Circulation

ORIGINAL RESEARCH ARTICLE

One-Year Committed Exercise Training Reverses Abnormal Left Ventricular Myocardial Stiffness in Patients With Stage B Heart Failure With Preserved Ejection Fraction

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BACKGROUND: Individuals with left ventricular (LV) hypertrophy and elevated cardiac biomarkers in middle age are at increased risk for the development of heart failure with preserved ejection fraction. Prolonged exercise training reverses the LV stiffening associated with healthy but sedentary aging; however, whether it can also normalize LV myocardial stiffness in patients at high risk for heart failure with preserved ejection fraction is unknown. In a prospective, randomized controlled trial, we hypothesized that 1-year prolonged exercise training would reduce LV myocardial stiffness in patients with LV hypertrophy.

METHODS: Forty-six patients with LV hypertrophy (LV septum >11 mm) and elevated cardiac biomarkers (N-terminal pro-B-type natriuretic peptide [>40 pg/mL] or high-sensitivity troponin T [>0.6 pg/mL]) were randomly assigned to either 1 year of high-intensity exercise training (n=30) or attention control (n=16). Right-heart catheterization and 3-dimensional echocardiography were performed while preload was manipulated using both lower body negative pressure and rapid saline infusion to define the LV end-diastolic pressure-volume relationship. A constant representing LV myocardial stiffness was calculated from the following: $P=S\times[\text{Exp}\ \{a\ (V-V_0)\}-1]$, where "P" is transmural pressure (pulmonary capillary wedge pressure – right atrial pressure), "S" is the pressure asymptote of the curve, "V" is the LV end-diastolic volume index, "V_0" is equilibrium volume, and "a" is the constant that characterizes LV myocardial stiffness.

RESULTS: Thirty-one participants (exercise group [n=20]: 54±6 years, 65% male; and controls (n=11): 51±6 years, 55% male) completed the study. One year of exercise training increased $\dot{V}o_2$ max by 21% (baseline 26.0±5.3 to 1 year later 31.3±5.8 $mL{\cdot}min^{-1}{\cdot}kg^{-1}$, $P<0.0001$, interaction $P=0.0004$), whereas there was no significant change in $\dot{V}o_2$ max in controls (baseline 24.6±3.4 to 1 year later 24.2±4.1 $mL{\cdot}min^{-1}{\cdot}kg^{-1}$, $P=0.986$). LV myocardial stiffness was reduced (right and downward shift in the end-diastolic pressure-volume relationship; LV myocardial stiffness: baseline 0.062±0.020 to 1 year later 0.031±0.009), whereas there was no significant change in controls (baseline 0.061±0.033 to 1 year later 0.066±0.031, interaction $P=0.001$).

CONCLUSIONS: In patients with LV hypertrophy and elevated cardiac biomarkers (stage B heart failure with preserved ejection fraction), 1 year of exercise training reduced LV myocardial stiffness. Thus, exercise training may provide protection against the future risk of heart failure with preserved ejection fraction in such patients.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03476785.

Key Words: blood volume ■ heart failure ■ hypertrophy, left ventricular ■ vascular stiffness

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This manuscript was sent to Walter Paulus, Guest Editor, for review by expert referees, editorial decision, and final disposition.

The Data Supplement, podcast, and transcript are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.121.054117.

For Sources of Funding and Disclosures, see page 944.

Circulation is available at www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- In middle-aged patients with left ventricular hypertrophy and elevated cardiac biomarkers (American Heart Association/American College of Cardiology stage B heart failure with preserved ejection fraction), 1 year of prolonged exercise training reversed left ventricular chamber and myocardial stiffening. Exercise training may provide protection against the future risk of heart failure with preserved ejection fraction in such patients.

What Are the Clinical Implications?

- Sustained, adequately dosed aerobic exercise training to improve left ventricular compliance may prevent the full manifestation of the heart failure with preserved ejection fraction syndrome in these high-risk individuals.
- Identifying such high-risk patients early in the evolution of heart failure with preserved ejection fraction, and focusing on lifestyle change with adoption of life-long exercise training may be an effective strategy against this difficult-to-treat syndrome.

Nonstandard Abbreviations and Acronyms

HF	heart failure
HFpEF	heart failure with preserved ejection fraction
LV	left ventricular
LVEDV	left ventricular end-diastolic volume
LVH	left ventricular hypertrophy
PCWP	pulmonary capillary wedge pressure
SV	stroke volume

Despite the evolution of guideline-directed management for heart failure (HF), HF remains a devastating disease that affects 6.5 million Americans (total noninstitutionalized civilian population of the United States) ≥20 years of age.[1] About half of patients with HF have an apparently preserved ejection fraction, also known as heart failure with preserved ejection fraction (HFpEF). The pathophysiology of HFpEF is associated with increased left ventricular (LV) stiffness and compromised ventricular-arterial coupling.[2–5] Therapeutic strategies for HFpEF are limited with high rehospitalization rates and mortality.[6] To date, no compellingly effective therapy for HFpEF has been found. Therefore, clinical strategies that may prevent HFpEF are critical.[7]

Our group has documented that LV stiffening begins in middle age and becomes progressively stiffer over the course of sedentary aging, even in the absence of cardiovascular disease.[8] This stiffening process can be prevented by life-long physical activity at the right dose (at least 4–5 days per week of endurance exercise).[9] However, when exercise training is initiated late in life, after 65 years of age, in either healthy older adults[10] or patients with HFpEF,[11] the cardiac atrophy and stiffening of sedentary aging cannot be reversed, although modest improvements in compliance have been demonstrated when exercise training is accompanied by a drug that can break advanced glycation end products.[12] Conversely, middle-aged hearts retain substantial plasticity and may respond to an adequate dose of training to restore youthful myocardial compliance.[13]

Identifying and targeting the patients most likely to benefit from such a preventive strategy may be problematic. Low physical fitness is clearly a powerful risk factor for the future development of HF and HFpEF.[14,15] Moreover, in a representative, population-based sample of adults with no previous HF, individuals with left ventricular hypertrophy (LVH) plus elevations in biomarkers reflecting subclinical myocardial injury (cardiac troponin T) or neurohormonal activation as a result of hemodynamic stress (N-terminal pro-B-type natriuretic peptide) had a substantially increased risk of developing HF, a substantial fraction of which was HFpEF.[16] Last, we have reported recently that LV myocardial stiffness in patients with LVH and elevated biomarkers (AHA/American College of Cardiology stage B HFpEF) was greater than in age- and sex-matched controls, which appears to represent a transitional state from a normal healthy heart to HFpEF[17] and could be the ideal population to target with behavioral modification.

Therefore, we hypothesized that committed exercise training, when implemented 4 to 5 times per week over a prolonged period in sedentary high-risk middle-aged men and women, 45 to 64 years of age, would improve LV compliance in patients with LVH and elevated biomarkers. To test this hypothesis, we performed comprehensive invasive and noninvasive assessments of cardiovascular structure and systolic/diastolic function in patients with LVH (as AHA/American College of Cardiology stage B HFpEF), before and after 1 year of a well-periodized exercise program including high-intensity aerobic intervals, lower-intensity endurance training, and strength training, compared with a control group.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Participant Population and Study Design

This study was a prospective, parallel group, randomized controlled 1-year exercise training study. Middle-aged (45–64 years) participants with LVH were recruited from the Dallas Heart Study,[18] enriched by review of hospital electrocardiography and echocardiography databases to identify patients with

asymptomatic LVH in whom N-terminal pro-B-type natriuretic peptide and high-sensitivity cardiac troponin T were measured subsequently. Subjects were stratified by sex and allocated to either exercise or yoga interventions using a stratified block randomization at a 2:1 exercise-to-control ratio (allowing for greater attrition for the exercise group). The randomization schema was programmed using SAS Proc Plan and performed by the study biostatistician. A yoga-based attention control allowed for equipoise for the volunteers by improving quality of life without affecting fitness.[19,20]

In total, 3597 potential candidates were screened; 814 adults met the initial inclusion criteria for our study including an ejection fraction >50% and documented LVH by MRI (125 g/m^2) or echocardiography (left ventricular septum >11 mm) without exclusion criteria. One hundred forty individuals who expressed an interest in the study underwent phone screening. Eighty-three subjects were tested for elevated biomarkers: either an elevated N-terminal pro-B-type natriuretic peptide (>40 pg/mL) or high-sensitivity troponin (>0.6 pg/mL).[16] Participants were excluded if they had signs or symptoms of HF, hypertrophic cardiomyopathy, cardiac amyloidosis, ischemic heart disease, prior myocardial infarction or stroke, greater than moderate valvular heart disease, chronic obstructive pulmonary disease, sleep apnea syndrome, exercised >3 days per week, or were unable to exercise. Fifty-six participants with LVH and elevated biomarkers were enrolled (signed a consent form) and randomly assigned, comprising 18 controls and 38 exercisers. After randomization, but before completing all preliminary testing and beginning the intervention, 2 patients assigned to the control group and 8 patients assigned to exercise withdrew, leaving 46 patients who completed all baseline studies and started their assigned intervention (30 exercisers and 16 controls; Figure 1). Over the course of the 1-year intervention, 15 of these subjects dropped out before completing postintervention testing (5 in the attention controls and 10 in the exercise group), leaving 11 attention controls and 20 exercise subjects who ultimately completed the intervention and all postintervention studies.

The experimental procedures were explained to all participants, with informed consent obtained as approved by the institutional review boards of the University of Texas Southwestern Medical Center at Dallas and the Texas Health Presbyterian Hospital Dallas. All procedures conformed to the standards set by the Declaration of Helsinki. The trial was registered prospectively on https://www.clinicaltrials.gov (Unique identifier: NCT03476785).

Intervention

Exercise Training

For the exercise group, a training program was developed individually for each subject with the goal of increasing duration and intensity consistent with modern training techniques.[21–23] A day-by-day training calendar was provided to the subjects. Workouts varied with respect to mode (walk, cycle, swim), duration (30–60 minutes), and intensity (base, interval, recovery) to optimize the training response. Each subject was assigned a personal trainer and a heart rate (HR) monitor to ensure that every session was carefully tracked and recorded. For high-intensity interval training, we used aerobic intervals that have been shown recently to be highly effective at improving $\dot{V}o_2$ max and cardiovascular function.[24–27] To individualize training intensity, the maximal steady state (MSS) zone was first determined from the ventilatory and lactate thresholds measured during the maximal exercise test as previously described.[13] On the basis of the MSS HR and peak HR, 4 training zones were established for each participant: (1) MSS; (2) base pace (1–20 beats below MSS); (3) interval (>95% HR peak); and (4) recovery (less than base pace). The early training phase (month 1–2) focused on establishing an endurance base and regular exercise routine with participants performing three 30-minute base pace sessions per week. As participants acclimated to the training, MSS sessions were added starting with 2 sessions per month during the second month and increasing to 3 sessions in month 3. In the third month, aerobic intervals consisting of 4×4 interval sessions (4 minutes of exercise at 95% peak HR followed by 3 minutes of active recovery at 60%–75% peak HR, repeated 4 times) were incorporated. The exercise program goal was gradually increased to 2 aerobic interval training sessions per week over the first 7 months and then included at least 2 interval sessions per week for the duration as maintenance. Subjects also performed strength training 1 to 2 days per week.[28] All studies were repeated after 1 year of training.

Control Intervention

Attention controls were prescribed a combination of yoga, balance, and strength training using light weights 3 times per week for 1 year. Participants attended group yoga or stretching classes or completed online or video classes at home. This prescription allowed for a similar level of interaction with research staff between both groups. To that end, each participant (exercise group and attention control group) was assigned an exercise physiologist who monitored their training compliance throughout the 1-year intervention. An exercise log and HR monitor (Polar) were used to monitor training compliance.

Cardiopulmonary Exercise Testing

Maximal oxygen uptake ($\dot{V}o_2$ max) was measured using a modified Astrand-Saltin treadmill protocol and the Douglas bag technique; gas fractions were analyzed by mass spectrometry, and ventilatory volumes were analyzed by a Tissot spirometer, as previously reported.[29] $\dot{V}o_2$ max was defined as the highest oxygen uptake measured from at least a 30-second Douglas bag.

Hemodynamics

All hemodynamic experiments were conducted in the morning, in a quiet environmentally controlled laboratory with an ambient temperature of 25 °C. All participants had a light breakfast at least 2 hours before experiments commenced and were asked to refrain from heavy exercise and caffeinated or alcoholic beverages for at least 24 hours before the day. A 6F balloon-tipped, fluid-filled catheter (Swan-Ganz catheter, Baxter) was placed through an antecubital vein into the pulmonary artery using fluoroscopic guidance. Intravascular pressures were referenced to atmospheric pressure, with the pressure transducer (Transpac IV, Abbott) zero reference point set at 5.0 cm below the sternal angle. After at least 20 minutes of quiet supine rest, baseline data were collected. Analog waveforms were sampled at 250 Hz, and the digital waveforms were analyzed offline using customized software (Biopac Systems Inc). The

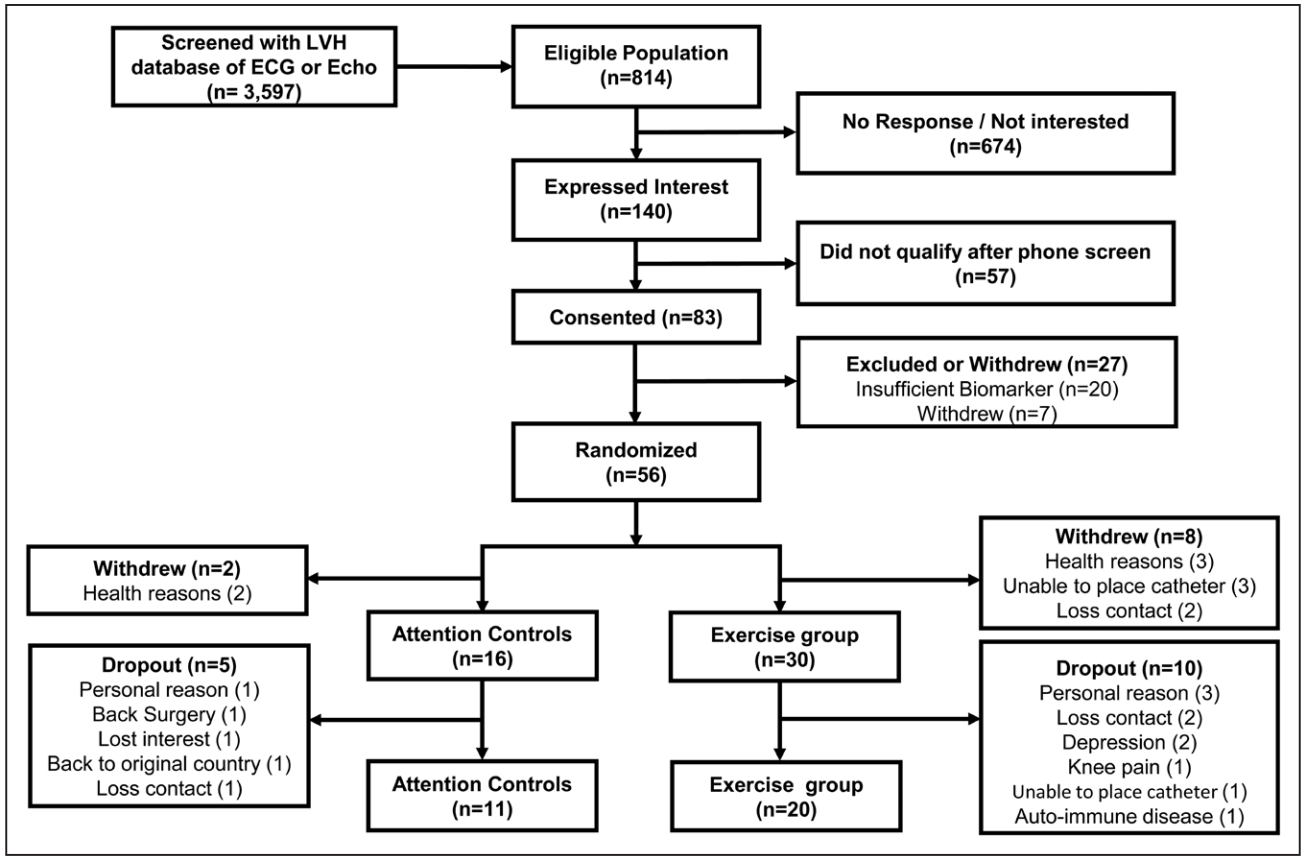

Figure 1. Consort diagram in the LVH study.
Study enrollment, randomization, and retention of study participants randomly assigned to the exercise training or control group. Echo indicates echocardiography; and LVH, left ventricular hypertrophy.

mean pulmonary capillary wedge pressure (PCWP) and right atrial pressure (RAP) were measured by using 3 separate measurements during a quiet, held end expiration (≈5 seconds), excluding the V waves. Because external constraint influences ventricular volumes and pressure, LV end-diastolic transmural pressure-volume relationships were constructed using estimated transmural pressure (TMP=PCWP–RAP).[30]

Cardiac filling and thus left ventricular end-diastolic pressure was decreased by 2-sequential levels of lower body negative pressure of −15 mm Hg and −30 mm Hg as previously described.[13,31] Five minutes into each level of cardiac unloading, 3 separate measurements of mean PCWP and right atrial pressure were obtained at end expiration. After release of the lower body negative pressure, subjects were given a small break. A resting baseline was then repeated to ensure return to hemodynamic steady state and to provide an additional, presaline measurement point before cardiac filling was increased by 2 sequential levels with a rapid infusion of 15 and 30 mL/kg warm (37 ℃) isotonic saline at 200 mL/min. Hemodynamic measurements were obtained as previously described.[17]

Echocardiography

The LV was imaged by 3-dimensional echocardiography (iE33; Phillips Medical System) at all loading conditions during the study. LV end-diastolic volume (LVEDV) was analyzed offline (Qlab 9.0; Phillips Medical System) by an experienced cardiologist who was blinded to filling pressures. The typical error of the LV volume measurement by echocardiography in our laboratory, expressed as a coefficient of variation, is 10% (95% CI, 8%–12%).

Analysis of Hemodynamic Data

Cardiac output was measured with the C_2H_2 rebreathing method during exercise testing and during manipulation of preload.[32] HR was monitored continuously by an ECG, and stroke volume (SV) was calculated from cardiac output divided by HR. Blood pressure was measured at the brachial artery during cardiac output measurements. Arm cuff systolic and diastolic blood pressures were measured by electrosphygmomanometry, with a microphone placed over the brachial artery to detect Korotkoff sounds. Lean body mass was measured by dual-energy X-ray absorptiometry. The body surface area was used to scale all chamber volume measurements.[17] A constant for LV chamber and myocardial stiffness was modeled using commercially available software (SigmaPlot version 12.0, Systat Software Inc), which uses an iterative technique to solve the following exponential equation: $P=S\,[\mathrm{Exp}\,\{a\,(V-V_0)\}-1]$,[33] where "P" is PCWP (for chamber stiffness calculations) or transmural pressure (for myocardial stiffness calculations), "S" is pressure asymptote of the curve, "V" is LVEDV index, "V_0" is the equilibrium volume at which transmural "P" is assumed to be 0 mm Hg, and "a" is the constant that characterizes chamber stiffness. Individual LV myocardial stiffness constants for each participant were averaged within each group and reported as

individual stiffness.[17] PCWP and SV data were used to construct Frank-Starling curves. The SV, mean arterial pressure (MAP), and 3-dimensional LVEDV data were used to calculate preload recruitable stroke work relationships (PRSW=[SV×MAP]/LVEDV),[34] where the slope was used as an index of global systolic function. The effective arterial elastance, representing afterload, was calculated using 0.9×systolic blood pressure divided by SV.[35]

Statistical Analysis

Continuous variables are expressed as mean±SD, and categorical variables are expressed as n (%). The primary analysis included all participants who completed the 1-year follow-up. Continuous variables were compared between groups by using mixed-effects model repeated-measures ANOVA analysis. The repeated-measures models included the intervention group factor (attention controls versus exercise group), a repeated factor for study visits (baseline and 1 year later), and a group×visit interaction; the study participant was modeled as a random effect. Pairwise comparisons were made using the least-squares contrasts derived from these mixed-effects models. We performed post hoc analyses to explore the effect of $\dot{V}o_2$ max, LVEDV, and LV stiffness. Random-effects linear regression models with quadratic terms were used to model the relationships in the PCWP and transmural pressure-volume curves and Frank-Starling curves, and to compare group responses with tests of interactions between group and independent variables, as well. The covariance structure for mixed-effects models was selected on the basis of Akaike information criteria and model parsimony. *P* value of <0.05 was considered statistically significant. Statistical analysis was performed using JMP version 11.0 (SAS Institute Inc).

RESULTS

Baseline Characteristics

Eighty-three candidate participants were consented and assessed for eligibility to participate in this study. Of these, 56 participants were randomly assigned, and 10 (2 participants in the controls and 8 in the exercise group) withdrew before completing baseline assessments and beginning their assigned intervention (Figure 1). The baseline characteristics of the 46 subjects who completed all baseline studies and began the study intervention are shown in Table 1. The 2 groups were comparable in age, sex, race, blood pressure, and maximal oxygen uptake.

In total, 31 participants completed the 1-year study, 20 participants in the exercise group and 11 in the control group. Figure 1 includes the reasons for withdrawal. The main reason for withdrawal and dropout from this study was related to personal reasons (n=5) or lost contact (n=5). Participants in the exercise group had favorable exercise compliance with the 1-year exercise training program (mean compliance rate, 67%), although somewhat lower than we have reported with healthy controls of this demographic.[13] Baseline characteristics, exercise, and hemodynamic parameters in subjects who completed all baseline assessments but dropped out during the intervention, compared with those who completed the whole intervention, are shown in Table I in the Data Supplement.

Table 1. Baseline Characteristics

Characteristics	Control group (n=16)	Exercise group (n=30)
Age, y	53±7	53±5
Sex, male/female	9/7	17/13
Body height, cm	172±9	172±12
Body weight, kg	96±14	87±16
Body surface area, m^2	2.14±0.20	2.03±0.24
Body mass index, kg/m^2	32.2±2.6	29.1±4.1
Lean body mass, kg	59±12	55±11
Race/ethnicity, n (%)		
White	9 (56)	15 (50)
Black	6 (38)	13 (43)
Hispanic	1 (6)	2 (7)
Risk factors, n (%)		
Hypertension	11 (69)	21 (70)
Diabetes mellites	1 (6)	3 (10)
Chronic kidney disease	0 (0)	0 (0)
Smoking	0 (0)	1 (3)
Medication, n (%)		
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	8 (50)	19 (63)
Ca^{2+} channel blocker	1 (6)	7 (23)
β-Blocker	2 (13)	4 (13)
Diuretics	5 (31)	5 (17)
24-hour ambulatory blood pressure monitoring		
Systolic blood pressure, mm Hg	131±13	134±15
Diastolic blood pressure, mm Hg	77±6	81±9
Mean blood pressure, mm Hg	95±8	97±14
Heart rate, bpm	74±8	74±13
Respiratory exchange ratio	1.15±0.07	1.13±0.08
$\dot{V}o_2$ max, L/min	2.38±0.71	2.16±0.56
$\dot{V}o_2$ max, $mL \cdot min^{-1} \cdot kg^{-1}$	24.5±5.3	24.7±5.2

Effect of Exercise Training on Oxygen Uptake and LVEDV

The exercise training program resulted in a significant increase in $\dot{V}o_2$ max in the exercise group (from 26.0±5.3 to 31.3±5.8 $mL \cdot min^{-1} \cdot kg^{-1}$, *P*<0.0001). In contrast, there was no significant change in the control group (from 24.6±3.4 to 24.1±4.1 $mL \cdot min^{-1} \cdot kg^{-1}$, *P*=0.986; interaction *P* value=0.0004; Table 2 and Figure 2).

We observed a similar pattern between changes in LVEDV in the 2 groups (interaction *P* value<0.0001; Figure 3). In the exercise group, LVEDV increased significantly

Table 2. Cardiopulmonary Exercise Test

Cardiopulmonary measures	Control group (n=11)		Exercise group (n=20)		Group×time interaction *P* value
	Baseline	1 year later	Baseline	1 year later	
Rest					
Heart rate, bpm	81±12	78±12	77±13	69±11	0.254
Systolic blood pressure, mm Hg	128±16	127±22	129±13	134±15	0.470
Diastolic blood pressure, mm Hg	83±8	80±14	89±7	88±7	0.450
Mean blood pressure, mm Hg	98±9	96±16	102±7	104±8	0.357
Cardiac output, L/min	5.4±0.9	4.9±1.0	4.7±1.0	4.8±0.8	0.110
$\dot{V}o_2$, L/min	0.33±0.06	0.30±0.07	0.30±0.06	0.29±0.05	0.424
$\dot{V}o_2$, mL·min^{-1}·kg^{-1}	3.4±0.4	3.2±0.3	3.6±0.9	3.5±0.5	0.647
Peak					
Respiratory exchange ratio	1.14±0.06	1.13±0.04	1.13±0.08	1.13±0.06	0.446
Heart rate, bpm	168±12	163±17	166±21	165±22	0.103
Systolic blood pressure, mm Hg	200±12	205±31	200±25	218±23	0.297
Diastolic blood pressure, mm Hg	91±13	80±8	88±16	91±19	0.075
Mean blood pressure, mm Hg	127±8	122±14	125±14	133±16	0.080
Cardiac output, L/min	17.3±4.2	16.2±3.9	17.6±4.1	18.1±3.4	0.220
$\dot{V}o_2$ max, L/min	2.4±0.6	2.3±0.6	2.3±0.6	2.6±0.6*	0.0003
$\dot{V}o_2$ max, mL·min^{-1}·kg^{-1}	24.6±3.4	24.1±4.1	26.0±5.3	31.3±5.8 *†‡	0.0004
Peak arteriovenous oxygen difference	14.3±2.0	14.0±1.7	13.1±2.3	14.3±2.1	0.068
Peak lactate, mmol/L	7.5±1.5	6.4±1.1	7.1±2.5	7.9±1.6	0.074

*P<0.05 denotes significantly different from baseline in the same group.
†P<0.05 denotes significantly different from the control group at baseline.
‡P<0.05 denotes significantly different from the control group 1 year later.

after 1 year of exercise training (P<0.0001). There was no significant change in LVEDV in the control group (P=0.175).

Supine Hemodynamic Parameters

The effect of the exercise training on the hemodynamic variables is summarized in Table 3. Resting blood pressure was unchanged in both groups. Resting SV in the exercise group increased, whereas it decreased in the yoga group (interaction P value=0.056). HR in the exercise group decreased from 68±11 to 64±11 bpm, with no significant change in the yoga group, although this difference was more variable (interaction P value=0.226). There were no significant changes in

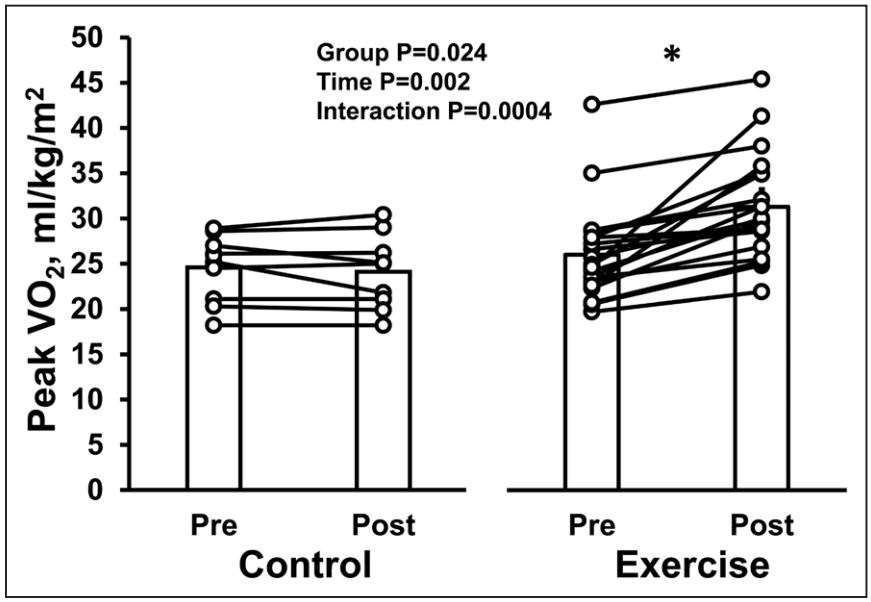

Figure 2. Effect of high-intensity exercise training on peak oxygen consumption in patients with left ventricular hypertrophy.
The individual change and group mean response for peak oxygen uptake are shown for the control and exercise group. *P<0.05 denotes significantly different from pre. Post indicates 1 year later; and pre, baseline.

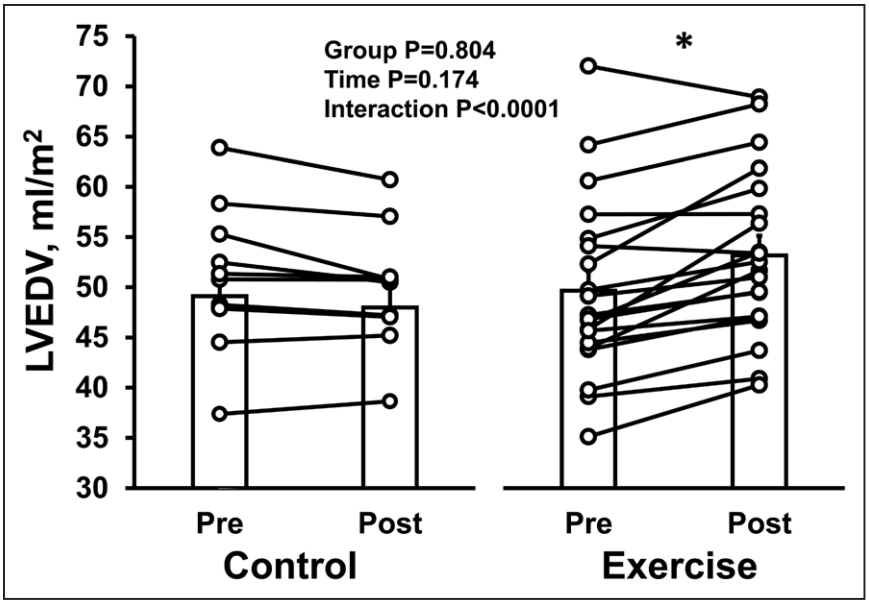

Figure 3. Effect of high-intensity exercise training on LVEDV.
The individual change and group mean response for LVEDV are shown for the control and exercise group. *P<0.05 denotes significantly different from pre. LVEDV indicates left ventricular end-diastolic volume; post, 1 year later; and pre, baseline.

resting supine cardiac output, central venous pressure, pulmonary capillary wedge pressure, and transmural pressure in either group (Table 3).

LV Pressure-Volume Relationship

Both LV chamber and myocardial stiffness constants at baseline were comparable between the 2 groups (P=0.198 and P=0.997, respectively). LV pressure-volume relationships are shown as LV chamber stiffness (Figure 4A) and LV myocardial stiffness (Figure 4B). One year of exercise training significantly reduced LV chamber and myocardial stiffness constants (LV chamber stiffness: from 0.060±0.031 to 0.042±0.025; LV myocardial stiffness: from 0.062±0.020 to 0.031±0.009), with no significant changes in the control group (LV chamber stiffness: from 0.041±0.016 to 0.049±0.020; LV myocardial stiffness: from 0.061±0.033 to 0.066±0.031; Figure 4A: interaction P value=0.015 and Figure 4B: interaction P value=0.023).

Table 3. Supine Hemodynamics and Cardiovascular Function

Cardiopulmonary measures	Control group (n=11)		Exercise group (n=20)		Group×time interaction P value
	Baseline	1 year later	Baseline	1 year later	
Heart rate, bpm	69±7	69±9	68±11	64±11	0.226
Systolic blood pressure, mm Hg	119±9	122±14	124±10	126±13	0.891
Diastolic blood pressure, mm Hg	73±9	70±8	77±8	77±9	0.411
Mean blood pressure, mm Hg	88±9	87±9	92±7	93±9	0.676
Cardiac output, L/min	6.2±1.0	5.7±1.0	5.5±1.1	5.3±1.0	0.250
Cardiac index, L·min^{-1}·m^{-2}	2.65±0.44	2.41±0.42	2.33±0.49	2.26±0.44	0.251
Stroke volume, mL	91±18	83±17	82±18	86±17	0.056
Stroke volume index, mL/m^2	39±8	35±7	35±7	36±7	0.062
Systemic vascular resistance, dyn·s^{-1}·cm^{-5}	1154±152	1270±289	1409±310	1464±357	0.511
Pulmonary capillary wedge pressure, mm Hg	14.1±2.5	12.9±2.4	13.1±2.6	12.3±2.8	0.783
Central venous pressure, mm Hg	10.8±2.0	9.1±2.1	9.6±2.5	8.7±1.9	0.418
Transmural pressure, mm Hg	3.2±1.0	3.7±1.4	3.5±1.1	3.6±1.2	0.480
Interventricular septum, mm	13.4±1.6	13.5±1.6	12.8±1.4	12.6±1.2	0.154
Posterior wall, mm	10.6±1.3	10.9±1.0	10.0±1.5	9.9±1.2	0.110
Body weight, kg	99±14	97±16	86±18	84±14	0.982
Visceral fat, kg	2.1±0.9	1.7±0.9	1.5±1.0	1.3±0.8	0.520
Lean body mass, kg	59±12	58±14	56±12	56±12	0.621
Body mass index, kg/m^2	33±2	32±2	28±4	28±3	0.638

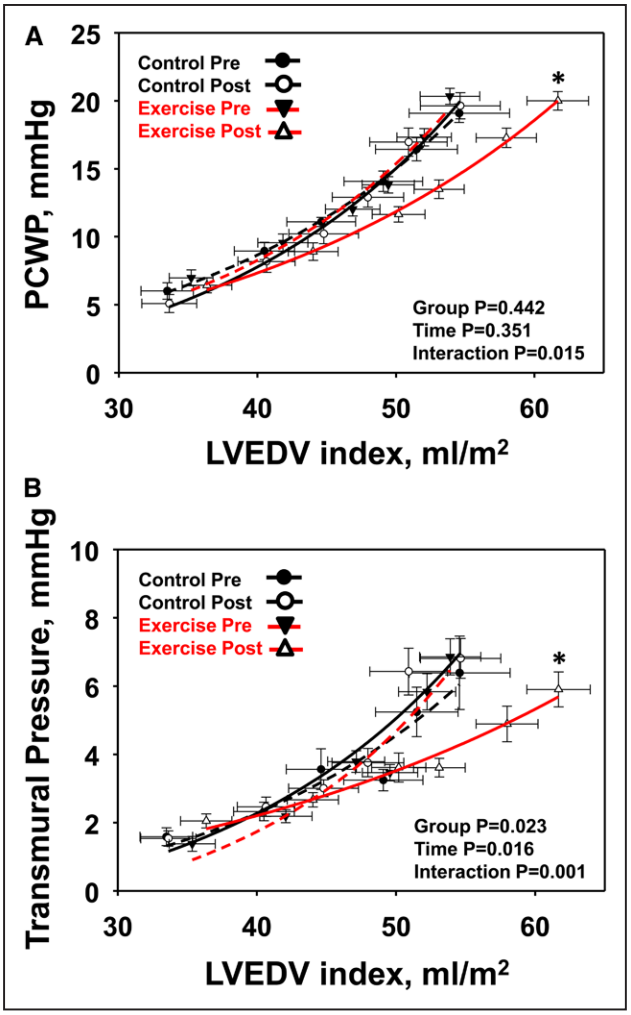

Figure 4. Effect of high-intensity exercise training on left ventricular chamber (A) and transmural stiffness (B).
The group mean left ventricular pressure-volume relationships before and after 1 year of intervention. In the exercise group, both the LV chamber (**A**) and LV transmural curves (**B**) were shifted rightward with a flattening slope demonstrating improved LV compliance and distensibility. Control group at pre, black dash line with closed black circle; Control group at post, black line with open circle; exercise group at pre, red dashed line with closed triangle; exercise group at post, red line with opened triangle. Those curves in the control group were unchanged. **P*<0.05 denotes significantly different from pre. LVEDV was scaled to body surface area. Transmural pressure=PCWP − right atrial pressure. LV indicates left ventricular; LVEDV, left ventricular end-diastolic volume; post, 1 year later; PCWP, pulmonary capillary wedge pressure; and pre, baseline.

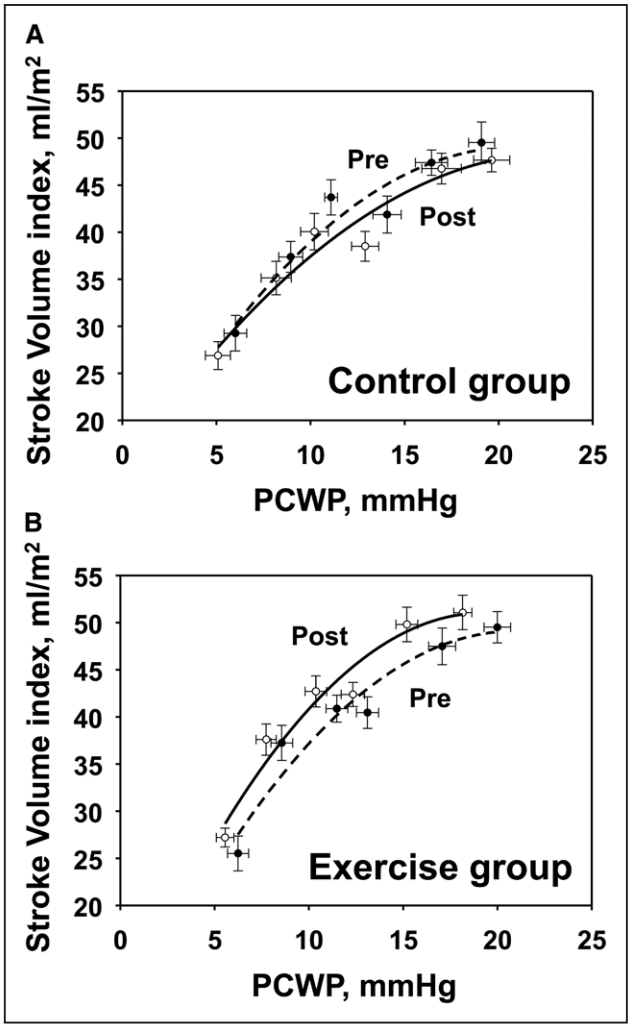

Figure 5. Starling mechanism.
Change in Starling relationship. Pre is the black dashed line with closed circle; Post is black line with open circle. There was no significant change in the control group (**A**), whereas 1 year of training improved Starling curves (**B**), such that an increase in stroke volume index was observed compared with baseline for a given left ventricular filling pressure. post indicates 1 year later; PCWP, pulmonary capillary wedge pressure; and pre, baseline.

Starling Mechanism and Preload Recruitable Stroke Work

The Starling curves in the control group were comparable between baseline and 1 year later (Figure 5A). In contrast, 1 year of exercise training resulted in an upward shift in the Starling curves in the exercise group, allowing for slightly greater SV for any given LV filling pressure (Figure 5B). Neither exercise nor control groups changed global systolic function as assessed by the slope of the preload recruitable stroke work (interaction *P* value=0.150; Figure 6A and 6B).

DISCUSSION

This study was a prospective randomized controlled trial to elucidate the effect of prolonged exercise training on LV end-diastolic pressure-volume relationships in patients with stage B HFpEF. The key new findings from this study are that 1 year of prolonged exercise training in this population can improve (a) physical fitness and $\dot{V}o_2$ max, (b) LV diastolic chamber and myocardial stiffness (right downward shift), and (c) the Starling mechanism (upward shift) in patients with LVH and elevated cardiac biomarkers. These patients have already demonstrated LV stiffening[17] and thus fit the AHA/American College

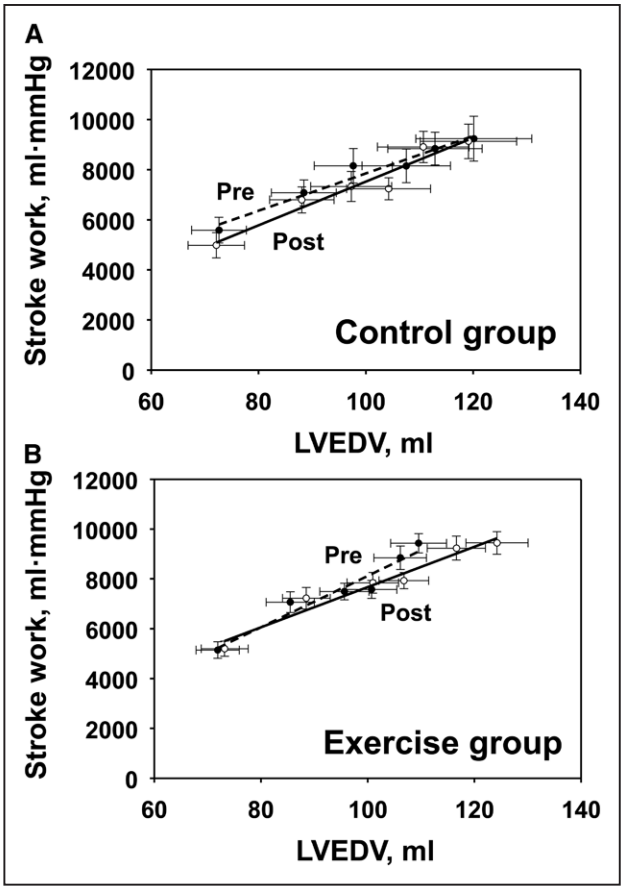

Figure 6. Preload-recruitable stroke work.
A, Control group; **B**, training group. Pre is the black-dash line with closed circle; Post is the black line with opened circle. There was no significant effect of exercise training or aging on preload recruitable stroke work. Interaction *P* value=0.150; group *P* value=0.940; and time *P* value=0.111. LVEDV indicates left ventricular end-diastolic volume; post, 1 year later; and pre, baseline.

of Cardiology definition of stage B HFpEF, specifically patients with structural heart disease but no current or prior symptoms of HF.[36] We propose that targeting such patients at an early stage of their disease with a pathophysiologically directed lifestyle intervention may be an especially attractive strategy to protect against the full elaboration of the HFpEF syndrome, which is so difficult to treat once established.

Cardiac Stiffening in HFpEF: A Target for Prevention

HFpEF is a syndrome characterized by older age, multiple comorbidities including diabetes and hypertension, and ultimately a stiff heart that relaxes slowly.[31,37] Symptoms in patients with HFpEF are dominated by exercise intolerance, in particular, dyspnea on exertion. Although there are many potential mechanisms for this core symptom, it is closely associated with very high filling pressures during exercise.[38] Hearts of patients with HFpEF evince steep (and stiff) LV pressure-volume curves with abnormal chamber and myocardial compliance,[2,31] suggesting that increased myocardial stiffness underlies much of the rapid rise of pulmonary capillary wedge pressure as LV filling increases during exercise.

Slowed relaxation, increased pericardial constraint, and increases in passive myocardial stiffness may all contribute to a rise in filling pressure during exercise, and all have been demonstrated to some degree or another in patients with HFpEF.[2,5,31,38,39] Increases in passive stiffness have been consistently demonstrated and have been attributed to alterations in both the collagen-dependent connective tissue matrix, and the phosphorylation of titin, the large spring-like protein that determines much of the compliance of myocardial tissue.[40,41] Patients with HFpEF also have increased fibrosis and myocardial cell hypertrophy, although the absolute magnitude of the fibrosis is relatively mild in the majority of such patients.[42]

Patients with hypertension alone without HFpEF though appear to be less clearly affected with limited evidence of excessive stiffening or fibrosis.[3,40] Moreover, sedentary aging, even without comorbidities, leads to LV chamber stiffness that is not radically different from patients with HFpEF.[31] Thus, sedentary aging by itself at least sets the stage for exacerbation and secondary remodeling from comorbidities such as obesity, diabetes, and hypertension that leads to the full expression of the HFpEF syndrome.[43]

Exercise Training Preserves or Increases Myocardial Compliance

In contrast with sedentary aging, high levels of physical activity throughout the lifespan preserve youthful LV chamber and myocardial compliance,[29] and vascular compliance, as well,[44] although fitness effects on preserving active myocardial relaxation are less protective.[45] Cross-sectional studies suggest that 4 to 5 days per week of committed exercise throughout the aging process are sufficient to achieve most of these effects,[9,46] which is consistent with recent physical activity guidelines for optimal health.[28]

Prolonged exercise training in youth can recapitulate much of the essential cardiac phenotype of the heart of the athlete that is characterized by a large, compliant LV that can accommodate large volumes during exercise.[23,47] However, once the heart has stiffened in older age, improvements in cardiac or vascular compliance are much harder to obtain. For example, a year of prolonged and intensive exercise training in previously sedentary healthy older men and women failed to change LV chamber and myocardial[10] or vascular[48] compliance. Training was similarly ineffective in changing cardiac compliance in patients with established HFpEF.[11] It is intriguing that the addition of a drug that breaks advanced glycation end products when combined with exercise training induced modest improvements in myocardial compliance in sed-

entary older adults,[12] suggesting that at least some of the changes in passive stiffness with sedentary aging that set the stage for HFpEF may accrue through changes in the connective tissue matrix.

Right Dose, Right Time, Right Patient Population

It is clear that once established, HFpEF is very difficult to treat with few effective therapies.[49] Therefore strategies to prevent this widespread disorder are essential.[7] Previous work from our group has shown that the heart begins to stiffen in late middle age,[8] which suggested that initiating an exercise training program earlier in the aging process might be more beneficial than once cardiac stiffening has become firmly established. A recent study showed that 2 years of exercise training in middle-aged men and women, at the dose (frequency and intensity) that preserved cardiac and vascular compliance with aging (ie, 4–5 days per week),[9] was able to reverse the cardiac effects of sedentary aging and restore youthful chamber and myocardial compliance.[13]

Patients with hypertension and LVH form a major population at high risk for developing HFpEF and thus are an ideal target for interventions to prevent HFpEF. Recent data from our group showed that patients with LVH who also have elevated biomarkers, including high-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide, representing ongoing cardiac injury and hemodynamic stress,[16] have a phenotype that is intermediate between healthy sedentary aging and HFpEF with increased myocardial stiffness (stage B HFpEF).[17] Whether they could respond similarly to exercise training as healthy middle-aged individuals, however, was unknown and the focus of this study.

The presence of elevated biomarkers in patients with LVH is not only a clinical marker of high risk, but suggests the presence of pathological remodeling, which involves distinct biological pathways compared with the physiological remodeling of exercise.[50,51] Pathological growth is characterized by activation of fetal gene programs that include the induction of natriuretic peptides, and other changes to the sarcomere, as wsell.[51] In contrast, such changes are not induced by exercise training that is mediated by completely different pathways.[52] Activation of physiological growth programs, involving Akt (protein kinase B), PI3K (phosphoinositide 3-kinase), and IGF-1 (insulin-like growth factor 1) signaling,[53] may directly antagonize the effects of pathological growth.[51] Numerous pathways mediating physiological growth have been identified, modulated by posttranscriptional regulation by microRNAs that alter titin isoforms, matrix metalloproteinases, and collagen expression.[52,54,55] These adaptations lead to increased length of cardiomyocytes,[52] thus adding sarcomeres in series (reducing the force required to stretch the spring action of titin) and improving passive myocardial compliance with exercise training.

In the present study, we demonstrated that a year of training in patients at high risk for developing HFpEF can be quite effective. $\dot{V}o_2$ max was increased by 20% confirming the expected response to training in this population. LVEDV increased consistent with physiological remodeling and was accompanied by a prominent increase in both LV chamber (including pericardial constraint) and myocardial compliance. Although these patients with stage B HFpEF started with greater myocardial stiffness (constant 0.062±0.020) than our previously reported healthy, sedentary middle-aged individuals (0.051±0.028),[13] their myocardial stiffness constant after training was smaller (ie, less stiff; 0.031±0.009) than the healthy, sedentary middle-aged individuals at baseline, and equivalent to those subjects after 2 years of training (0.039±0.020).[13]

Although the exact mechanism of this increased compliance cannot be determined from this study, this outcome is consistent with activation of physiological growth pathways that antagonized the pathological growth initiated by both sedentary behavior and the presence of LVH with elevated biomarkers. Whether these changes can be sustained over time, especially if patients revert to their previous sedentary habits, is unknown. Moreover, 1 year is too short to determine whether HFpEF can actually be prevented with such an intervention. However, such adaptations as we observed do suggest that the underlying pathophysiology of these patients with stage B HFpEF can be altered. Last, cross-sectional studies of patients with documented sustained high levels of physical activity demonstrate normal and youthful levels of cardiac compliance even into the 7th and 8th decades of life,[9] providing some support for the concept that sustained physical activity in high-risk patients may be able to forestall HFpEF.

Although the practice of exercise training to improve cardiovascular function is not new, the idea of "Exercise is Medicine" is paradigm shifting.[13,56] This concept refers to the global idea that daily physical activity has such profound and important benefits that it should be considered as a specific medical therapy. Considering exercise as a drug with a specific dose (frequency, intensity, duration) targeted for a well-defined, high-risk population and a specific biological outcome using evidence-based training strategies is especially relevant to diseases like HFpEF where prevention may be more effective than treatment.[57–59]

Study Limitations

This study has several limitations. First, this study had a relatively high dropout rate and the training compliance in the exercise group was relatively low (67%) compared with our previous study in healthy middle-aged men and

women.[13] Moreover, the effective number of participants was small. Nevertheless, the outcomes for performance variables such as $\dot{V}o_2$ max was clear, and the changes in LVEDV, LV chamber, and myocardial compliance were compelling, especially compared with a control group where no significant changes were observed. Moreover, there were no significant differences in baseline characteristics, cardiorespiratory fitness, or hemodynamic parameters between those participants who completed the intervention and those who withdrew. Compliance with exercise training, like any therapeutic intervention, may be challenging, although there are many proposed strategies to sustain higher rates of physical activity in clinical populations.[60,61] Second, our study is limited to patients with stage B HFpEF with LVH and elevated biomarkers and may not be generalizable to other pre-HFpEF patient populations, such as patients with diabetes or marked obesity. In addition, we did not study patients who had LVH without elevated biomarkers. We suspect, but cannot prove, that it is unlikely that such patients would have stiffer LVs than patients with LVH with elevated biomarkers, especially given the lack of apparent increased passive stiffness in biopsies from patients with hypertension but not HFpEF taken during cardiac surgery.[40] Thus, although other groups of patients might also demonstrate an intermediate stage B phenotype, we strongly believe that the specific patients studied here represent a particularly high-risk group and should be considered for targeted preventative therapies.

Conclusion

In patients with LVH and elevated cardiac biomarkers (stage B HFpEF), 1 year of committed exercise training can improve fitness and reverse LV myocardial stiffening. Vigorous exercise training, implemented 4 to 5 times per week in high-risk middle-aged men and women over a prolonged period, holds promise as a potential intervention to protect against the future risk of HFpEF in such patients.

ARTICLE INFORMATION

Received February 7, 2021; accepted July 26, 2021.

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Acknowledgments

The authors gratefully acknowledge the participants in this study for their time and patience, and the work of past and present members of our laboratory. They also thank C. Oufi and R. Murugappan for their technical support in performing the experiments.

Sources of Funding

This study was supported by National Institutes of Health grant AG017479, and by the American Heart Association Strategically Focused Research Network (14SFRN20600009-03). Dr Hieda was also supported by American Heart Association postdoctoral fellowship grant 18POST33960092 and the Harry S. Moss Heart Trust. Dr Hearon was supported by National Institutes of Health grants F32HL137285 and K99HL153777-01.

Disclosures

None.

Supplement Materials

Data Supplement Table I

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