0.06
A ($m \cdot s^{-1}$)	0.64 ± 0.03	0.60 ± 0.04	0.77 ± 0.07	0.74 ± 0.07
E/A ratio	1.21 ± 0.07	1.29 ± 0.07	1.24 ± 0.14	1.32 ± 0.13
IVRT ($m \cdot s^{-1}$)	76 ± 5	71 ± 5	75 ± 8	61 ± 5
Dec T ($m \cdot s^{-1}$)	203 ± 12	204 ± 14	193 ± 9	175 ± 8
e' ($m \cdot s^{-1}$)	0.12 ± 0.01	0.13 ± 0.01	0.11 ± 0.01	0.11 ± 0.01
E/e'	6.20 ± 0.26	6.21 ± 0.46	9.28 ± 1.05	9.13 ± 1.18
LV EDP (mm Hg)	16 ± 1	16 ± 1	18 ± 1	17 ± 1

Values are mean ± SEM.
No significant differences were found upon comparing pre- and postintervention values within a group.
A, peak velocity of the late diastolic mitral flow; Dec T, mitral flow deceleration time of early filling velocity; E, peak velocity of the early diastolic mitral flow; e', mitral annular early diastolic velocity; E/A, E divided by A; E/e', E divided by e'; IVRT, isovolumetric relaxation time; LV EDP, left ventricular end-diastolic pressure.

means ± SEM unless otherwise stated. $P \leq 0.05$ was defined as significant.

RESULTS

Age and anthropometric and metabolic characteristics of individuals with MetS are shown in Table 1. The breakdown of metabolic components were as follows: 100% had a waist circumference >102 cm (men) or >88 cm (women), 75% had elevated BP (130/85 mm Hg or use of medications for hypertension), 70% had low HDL cholesterol (men, <40 mg·dL^{-1}; women, <50 mg·dL^{-1}), 30% had hypertriglyceridemia (≥150 mg·dL^{-1}), and 50% had elevated glucose (≥100 mg·dL^{-1}). In terms of LV remodeling, 15% had normal LV geometry and concentric remodeling, 50% had eccentric LVH, and 20% had concentric LVH.

Effects of exercise training on metabolic profile, body composition, and LV geometry. Eight weeks of exercise training did not alter basal fasting HbA1C, glucose, insulin, HDL, triglycerides, or HOMA-IR (Table 1). Furthermore, exercise training was insufficient to significantly alter body composition (weight, lean mass, or percentage of body fat), LV mass (in absolute terms and relative to BSA), internal LV dimensions (internal diameter and septal and posterior wall thickness), and relative wall thickness in those with MetS (Table 2).

Effects of exercise training on LV diastolic function. Resting LV diastolic function (i.e., E-wave, A-wave, E/A ratio, IVRT, Dec T, E/e', and EDP) was not affected by 8 wk of exercise training in those with MetS (Table 2). During exercise, we were limited to examining changes in components of LV diastolic function, namely IVRT and A-wave. No significant differences in peak IVRT (MetS-ExT, 16 ± 1 vs 16 ± 2; MetS-NonT, 15 ± 1 vs 15 ± 2) and A-wave (MetS-ExT, 1.38 ± 0.06 vs 1.28 ± 0.11; MetS-NonT, 1.48 ± 0.08 vs 1.53 ± 0.06) were found in either MetS-ExT or MetS-NonT before and after the intervention.

Effects of exercise training on arterial ventricular coupling. Exercise training in those with MetS did not alter resting Ea/Ees, Ea, or Ees (Fig. 1). Furthermore, with the exception of resting SVRi, which was lower in the MetS-NonT, no differences in resting CV function were evident in either MetS group (Table 3). There were no significant time (before and after)–group (MetS-ExT vs MetS-NonT) interactions at rest for any CV parameter.

At peak exercise, aerobic training in those with MetS lowered peak Ea/Ees (−27%, $P < 0.01$) by increasing peak Ees (40%, $P < 0.01$) and no change in peak Ea in MetS-ExT (Fig. 1). In contrast, peak Ea/Ees, Ea, and Ees did not significantly differ between pre- and postvisits in MetS-NonT. Similarly, peak EF and Ci were significantly increased ($P < 0.05$) and peak ESV index (ESVi) and SVRi were reduced ($P < 0.05$) after exercise training in MetS-ExT, whereas no differences were found in MetS-NonT (Table 4). Furthermore, significant time (before and after)–group (MetS-ExT vs NonT) interactions for peak Ea/Ees, Ees, EF, and SVRi were evident.

Exercise capacity, in both absolute (L·min^{-1}) and relative (mL·min^{-1}·kg^{-1} of body mass or lean mass) terms was improved in those with MetS after 8 wk of exercise training, as reflected by a 19%–20% increase ($P < 0.01$) in $\dot{V}O_{2peak}$ and a 4% increase ($P < 0.05$) in $\dot{V}E/\dot{V}CO_2$ (Table 4). Of note, a time (before and after)–group (MetS-ExT vs NonT) interaction for $\dot{V}O_{2peak}$ was identified despite the lack of differences in RER or RPE in either MetS group. Furthermore, no differences in peak arteriovenous oxygen difference were evident before or after intervention in those with MetS (Table 4). Taking all individuals into consideration, an initial relation between preintervention values for Ea/Ees delta (maximum − rest) and $\dot{V}O_{2peak}$ ($r = -0.58$, $P < 0.01$) was found. We then examined whether the difference in Ea/Ees delta from visits 1 and 2 was correlated with the change from visits 1 and 2 in $\dot{V}O_{2peak}$; however, this relation did not reach statistical significance ($r = -0.40$, $P = 0.09$). In a

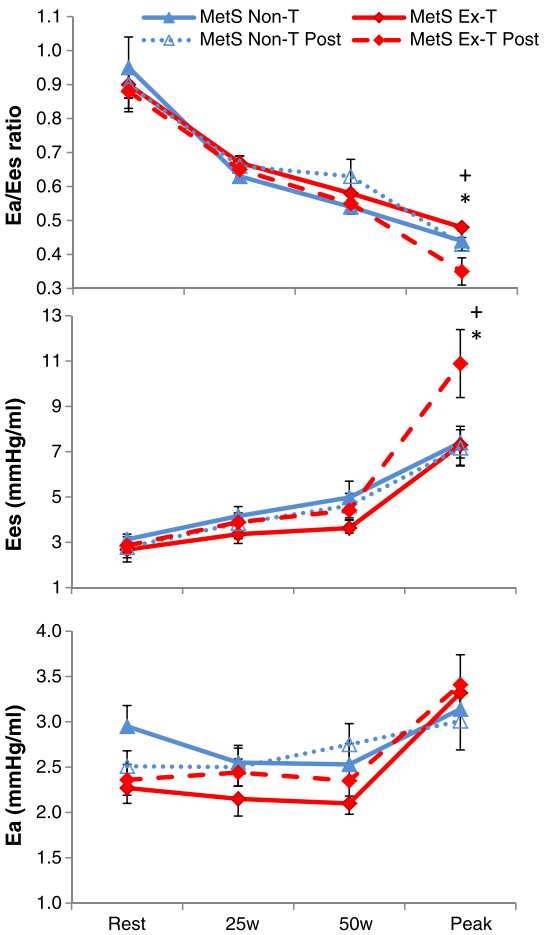

FIGURE 1—Change in arterial–ventricular coupling (Ea/Ees), LV Ees, and Ea from rest to peak exercise in those with MetS who underwent exercise training (MetS-ExT, *diamond*) and in those with MetS who remained inactive (MetS-NonT, *triangles*). Postintervention for both MetS groups is depicted by a *dashed line*. Exercise training significantly reduced peak Ea/Ees and increased peak Ees in those with MetS, and there was a significant time (before and after the intervention)–group (MetS-ExT vs MetS-NonT) interaction for Ea/Ees and Ees. *$P < 0.05$ illustrates significant differences before and after intervention in MetS ExT; +$P < 0.05$, time–group interaction. Data are presented as means ± SEM.

TABLE 3. Effects of exercise training on CV function in those with MetS.

		MetS-NonT (n = 10)		MetS-ExT (n = 10)	
		Before	After	Before	After
EDVi ($mL \cdot m^{-2}$)	Seated	47 ± 2	53 ± 3	47 ± 2	49 ± 2
	Peak	49 ± 2	51 ± 2	46 ± 2	52 ± 3
ESVi ($mL \cdot m^{-2}$)	Seated	21 ± 1	23 ± 2	20 ± 1	20 ± 1
	Peak	18 ± 1	17 ± 1	17 ± 2	14 ± 2*
SVi ($mL \cdot m^{-2}$)	Seated	26 ± 2	30 ± 2	26 ± 2	29 ± 1
	Peak	31 ± 2	35 ± 2	29 ± 2	38 ± 2*
HR (bpm)	Seated	68 ± 4	67 ± 4	65 ± 3	64 ± 3
	Peak	164 ± 4	157 ± 4*	154 ± 6	151 ± 6
Ci ($L \cdot min^{-1} \cdot m^{-2}$)	Seated	1.81 ± 0.16	2.05 ± 0.15	1.70 ± 0.11	1.85 ± 0.12
	Peak	4.98 ± 0.27	5.39 ± 0.32	4.50 ± 0.42	5.78 ± 0.46*
EF (%)	Seated	56 ± 2	58 ± 2	56 ± 2	60 ± 1
	Peak**	62 ± 2	67 ± 3	63 ± 3	74 ± 2*,***
SBP (mm Hg)	Seated	127 ± 4	122 ± 3	121 ± 4	122 ± 3
	Peak	192 ± 6	190 ± 6	188 ± 5	185 ± 7
DBP (mm Hg)	Seated	82 ± 3	80 ± 3	83 ± 2	80 ± 1
	Peak	73 ± 8	76 ± 4	76 ± 5	64 ± 7
ESP (mm Hg)	Seated	117 ± 4	110 ± 2	109 ± 4	110 ± 3
	Peak	173 ± 5	171 ± 5	169 ± 4	167 ± 6
SVRi ($dyn \cdot m^{-2} \cdot s^{-1} \cdot cm^{-5}$)	Seated	4593 ± 381	3848 ± 256*	4729 ± 360	4245 ± 301
	Peak**	1877 ± 141	1755 ± 115	2243 ± 244	1565 ± 167*

Values are mean ± SEM.
*$P \leq 0.05$ compared with preintervention values within a group (MetS-NonT or MetS-ExT).
**Significant ($P \leq 0.05$) group (MetS-NonT vs MetS-ExT)–time (before to after) interaction.
***$P < 0.05$ vs MetS-NonT at specific visit (i.e., before or after).
Ci, cardiac output index; DBP, diastolic blood pressure; EDVi, end-diastolic volume index; EF, ejection fraction; ESP, end systolic blood pressure; ESVi, end-systolic volume index; SBP, systolic blood pressure; SVi, stroke volume index; SVRi, systemic vascular resistance index.

stepwise mixed model approach with repeated measures and a time-varying covariate, we found that Ea/Ees delta contributed toward 16% of the variance on the effects of exercise training on $\dot{V}O_{2peak}$.

Lifetime risk score. In the MetS-ExT group, the lifetime risk score was significantly reduced (20% ± 7% to 16% ± 6%, $P = 0.01$) after training, whereas in the MetS-NonT group, no difference was found (13% ± 2% vs 13% ± 2%, $P = 0.8$). Furthermore, we identified a significant inverse correlation between the lifetime risk score and $\dot{V}O_{2peak}$ ($r = -0.53$, $P = 0.02$).

DISCUSSION

This is the first study to examine the effects of aerobic exercise training on peak arterial–ventricular coupling in patients with MetS. We report that after 8 wk of aerobic exercise training, peak arterial–ventricular coupling, peak LV contractility, and aerobic capacity were significantly improved and similar to levels noted in healthy untrained controls (15). Our unique patient population afforded the opportunity to assess whether exercise training can reverse impaired CV function reported in patients with MetS before a diagnosis of CVD and/or diabetes. Because MetS is believed to be a harbinger in the pathogenesis of diabetes and CVD, these data provide evidence that exercise-based interventions at this critical (preclinical disease) time point may help reverse the pathophysiological progress of CVD and/or delay the progression to overt CVD and/or diabetes.

The MetS is associated with pathophysiological changes to the CV system associated with an increased CVD mortality risk. Recently, we reported that resting LV systolic function was well preserved in patients with MetS who clearly manifested the symptoms of the metabolic disorder (including hypertension, insulin resistance, and hyperlipidemia) but who are free from overt CVD and/or diabetes (15). Conversely, in this same population, we observed LV remodeling, LVH, and reduced LV diastolic function at rest

TABLE 4. Effects of exercise training on aerobic capacity in those with MetS.

	MetS-NonT (n = 10)		MetS-ExT (n = 10)	
	Before	After	Before	After
Ventilatory threshold ($L \cdot min^{-1}$)	1.13 ± 0.14	1.27 ± 0.12	1.20 ± 0.13	1.56 ± 0.21*
$\dot{V}_E/\dot{V}CO_2$ slope	34.8 ± 1.49	34.4 ± 1.27	34.4 ± 1.4	35.7 ± 1.2*
RER	1.13 ± 0.03	1.10 ± 0.01	1.10 ± 0.02	1.09 ± 0.02
Borg scale	19 ± 0.3	19 ± 0.2	19 ± 0.5	19 ± 0.4
$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)**	1.89 ± 0.20	1.84 ± 0.18	1.68 ± 0.16	2.00 ± 0.19*
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) LM**	29.4 ± 2.2	28.7 ± 1.5	29.4 ± 1.6	35.0 ± 1.7*,***
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) BW**	19.1 ± 1.6	18.6 ± 1.2	16.2 ± 1.0	19.4 ± 1.0*,***
Peak A-$\dot{V}O_2$ diff (mL per 100 mL)	18.4 ± 2.0	16.4 ± 1.2	18.5 ± 1.5	16.2 ± 1.0

Values are mean ± SEM.
*$P \leq 0.05$ compared with preintervention values within a group (MetS-NonT or MetS-ExT).
**Significant ($P \leq 0.05$) group (MetS-NonT vs MetS-ExT)–time (before to after) interaction.
***$P < 0.05$ vs MetS-NonT at specific visit (i.e., before or after).
A-$\dot{V}O_2$ diff, arteriovenous oxygen difference; BW, body weight; LM, lean mass.

(15). The progression from MetS to type 2 Diabetes is characterized by additional LV enlargement and LV diastolic dysfunction, with evidence of LV systolic dysfunction and related sympathetic alterations (39). In our population with MetS, exercise training was unable to reverse the LV structural changes or impairments in LV diastolic function. The lack of an observed effect of exercise training on LV mass is likely due to the duration of the exercise stimulus (8 wk). Indeed, an intervention consisting of several months of aerobic training was found to be sufficient to exert physiological LV remodeling (16), reduce LV wall thickness, and reduce LV wall thickness-to-radius ratio (43). The extent to which exercise training can improve LV diastolic function by improving the compliance of the heart remains controversial. Two recent studies examining a full year of exercise training in patients with MetS without type 2 diabetes or CVD (23) and healthy senior individuals (16) found no significant improvements in resting LV diastolic function. Advancing age and the development of CVD induce structural and functional alterations to the heart that is reflected by a reduction in the number of cardiomyocytes, an increase in connective tissue volume, and an increase in the formation of advanced glycation end products, which collectively result in impairment of LV diastolic function (22). Data would suggest that once these cross-linked collagen proteins are formed, they are pathologically irreversible. Thus, any potential improvements in LV diastolic function to be gained from exercise training may be limited by cross-linked collagen (16).

The coupling between the heart and arterial system is an important and largely underappreciated determinant of cardiac performance and energetics (9). At rest, the coupling ratio is well maintained at approximately 0.7–1.0 to optimize CV efficiency. This ratio is preserved with advancing age and in patients with heart failure (24,31). Indeed, we have also recently shown that resting Ea/Ees is around 0.9 in patients with MetS (15). In this study, exercise training in MetS did not alter resting Ea/Ees or its components. Whereas resting Ea/Ees is fairly well conserved, the ability of the CV system to respond to stress, particularly exercise, is blunted with age and in heart failure patients (8,31). We have previously shown that the Ea/Ees response to exercise is significantly impaired in patients with MetS (15), which is partly due to impaired LV contractility and a blunted peripheral vasodilatory response to exercise (15). Importantly, this study indicates that 8 wk of exercise training is sufficient to increase the peak LV contractile response and improve peak exercise Ea/Ees in patients with MetS as a direct result of improved peak Ees.

Although we have shown that arterial–ventricular coupling is improved after exercise training in middle-age individuals with MetS, it is also important to identify whether older individuals with MetS would have the same beneficial effects of exercise training. In older (age, >60 yr) healthy individuals, peak exercise cardiac function is typically improved, at least up to the seventh decade, after exercise training, as depicted by increases in Ci, SV, EF, LV contractility, and $\dot{V}O_{2peak}$ (2,18,34,36). Future research should establish the extent to which older individuals with MetS demonstrate improvements in arterial and cardiac function after exercise training. This is especially important, given that the presence of MetS with older age is often accompanied by CVD (i.e., type 2 diabetes mellitus, CAD, etc.) and by increased formation of cross-linked advanced glycation end products in the LV and arterial walls, which may limit the physiological responses to exercise training (1).

A blunted Ea/Ees response during exercise has been shown to correspond with a decrease in $\dot{V}O_{2peak}$ in patients with MetS (15) and heart failure (8). An inverse relation has also been reported between $\dot{V}O_{2peak}$ and Ea/Ees during exercise (14), which was confirmed in our study. In addition, acute infusion of verapamil improved arterial–ventricular coupling and resulted in a corresponding improvement in exercise capacity (11). These data suggest a direct link between Ea/Ees and aerobic capacity, in that an improvement in the coupling likely results in a more effective transfer of blood from the heart to periphery, thereby increasing functional reserve capacity. Indeed, in the presence of a stiffer heart, there is a greater change in BP for a given change in volume, which can amplify the BP response and impair net cardiac ejection in a closed system (11). In the current study, we found an increase in peak SV without a significant change in BP, suggesting a more compliant cardiac response after exercise training. Furthermore, the improvement in peak Ea/Ees was accompanied by a 20% increase in $\dot{V}O_{2peak}$ and the change in Ea/Ees seemed to contribute (approximately 16%) toward the improved $\dot{V}O_{2peak}$. Given that aerobic capacity is determined by both central (HR and SV) and peripheral factors (skeletal muscle mass, calcium cycling, mitochondrion capacity, capillary density, etc.), it is likely that the improved coupling, along with other physiological adaptations that were not examined in our study, contributed toward the improved $\dot{V}O_{2peak}$ in those with MetS after exercise training. Indeed, Tjonna et al. (42) observed a 16% and 36% increase in $\dot{V}O_{2peak}$ after 16 wk of either continuous aerobic exercise or high-intensity aerobic interval training in those with MetS, respectively. It was suggested that enhanced skeletal muscle capacity (improved calcium cycling and mitochondrion capacity) contributed to the exercise-induced improvement in $\dot{V}O_{2peak}$ (42). However, we did not directly measure skeletal muscle oxidative capacity or oxygen extraction; these responses to exercise training have been reported elsewhere (42,45). In contrast to these findings, we did not observe an improvement in peak arteriovenous oxygen difference (estimated from the Fick equation) after 8 wk of exercise training in those with MetS, suggesting that muscle adaptation played a minor role in the reported improvements in the aerobic exercise capacity of our patients. The effects of exercise training on improving peak arteriovenous oxygen difference in other populations are mixed with some reporting no changes (16,34) and others showing an increase (27,36). This lack of change may be related to the intensity of exercise training, whereby an increase in arteriovenous oxygen difference was reported after high-intensity exercise training but not after

low-intensity training (36). An increase in exercise intensity and duration may be required to increase peripheral oxygen extraction in individuals with MetS. Furthermore, research is needed to clarify the relation between Ea/Ees and $\dot{V}O_{2peak}$.

The improvement in LV contractility during exercise may have been partly due to an increased SV, a decreased afterload, and improved arterial–ventricular coupling. Indeed, improvements in peak exercise SVi and ESVi were reported in those with MetS after exercise training. Similar improvements in cardiac volumes have been reported after exercise training in older sedentary individuals (16,37). Improved peak LV performance after exercise training is unlikely to be due to enhanced myocardial β-adrenergic responses, as chronic exercise training has not been reported to alter β-adrenergic function (38). However, exercise training has been shown to improve calcium handling in experimental animal models, thereby improving cardiomyocyte function (46). Accordingly, improvements in calcium handling may have contributed to the improvement in LV contractility noted in those with MetS. The enhanced ability of the LV to empty as fitness increases may relate to a reduction in arterial stiffness/afterload in the conditioned state (44). However, after 8 wk of exercise training, no improvements in Ea during exercise were reported in those with MetS. In contrast, a significant reduction in peak vascular resistance was established in the exercise-trained patients with MetS. Ea is an integrative index that incorporates the principal elements of arterial load, including systemic vascular resistance, total arterial compliance, characteristic impedance, and systolic and diastolic time intervals. Ea is therefore regarded a measure of the net arterial load that is imposed on the LV (9). Thus, the lack of change in Ea does not necessarily indicate that specific components of arterial load were not improved at peak exercise after training. This was clearly evident with the improvement in peak SVRi. Furthermore, the improvement in SVRi or the lack of change in Ea was not attributed to the slight changes in HR_{max} noted in the control group, as evidenced by similar findings after adjusting for HR as a time-varying covariate in a mixed effects model. Whether the improvement in SVRi at peak exercise is due to release of vasodilators causing vascular relaxation remains to be elucidated. Improvements have also been noted in resting endothelium-dependent vasodilatation in obese patients and patients with MetS after exercise training (42). Accordingly, despite the lack of change in Ea, peak arterial function may have been improved in those with MetS, thus contributing to improved aerobic capacity.

The beneficial CV effects at peak exercise attributed to exercise training were not a reflection of a change in body fat or lean mass. However, numerous studies have reported that regular moderate-intensity exercise can result in reductions in weight and fat mass (20,28). Thus, the lack of change in body composition in our study is likely due to the short duration of exercise training (8 wk). Furthermore, clinical metabolic biomarkers (HDL, triglycerides, glucose, etc.) remained unchanged. Although we did not find improvements in body composition or clinical blood biomarkers after training in those with MetS, we believe that improvements in peak CV function and aerobic capacity reflect a reduction in CV risk in patients with MetS. A strong association exists between aerobic capacity and mortality, with a positive correlation between improvements in aerobic capacity and an improved prognosis (7). This relation seems to be more robust than the relation between weight loss and mortality (6). For example, each MET (3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) increase in exercise capacity confers a 12% improvement in survival (30). The average increase in peak $\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$) in the MetS-ExT group was 3.2 $mL \cdot kg^{-1} \cdot min^{-1}$, suggesting an improvement in survival. Furthermore, the lifetime risk score in MetS-ExT was significantly reduced by 4% and the lifetime risk score was inversely correlated with $\dot{V}O_{2peak}$. However, to fully prevent the progression to overt CVD and/or diabetes and the pathophysiological changes to the CV system that accompany this transition, persistent physical activity in combination with a nutritional dietary regimen (that includes optimal vitamin/mineral consumption) is required.

STUDY LIMITATIONS

There are several limitations. First, the sample size for our training and nontraining group is modest (n = 10 in each). Although we found significant differences in peak Ea/Ees, this was principally due to a significant change in peak Ees ($P < 0.05$ with statistical power >0.75), but we were underpowered in our statistical power for Ea (power, 0.10). Although it is evident that we have sufficient power in those CV variables where significance was observed, we cannot exclude the possibility of a type II statistical error (i.e., that we have falsely accepted the null hypothesis) in the CV variables that were not significantly different where power was low. Therefore, these data should be regarded as preliminary, until we or others can obtain data on a larger population sample. In the current study, we examined the effects of exercise training on Ea (net arterial load) as our arterial function parameter. Although it is important to study the interaction between the heart and arterial system in the same domain (i.e., elastance), measuring specific aspects of arterial function such as characteristic impedance, arterial stiffness (via pulse wave velocity), and intimal medial thickness would provide additional insights into the beneficial effects of exercise training in those with MetS. Furthermore, sex differences in the effects of exercise training on LV stiffness may have gone undetected, given the small number of male versus female subjects. Future research should examine whether there are sex-related differences in the coupling response, at rest and during exercise, after exercise training.

Second, pressure and flow were not directly measured but rather estimated from noninvasive surrogates. However, the methods we used have been previously validated against invasive hemodynamic measurements (12). Our peak cardiac data may be underestimated because of systematic

underestimation of LV volumes from two-dimensional echocardiography (17,41) and the challenge of acquiring echocardiographic images during exercise. However, the technique we used has been successfully used by others (8,40), and similar values have been observed, suggesting fidelity in our data.

Third, we were limited in our ability to comprehensively characterize the extent of diastolic function during exercise because the focus of this study was to examine the effect of exercise training on peak exercise Ea/Ees and LV systolic function, and therefore, echocardiographic views were optimized to examine systolic function. Furthermore, the acquisition of LV diastolic parameters during exercise is challenging. Thus, we cannot rule out that exercise training in those with MetS also improved peak exercise LV diastolic function.

Fourth, peak arteriovenous oxygen difference was not measured, but rather, it was estimated using the Fick equation ($\dot{V}O_2$ divided by cardiac output). The Fick technique has been used to calculate arteriovenous oxygen difference in a number of recent physiological studies investigating mechanisms of exercise intolerance (5,19). Our peak arteriovenous oxygen difference values were somewhat higher than those reported by others (5) possibly because of underestimation of cardiac output. Most importantly, because key variables were measured at all testing times using identical methods in both groups and because we assessed changes in reserve capacity (peak values − resting values) within individuals, comparisons of cardiac output and estimated arteriovenous oxygen difference between groups are valid.

Lastly, the short duration of exercise training (8 wk) may have been insufficient to alter cardiac structure, body composition, and metabolic blood biomarkers. Thus, longer exercise training programs that incorporate different exercise modalities (interval, aerobic, and resistance training) are important to fully understand the role that exercise training has on improving CV structure/function in patients with MetS.

CONCLUSIONS

In conclusion, 8 wk of aerobic exercise training of moderate-to-high intensity significantly improved peak exercise arterial–ventricular coupling, LV contractility, peripheral vascular resistance, and aerobic capacity in individuals with MetS without overt CVD and type 2 diabetes. However, no improvements were evident in resting LV structure and diastolic function, metabolic profile, or body composition after exercise training.

The authors thank Charles Murray and Diana Stofcheck for their help with the echocardiography.

This study was partly supported by the American Heart Association 11CRP7370056 (P. C.), National Heart, Lung, and Blood Institute T32-HL090610 (S. F.), and the National Institute Of General Medical Sciences of the National Institutes of Health under award number U54GM104942.

All authors report that there are no conflicts of interest, financial or otherwise, to disclose regarding the submitted article.

The results of the present study do not constitute endorsement by the American College of Sports Medicine.

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