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ORIGINAL RESEARCH ARTICLE

# Reversing the Cardiac Effects of Sedentary Aging in Middle Age—A Randomized Controlled Trial

## Implications For Heart Failure Prevention

**Erin J. Howden, PhD**
**Satyam Sarma, MD**
**Justin S. Lawley, PhD**
**Mildred Opondo, MD**
**William Cornwell, MD**
**Douglas Stoller, MD, PhD**
**Marcus A. Urey, MD**
**Beverley Adams-Huet, MS**
**Benjamin D. Levine, MD**

**BACKGROUND:** Poor fitness in middle age is a risk factor for heart failure, particularly heart failure with a preserved ejection fraction. The development of heart failure with a preserved ejection fraction is likely mediated through increased left ventricular (LV) stiffness, a consequence of sedentary aging. In a prospective, parallel group, randomized controlled trial, we examined the effect of 2 years of supervised high-intensity exercise training on LV stiffness.

**METHODS:** Sixty-one (48% male) healthy, sedentary, middle-aged participants (53±5 years) were randomly assigned to either 2 years of exercise training (n=34) or attention control (control; n=27). Right heart catheterization and 3-dimensional echocardiography were performed with preload manipulations to define LV end-diastolic pressure-volume relationships and Frank-Starling curves. LV stiffness was calculated by curve fit of the diastolic pressure-volume curve. Maximal oxygen uptake ($\dot{V}o_2max$) was measured to quantify changes in fitness.

**RESULTS:** Fifty-three participants completed the study. Adherence to prescribed exercise sessions was 88±11%. $\dot{V}o_2max$ increased by 18% (exercise training: pre 29.0±4.8 to post 34.4±6.4; control: pre 29.5±5.3 to post 28.7±5.4, group×time $P<0.001$) and LV stiffness was reduced (right/downward shift in the end-diastolic pressure-volume relationships; preexercise training stiffness constant 0.072±0.037 to postexercise training 0.051±0.0268, $P=0.0018$), whereas there was no change in controls (group×time $P<0.001$; pre stiffness constant 0.0635±0.026 to post 0.062±0.031, $P=0.83$). Exercise increased LV end-diastolic volume (group×time $P<0.001$), whereas pulmonary capillary wedge pressure was unchanged, providing greater stroke volume for any given filling pressure (loading×group×time $P=0.007$).

**CONCLUSIONS:** In previously sedentary healthy middle-aged adults, 2 years of exercise training improved maximal oxygen uptake and decreased cardiac stiffness. Regular exercise training may provide protection against the future risk of heart failure with a preserved ejection fraction by preventing the increase in cardiac stiffness attributable to sedentary aging.

**CLINICAL TRIAL REGISTRATION:** URL: https://clinicaltrials.gov. Unique identifier: NCT02039154.

**Key Words:** catheterization ■ diastole ■ exercise ■ humans ■ monitoring, physiological ■ prevention & control ■ ventricular function ■ ventricular remodeling

Sources of Funding, see page xxx

## Clinical Perspective

### What Is New?

- Poor fitness in middle age is a strong predictor of future risk of heart failure and is associated with increased cardiac stiffness, a potential precursor to heart failure with preserved ejection fraction.
- However, waiting until heart failure develops or older age cements the effects of a sedentary lifestyle may be too late.
- This study demonstrates that prolonged (2 years) exercise training, initiated in middle age, can forestall the deleterious effects of sedentary aging by reducing cardiac stiffness and increasing fitness.
- These results provide a mechanistic underpinning and substantial evidence in support of physical activity guidelines.

### What Are the Clinical Implications?

- Lifestyle modification with an optimized exercise program including high-intensity and moderate-intensity exercise training is an effective strategy to reverse the effects of sedentary aging on the heart.
- Findings support the need for future prospective studies to evaluate the role of exercise training in specific populations at risk of developing heart failure with a preserved ejection fraction.

Sedentary aging is strongly associated with deleterious changes in cardiovascular function, including an increase in left ventricular (LV) stiffness.[1] Sedentary seniors have small stiff LVs, which are comparable to patients with heart failure with a preserved ejection fraction (HFpEF).[2] In contrast, competitive Masters athletes have large, compliant LVs equivalent to much younger individuals,[3] suggesting that exercise training, performed at a very high level over a lifetime, may counteract the detrimental effects of aging and inactivity on the LV.

Although competitive Masters athletes are a useful model for characterizing the upper limits of cardiovascular protection from prolonged exercise training, the volume of training performed by these individuals (≥6 days/wk plus competitions) is not feasible for the general population. Although it appears that 4 to 5 days of committed exercise training over decades is adequate to achieve most of this benefit,[4] it is unclear whether exercise training can restore or improve LV compliance in previously sedentary individuals, and if so, when is the optimal stage of life to intervene.

Epidemiological studies show that a measurement of fitness in middle age is the strongest predictor of future heart failure.[5–7] Moreover, in observational studies, the dose of exercise associated with reduced heart failure incidence is much higher than that associated with reduced mortality.[8] However, if exercise is started too late in life (ie, after 65 years) in sedentary individuals, there is little effect on LV stiffness.[9,10] Thus, a lifetime of sedentary aging is associated with a reduction of cardiac plasticity, which cannot be overcome with a year of moderate-intensity exercise training. We recently documented that this LV stiffening begins to be identifiable during middle age with a leftward shift in the LV end-diastolic pressure volume curve.[11] We hypothesize that middle-aged hearts retain some degree of cardiac plasticity and may represent a more optimal time to intervene with aggressive lifestyle modification aimed at improving cardiac stiffness.

Based on these observations and the growing body of literature on the benefits of high-intensity interval training,[12,13] we hypothesized that an optimized exercise prescription (≥4 days/wk including high-intensity interval training) initiated in middle age may be an effective strategy to prevent LV stiffening, a key pathophysiologic characteristic of HFpEF. Therefore, we sought to determine the effects of 2 years of supervised exercise training on LV compliance and distensibility in previously sedentary, middle-aged individuals.

## METHODS

### Participant Population and Study Design

This study was a prospective, parallel group, randomized controlled 2-year exercise training study. Sixty-one healthy, sedentary middle-aged (45–64 years) participants were recruited from the Dallas Heart Study,[14] employees at Texas Health Resources and the University of Texas Southwestern Medical Center, and through local media. For the latter, emails and electronic newsletters were distributed to staff at Texas Health Resources and the University of Texas Southwestern Medical Center. In brief, Texas Health Resources has ≈20 500 employees. Emails were sent to all employees in a staggered fashion (ie, the first half or the alphabet followed by the second half of the alphabet ≈1 month later). Three rounds of emails were sent between September 2012 and February 2014. Employees from the University of Texas Southwestern Medical Center responded to a call for participants posted in a weekly institute-wide email circulated to all staff and students. In addition, local newspapers and online media published articles on the benefits of exercise that referred to the trial and included contact information for interested readers. Two hundred sixty-two individuals expressed interest in participating in the study and underwent screening (Figure 1). After obtaining informed consent, all participants were rigorously screened for comorbidities, and were excluded if any of the following conditions were present: hypertension (use of antihypertensive medication or ambulatory systolic blood pressure >135 mm Hg), body mass index ≥30 kg/m$^2$, untreated hypo- or hyperthyroidism, obstructive sleep apnea, chronic obstructive pulmonary disease, tobacco use during past 10 years, coronary artery disease, or structural heart disease. Participants were also excluded if they reported a consistent exercise history that involved exercising for >30 minutes, 3



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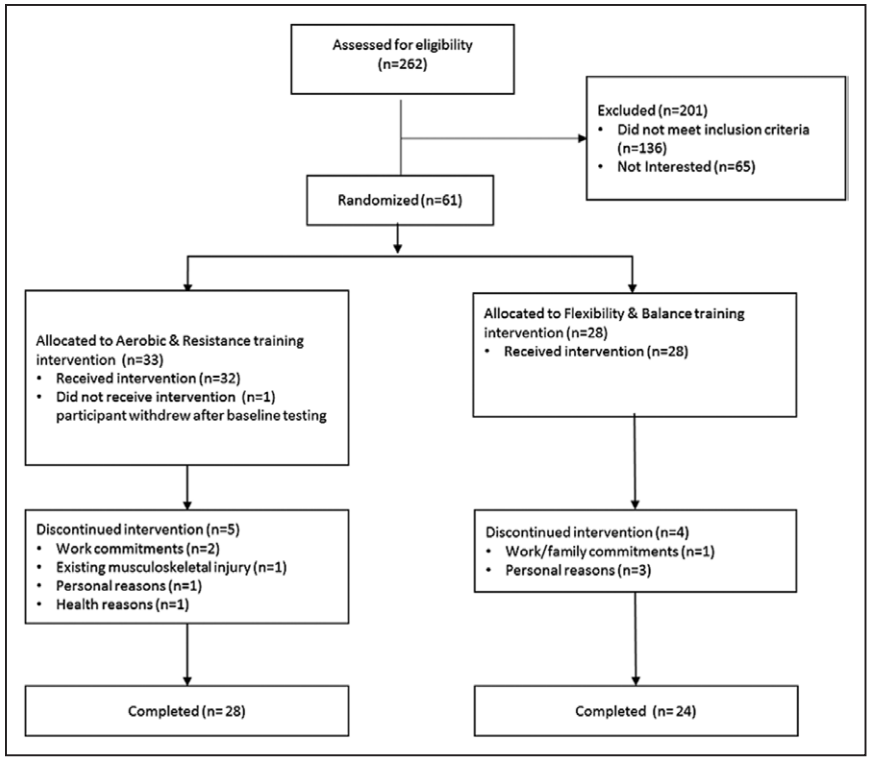


**Figure 1. Enrollment, randomization, and retention of study participants randomly assigned to the exercise training or control group.**

times/wk or more. A detailed medical history, physical examination, echocardiogram, and exercise stress test for detection of ischemia were performed before participants were enrolled in the study. Eligible participants were randomly assigned by using block randomization by a statistician (B.A.-H.), to either exercise training (ExT) or a balance and flexibility (yoga) control group (control). The ratio was 1.2 ExT to 1 control, because of an expected higher attrition in the ExT group (see sample size calculation below), and groups were stratified by sex. 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 and Texas Health Presbyterian Hospital Dallas. All procedures conformed to the standards set by the Declaration of Helsinki. This trial was registered on ClinicalTrials.gov (NCT02039154) and was overseen by an independent data safety and monitoring board. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

## Sample Size Calculation

The primary outcome variable was the change in ventricular chamber stiffness after 2 years of exercise training. Sample size calculations were based on the difference between individually calculated mean stiffness constants of our previous work, which characterized the effects of aging on LV stiffness.[11] Based on these findings, we assumed a significant difference in stiffness constant of 24 U with a standard deviation of 30 U, and a within-participant correlation of $\rho$=0.6 in a 2-factor (intervention and evaluation time) mixed-model repeated-measures design (intervention is the between-group factor, time is repeated) from before to after 2 years of training. Based on the required between-groups difference and assuming that there would be no change in LV stiffness in controls, with an $\alpha$-error of 0.05 and a power of 0.80, we required 21 participants per group to be adequately powered to address our hypothesis.

## Intervention

### *Exercise Training*

The ExT program followed a periodized approach, where increases in training frequency, duration, and intensity progressed over time. Each participant was provided with an individualized training plan. Exercise physiologists met with participants monthly throughout the intervention. The majority of monthly meetings were conducted in person; however, if this was not logistically possible, meetings were conducted electronically. During the initial training phase, exercise physiologists directly supervised many exercise sessions with the goal of educating participants about the different type of sessions and providing support and guidance to build self-confidence, develop self-efficacy to facilitate the independent completion of the exercise program. During monthly consults, exercise physiologists discussed the individual's progress, reviewed adherence to the intervention, and noted any issues (eg, musculoskeletal injuries, acute illness). The majority of exercise sessions throughout the training program were not supervised, although every session was carefully tracked using heart rate (HR) monitors. 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.[15] Based on the MSS HR and peak HR (HRpeak), 4 training zones were established for each participant: (1) MSS; (2) base pace (1–20 beats below

MSS); (3) interval (>95% HR peak); and recovery (<base pace). The early training phase (month 1–2) focused on establishing an endurance base and regular exercise routine with participants performing 3, 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 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.[16] A recovery day consisting of 20 to 30 minutes of walking or light aerobic activity followed each interval day. By the sixth month, participants were training 5 to 6 hours per week, including 2 interval sessions, and 1 long (at least an hour) and one 30-minute base pace session each week. This training load was maintained for 4 months. After completion of the 10-month progression, exercise capacity was retested and then participants began the maintenance training phase. Training zones were adjusted to reflect the results of the most recent exercise test. During this period, participants performed only 1 interval session per week plus continuous training. Participants were encouraged to use a variety of exercise equipment (eg, stationary cycle ergometer, treadmill, elliptical trainer) or perform exercise sessions outdoors (eg, running on trails, cycling, swimming) to ensure participant enjoyment and to avoid overuse injuries. To supplement the endurance training, 2 weekly strength training sessions were prescribed. These sessions were designed to focus on whole body functional and core strength to complement the endurance training.

### Balance and Flexibility Training (Control)

The balance and flexibility group was prescribed a combination of yoga, balance, and strength training 3 times per week for 2 years. Participants attended group yoga or stretching classes, or completed online or video classes at home. Participants were asked to refrain from attending hot yoga classes or completing prolonged endurance activities. This prescription allowed for a similar level of interaction with research staff between both groups.

To that end, each participant (ExT group and control group) was assigned an exercise physiologist who monitored their training compliance throughout the 2-year intervention. An exercise log and heart rate monitor (Polar) were used to monitor training compliance. Training load was quantified by the training impulse.[17] Specific training impulse calculations for continuous and interval training were used.[18] The mean monthly training load is presented in Figure I in the online-only Data Supplement.

## Measurements

### Exercise Testing

Measurements of maximal oxygen uptake were performed with a modified Astrand-Saltin protocol involving incremental exercise on a treadmill, at baseline, 10 months (after the peak training phase), and at 2 years by using the Douglas bag technique; gas fractions were analyzed by mass spectrometry, and ventilatory volumes were analyzed by a Tissot spirometer, as previously reported.[3] Maximal oxygen uptake ($\dot{V}o_2max$) was defined as the highest oxygen uptake measured from at least a 30-second Douglas bag.

### Echocardiography

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

### Total Blood Volume

Total blood volume was measured using the carbon monoxide rebreathing method, modified from that described by Burge and Skinner,[19] and has been reported in detail previously.[20]

### Body Composition

Body density and composition were determined by underwater weighing with correction for residual lung volume.[21]

### Right Heart Catheterization

Right heart catheterization was performed before and after the 2-year intervention. A 6F Swan-Ganz catheter was placed under fluoroscopic guidance through an antecubital vein and advanced into the pulmonary artery. The wedge position of the catheter was confirmed by both fluoroscopy and the presence of typical waveforms. Mean pulmonary capillary wedge pressure (PCWP) and right atrial pressure were determined visually at end expiration using an electronic data measurement system (BIOPAC Systems Inc., Santa Barbara, CA).

### Hemodynamics

Cardiac output (Qc) was determined by the rebreathing technique with acetylene as the soluble gas and helium as the insoluble gas[22] as the primary measure of Qc; in a few subjects who experienced technical difficulty with the rebreathing maneuver, Qc was calculated from thermodilution. Stroke volume (SV) was calculated from Qc and HR. Total arterial compliance was determined by the ratio of SV and pulse pressure to evaluate central aortic function. Effective arterial elastance was defined as the ratio of end-systolic pressure over SV[23] with end-systolic pressure estimated by use of the single-beat method as previously described and validated.[24]

## Experimental Protocol

After 20 minutes of quiet rest, serial hemodynamic measurements (eg, Qc, blood pressure, and HR) were performed to establish a stable baseline. Lower body negative pressure was then used to decrease cardiac filling as previously reported.[3,9,25] Measurements including HR, PCWP, right atrial pressure, blood pressure, LVEDV, and Qc were performed after 5 minutes each of –15 mm Hg and –30 mm Hg lower body negative pressure. The lower body negative pressure was then released. Thereafter, baseline measurements were repeated, and the cardiac filling pressure was measured after rapid infusion (≈200 mL/min) of warm (37°C) isotonic saline. Measurements were repeated after 10 to 15 mL/kg and 20 to 30 mL/kg of saline infusion had been infused.

### Assessment of Cardiac Catheterization Data

In each participant, a LV end-diastolic pressure-volume relationship was constructed by using the PCWP and scaled LVEDV index obtained at each stage of the preload manipulation,

as previously reported.[4,10] A constant for LV chamber stiffness (stiffness being the inverse of compliance) was modeled using commercially available software (SigmaPlot version 13.0, Systat Software Inc), which uses an iterative technique to solve the following exponential equation[26]: $= P_{\infty}(exp^{a(V-V0)} - 1)$, where $P$ is PCWP, $P_{\infty}$ is pressure asymptote of the curve, $V$ is LVEDV, $V_0$ is the equilibrium volume at which $P$ is assumed to be 0 mm Hg, and $a$ is the constant that characterizes chamber stiffness. Modeling was performed for each individual participant, at baseline and repeated after 2 years. The averages of the individual LV chamber stiffness constants for all the participants within each group are reported and denoted as individual stiffness. To characterize the overall groups in terms of pressure-volume curves prior to initiating either intervention and after completion of 2 years follow-up–post intervention, a single curve was also fit to the data that were derived from the means of each loading condition, which are referred to as group curves. Because external constraint influences ventricular volumes and pressure, LV end-diastolic transmural pressure-volume relationships were constructed using estimated transmural pressure (PCWP-right atrial pressure).[27] Transmural stiffness constants were modeled as described above. PCWP and SV data were used to construct Frank-Starling relationships. The SV, mean arterial pressure (MAP), and 3-dimensional LVEDV data were used to construct preload recruitable stroke work relationships (PRSW=[SV×MAP]/LVEDV). The slope of this relationship was used as an index of global systolic function.[28]

### *Statistical Analysis*

Continuous variables are expressed as mean, 95% confidence intervals (CIs), and categorical variables are expressed as n (%). The primary analysis included all participants who completed the 2-year follow-up. Continuous end points were compared between groups by using mixed-effects model repeated-measures analysis. The repeated-measures models included the intervention group factor (control versus ExT), a repeated factor for study visits, and a group×visit interaction term; the study participant was modeled as a random effect. The difference in response between control and ExT groups was assessed via the interaction effect. Pairwise comparisons were made using the least square contrasts derived from these mixed-effects models. Based on prior observations of sex differences in response to exercise training,[15] we performed a post hoc analysis to explore the impact of sex on exercise capacity ($\dot{V}o_2$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. The covariance structure for mixed-effects models was selected based on Akaike Information Criteria and model parsimony. A 2-sided $P$ value of <0.05 was considered statistically significant. The analysis was performed using SAS version 9.4, SAS Institute.

# RESULTS

## Participant Characteristics

Two-hundred sixty-two participants were screened and assessed for eligibility to participate in this study between August 2012 and February 2014. Of these, 61 participants were randomly assigned (see Figure 1 for Consort diagram and a detailed description in the online-only Data Supplement). The participant characteristics are summarized in Table 1. The 2 groups exhibited similar clinical characteristics including age, sex, ambulatory blood pressure, BMI, and maximal oxygen uptake. In total, 52 participants completed the 2-year study, 28 in the ExT group and 24 in the control group. The primary reason for withdrawal from the study was related to either work or family commitments (n=3) or personal reasons (n=4). One participant withdrew immediately after completion of the pretesting before initiating any intervention.

## Compliance With Prescribed ExT

Participants in the ExT group maintained excellent compliance with the 2-year exercise intervention (mean 88±11%). Six participants maintained almost perfect compliance to the prescribed training (completing ≥97% of prescribed sessions).

## Effect of Exercise Intervention

We observed a classic training response in the ExT group. Maximal oxygen uptake increased in response to the progressive exercise load from month 1 to 9, before remaining stable during the maintenance training phase. Overall, the intervention resulted in a significant increase in $\dot{V}o_2$max of 5.3 (95% CI, 4.15–6.40) mL·kg$^{-1}$·min$^{-1}$ or 18 (95% CI, 15–22)%; in contrast,

**Table 1. Participant Baseline Characteristics**

| Variable | Control Group (n=28) | Exercise Training Group (n=33) |
|---|---|---|
| Age, y | 51.4 (49.4–53.4) | 53.2 (51.5–54.9) |
| Sex, male, n (%) | 13 (46) | 15 (45) |
| Weight, kg | 75.4 (70.0–80.9) | 75.1 (70.2–80.0) |
| Height, cm | 169 (165–173) | 170 (167–173) |
| Body mass index, kg/m$^2$ | 26.2 (25.0–27.5) | 25.8 (24.7–26.8) |
| Body surface area, m$^2$ | 1.88 (1.79–1.96) | 1.88 (1.80–1.96) |
| Race, n (%) | | |
| White | 23 (82) | 26 (79) |
| Black | – | 1 (3) |
| Hispanic | 2 (7) | 2 (6) |
| Asian | 3 (11) | 4 (12) |
| 24-hour ambulatory systolic blood pressure, mm Hg | 123 (120–126) | 120 (118–123) |
| 24-hour ambulatory diastolic blood pressure, mm Hg | 74 (72–76) | 72 (70–74) |
| $\dot{V}o_2$max, mL·kg$^{-1}$·min$^{-1}$ | 29.5 (27.6–31.4) | 29.0 (27.3–30.7) |

Values are shown as mean (95% confidence intervals) or n (%). $\dot{V}o_2$max indicates maximal oxygen uptake.

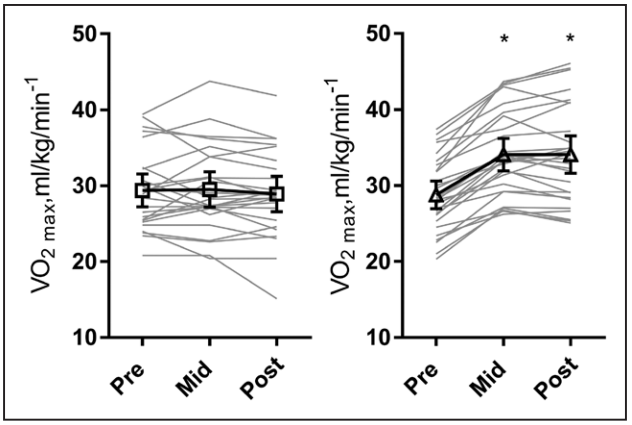


**Figure 2. Effect of intervention on maximal exercise capacity.**
The individual change and group mean response for maximal oxygen uptake are shown in **A** and **B** for the control and exercise group. As expected, with sedentary aging there was a small decrease in maximal oxygen uptake in the control group over the 2 years, whereas, in the ExT group, $\dot{V}o_2$max increased from the value measured before randomization to the intervention to testing at 10 months, before remaining unchanged for the remaining 14 months of the study. **P*<0.05 denotes significantly different from pre. LVEDV indicates left ventricular end-diastolic volume.

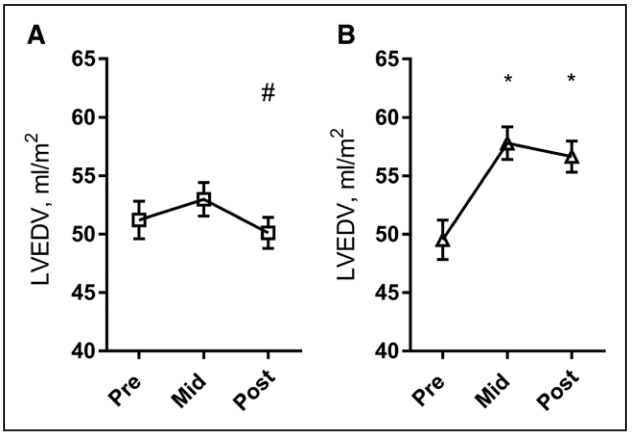


**Figure 3. Effect of intervention on left ventricular end-diastolic volume index.**
The group mean response for LVEDV are shown in **A** and **B** for the control and exercise group, respectively. The progressive exercise training from pre to testing at 10 months resulted in a 17% increase in LVEDV, without further increase when training intensity maintained. **P*<0.05 denotes significantly different from pre. #*P*<0.05 denotes significantly different from mid. LVEDV indicates left ventricular end-diastolic volume.

there was no improvement in maximal oxygen uptake in the control group –0.3 (95% CI, –1.3 to 0.7) mL·kg$^{-1}$·min$^{-1}$ or –1.0 (95% CI, 4.8–2.7)% (Figure 2A and 2B; group×time *P*<0.0001; control, time *P*=0.14; ExT, time *P*<0.0001). We observed a similar pattern between changes in LV end-diastolic volume and $\dot{V}o_2$max in both groups (Figure 3A and 3B; group×time *P*=0.0001; control, time *P*=0.018; ExT, time *P*<0.0001), such that LV end-diastolic volume increased significantly after the progressive training phase, without further increase after the maintenance training phase. The exercise intervention also prevented modest increases in body weight and fat mass and decreases in plasma volume, which was observed in the control group (Table 2).

**Table 2. Supine Hemodynamics and Cardiovascular Function**

| | Control Group | | Exercise Training Group | | |
|---|---|---|---|---|---|
| | Pre | Post | Pre | Post | Group×Time |
| Heart rate, bpm | 64 (60–67) | 64 (61–67) | 63 (60–67) | 58 (55–61)* | 0.0003 |
| Systolic blood pressure, mm Hg | 109 (106–113) | 107 (103–110) | 107 (104–110) | 104 (102–107) | 0.953 |
| Diastolic blood pressure, mm Hg | 69 (67–72) | 70 (67–73) | 67 (65 - 69) | 68 (65–71) | 0.953 |
| Cardiac index, L/min$^2$ | 2.5 (2.4–2.7) | 2.6 (2.4–2.7) | 2.5 (2.4–2.7) | 2.5 (2.3–2.6) | 0.417 |
| Stroke index, mL/m$^2$ | 41 (38–43) | 42 (39–44) | 42 (39–45) | 45 (42–49)* | 0.315 |
| Total arterial compliance index, mL·mm Hg$^{-1}$·m$^{-2}$ | 1.05 (0.96–1.13) | 1.20 (1.08–1.32) | 1.07 (0.97–1.17) | 1.29 (1.16–1.42)* | 0.501 |
| Effective arterial elastance index, mL·mm Hg$^{-1}$·m$^{-2}$ | 2.47 (2.30–2.64) | 2.35 (2.18–2.52) | 2.37 (2.18–2.57) | 2.16 (2.00–2.32)* | 0.48 |
| Weight, kg | 75.8 (70.0–81.6) | 77.1 (71.4–82.8) | 74.3 (68.9–79.6) | 73.6 (68.1–79.0) | 0.0288 |
| Body fat, % | 32.9 (30.0–35.7) | 35.5 (33.1–37.9) | 32.3 (30.3–34.2) | 33.0 (31.0–35.1) | 0.0578 |
| Fat-free mass, kg | 50.9 (46.4–55.3) | 49.9 (45.4–54.4) | 50.4 (46.3–54.5) | 49.3 (45.2–53.5) | 0.0831 |
| Hemoglobin, g/dL | 13.3 (12.9–13.7) | 14.0 (13.5–14.6)* | 13.1 (12.6–13.5) | 13.6 (13.1–14.0)* | 0.310 |
| Plasma volume, mL | 3302 (3058–3546) | 3122 (2891–3354)* | 3337 (3061–3614) | 3290 (3024–3555) | 0.164 |
| Plasma volume, mL/kg | 43.9 (41.5–46.4) | 40.8 (38.6–43.0)* | 44.9 (42.8–46.9) | 44.0 (41.6–46.4) | 0.156 |
| Total blood volume, mL | 5245 (4822–5668) | 5081 (4657–5504) | 5247 (4787–5707) | 5263 (4797–5729) | 0.148 |
| Total blood volume, mL/kg | 69.4 (66.1–72.7) | 65.9 (62.8–69.0)* | 70.3 (67.2–73.4) | 71.2 (68.3–74.1) | 0.0157 |

Values are mean (95% confidence interval).
**P*<0.05 in comparison with pre within group.

## Resting Supine Hemodynamics

The effect of the exercise intervention on resting hemodynamic variables is summarized in Table 2. ExT increased supine resting SV, causing a decrease in HR and maintenance of Qc. Blood pressure was unchanged in either group. There was an increase in arterial compliance and reduction in arterial elastance in both groups, which was statistically significant in the ExT group.

## LV Pressure-Volume Curves

Individual stiffness constants and group mean LV pressure-volume relationships are shown in Figure 4A through 4D for all participants who completed the follow-up visit. Two-years of exercise training significantly reduced individual LV and myocardial stiffness constants, with no change observed in the control participants (Figure 4A, group×time $P$=0.040, control, time $P$=0.83, ExT, time $P$=0.0018; Figure 4B, group × time $P$=0.0247; control, time $P$=0.41; ExT, time $P$=0.0158). There was a significant group×time interaction for the PCWP and TMP pressure-volume curves ($P$<0.0001, $P$=0.004, respectively; Figure 4C and 4D). The PCWP and TMP pressure-volume curves were not significantly altered in the control group ($P$=0.933, $P$=0.602, respectively). In contrast, in the ExT group, PCWP and TMP pressure-volume curves were shifted to the right and downward ($P$<0.0001, $P$<0.0001, respectively). ExT increased LVEDV (ExT 7.1 (95% CI, 5.6–8.6) mL/m$^2$ versus control group, −1.0 [95% CI, −3.0 to 1.0]), whereas PCWP was unchanged (group×time $P$<0.001), allowing for greater SV for any given filling pressure

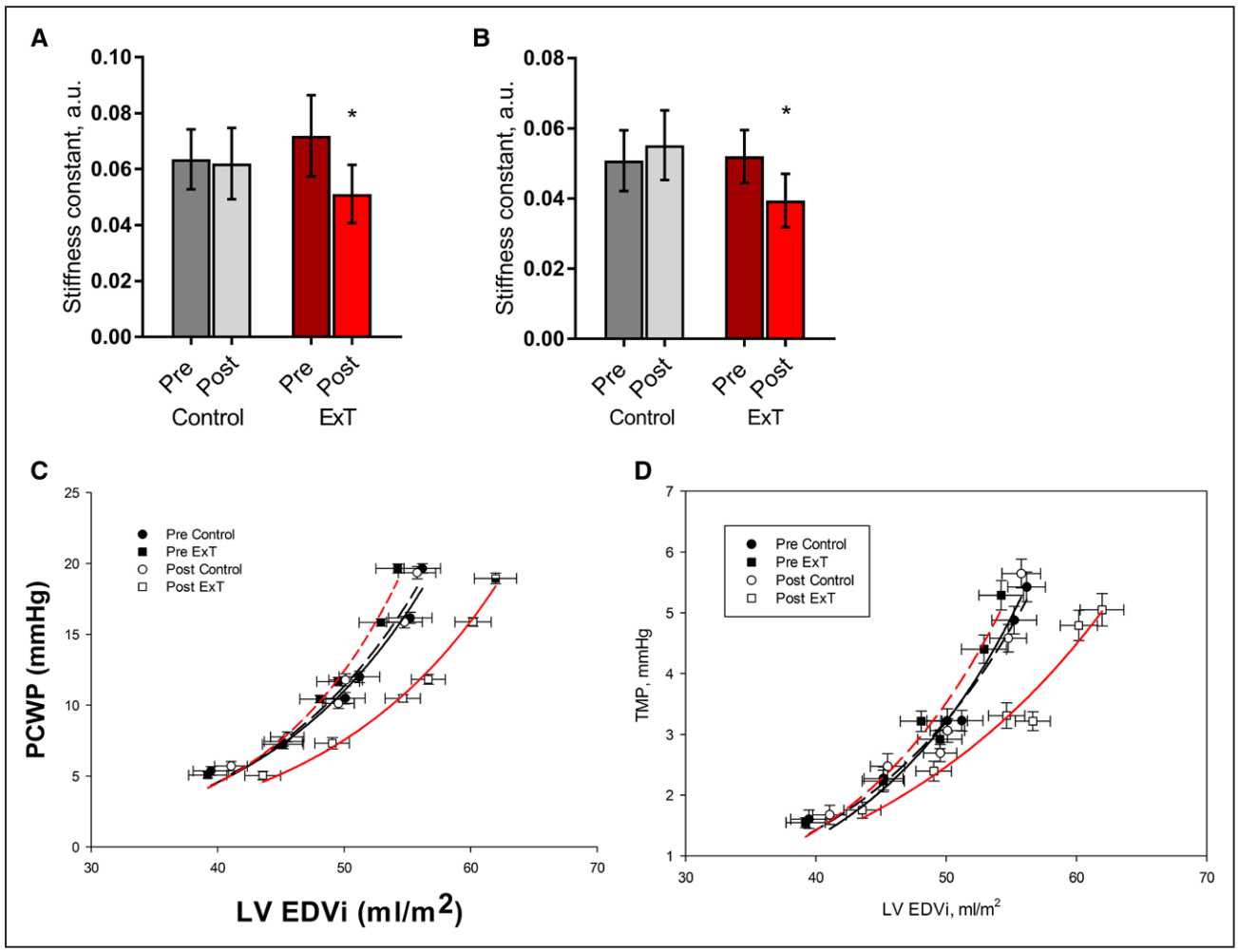


**Figure 4. Effect of intervention on diastolic function.**
**A** and **B,** Change in individual stiffness constants from the diastolic portion of the LV diastolic pressure-volume relationships and LV diastolic transmural pressure-volume relationship, respectively. Modeling was performed for each individual participant, at baseline and repeated after 2 years. **C** and **D,** The group mean LV diastolic pressure-volume and LV diastolic transmural pressure-volume relationships before and after 2 years of intervention. In the ExT group, both the LV pressure-volume and transmural curves were shifted rightward with a flattening slope demonstrating improved LV compliance and distensibility. The control group was unchanged. *$P$<0.05 denotes significantly different from pre. ExT indicates exercise training; LVEDVi, left ventricular end-diastolic volume index; PCWP, pulmonary capillary wedge pressure; and TMP, transmural pressure.

in the ExT group (pre/post ExT, *P*=0.001 and control, *P*=0.644; loading condition×group×time *P*=0.0075; Figure 5A and 5B). Thus, 2 years of training resulted in an upward shift in the Starling curves, driven primarily by an increase in heart size. Furthermore, heart rate was lower in the ExT group, across the range of filling pressure following training (4–6 beats lower; loading condition×group×time *P*=0.064; Table I in the online-only Data Supplement). Neither ExT nor sedentary aging changed global systolic function, measured as the slope of preload recruitable stroke work (group×time *P*=0.68, time *P*=0.90; Figures 5C and 5D).

## Sex Differences

Post hoc analysis suggests that in contrast to prior observations, the response to ExT was not modified by sex for $\dot{V}o_2$max (sex×group×time *P*=0.74), LVEDV index (sex×group×time *P*=0.50), or LV stiffness constant (sex×group×time *P*=0.10). These observations should be interpreted with caution because our study was not adequately powered to make distinctions by sex.

# DISCUSSION

This study is the longest, prospective randomized controlled trial that has documented the physiological effects of supervised, structured ExT in a group of sedentary but healthy middle-aged adults. The key finding is that 2 years of exercise training performed for at least 30 minutes, 4 to 5 days per week, and including at least 1 high-intensity interval session per week results in a significant reduction in LV chamber and myocardial stiffness. The use of high-resolution, invasively measured LV pressure-volume curves and comparison with an attention control group enhances the confidence in this conclusion. This study also demonstrated that ExT can be adhered to by middle-aged adults over a prolonged period, suggesting that this may be an effective strategy to mitigate the deleterious effects of sedentary aging on the heart and forestall the development of HFpEF.

## Optimized ExT Program Enhances Maximal Exercise Capacity and LV Structure and Function

We used a periodized ExT program that incorporated a progressive increase in training load (preparatory period), followed by a peak and maintenance training periods. This training approach is routinely used by competitive athletes,[29,30] but has not been used in exercise-naïve participants in a controlled manner. Consistent with current physical activity guidelines,[31] participants were

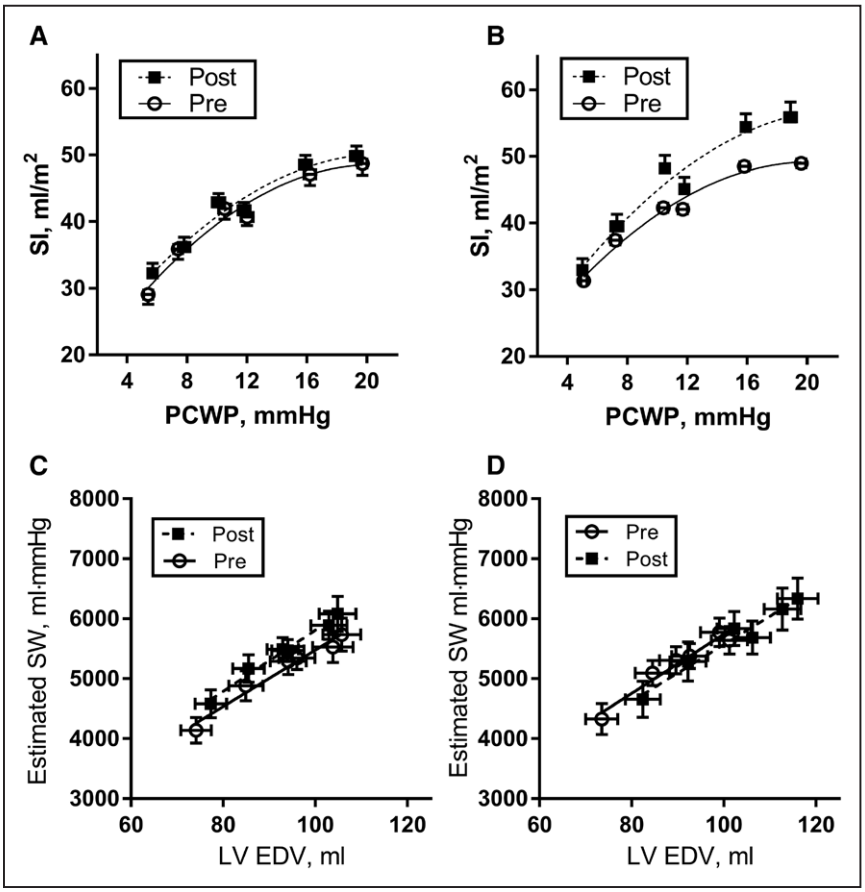


**Figure 5. Frank-Starling relationship and preload-recruitable stroke work.**
**A** and **B,** Change in Frank-Starling relationship. There was no change in the control group (**A**), whereas 2 years of training improved Frank-Starling curves (**B**), such that a statistically significant increase in stroke volume index was observed in comparison with baseline for a given filling pressure. In contrast, there was no significant effect of exercise training or aging on preload recruitable stroke work. (**C** and **D** represent the pre/post changes in the control and ExT group, respectively). LVEDV indicates left ventricular end-diastolic volume; PCWP, pulmonary capillary wedge pressure; SI, stroke index; and SW, stroke work.

prescribed a combination of high-, moderate-, and low-intensity aerobic exercise equating to ≈150 to 180 minutes per week. In response to this training stimulus, we observed a classical physiological response, where maximal oxygen uptake was markedly increased, resting HR was reduced, and LVEDV was expanded. Epidemiological evidence suggests that each 1–metabolic equivalent increase in exercise capacity is associated with a 13% and 15% reduction in all-cause and cardiovascular disease mortality.[32] Furthermore, higher fitness levels in middle age are associated with a reduced risk of heart failure.[5–7,33] Lower resting HR is also associated with reductions in mortality, independent of objectively measured fitness levels.[34] Thus, 2 years of exercise training at a frequency of 4 to 5 days per week had considerable cardiovascular benefits and may improve longevity and prevent the development of heart failure.

We used a mixture of continuous moderate-intensity ExT combined with high-intensity training, which has been demonstrated to have superior cardiovascular benefit in comparison with moderate- intensity exercise alone.[35] The possible enhanced efficacy of high-intensity interval training and threshold training is likely attributable to the complex integrative physiological response required to perform high-intensity work. The high intensity interval training protocol used in this study required participants to exercise at 90% to 95% of HR maximum for 4 minutes, followed by a 3-minute active recovery period, repeated 4 times, termed the 4×4 by the Norwegian group.[35] During the 4 minutes of intense exercise, there is a large increase in Qc to meet the increased demand for oxygen delivery and utilization within the skeletal muscle. The near-maximal Qc and repeated exposure to this intense stimulus are the likely drivers of the ventricular remodeling and resultant increase in $\dot{V}o_2$max. Our study provides compelling evidence of the powerful cardiovascular benefits of high-intensity training in humans and provides a rationale that the improvements are in part attributable to enhanced diastolic function.

## Interindividual Variability in the Training Response

In the present study, we observed a phasic increase in $\dot{V}o_2$ and ventricular volume adaptation, such that the majority of $\dot{V}o_2$max increase occurred after completion of the progressive and peak phase of training (when training volume continued to increase). When training volume was maintained from month 10 to 24, the additional change in $\dot{V}o_2$max was negligible, –0.18 (range, –4.5 to 4.4) mL·kg$^{-1}$·min$^{-1}$. With the use of our repeated-measures, parallel control design, we can address several recent concerns that have arisen regarding interindividual variability in the exercise training response.[36] For example, many of the studies reporting on training variability lack a comparative control group, calling into question the reported wide variability in the response to training and the concept of the nonresponder.[37] In our present study, we observed a very small change in $\dot{V}o_2$max in the control group at 9 months (–0.11 [range, –6.5 to 5.4] mL·kg$^{-1}$·min$^{-1}$), with an additional reduction from month 10 to 24 (–0.58 [range, –3.4 to 7.0] mL·kg$^{-1}$·min$^{-1}$). In contrast to this clear lack of change in controls, we observed virtually no nonresponders in our ExT group. This near-universal response to ExT in these middle-aged subjects may have been attributable to the high levels of adherence, the long duration of the intervention, or the intensity of the training stimulus. Although, of course, there was some individual variability in the ultimate responses, our data support other recent observations that, given an adequate training stimulus, the vast majority of individuals will have a clear physiological response to exercise training.[38]

## Exercise Commenced in Middle Age Alters Cardiac Compliance and Is a Reasonable Target to Prevent HFpEF

At present, spironolactone is the only treatment strategy recommended (class II recommendation) to counteract the debilitating effects of HFpEF.[39] Thus, establishing additional effective prevention strategies is key, especially in light of the aging population and growing levels of sedentary behavior, 2 leading risk factors for the development of HFpEF.[40] Exercise training has been demonstrated to improve fitness and quality of life in patients with HFpEF[41] and in those at risk of developing HFpEF.[42] Yet, the effects of training on LV function when assessed noninvasively via echocardiography indices are less clear; with 1 study demonstrating improved E/e′ and reduced left atrial volume,[43] whereas others report no change in mitral inflow or early deceleration time.[44] It is important to note that 2 key characteristics of patients with HFpEF are abnormal active relaxation and markedly elevated passive LV stiffness in comparison with controls,[45] such that increases in ventricular filling pressure result in very few changes in ventricular volume,[46] demonstrating reduced cardiac compliance. This reduction in compliance limits the capacity of the heart to distend during increases in venous return and thus limits exercise tolerance in patients with impaired diastolic function.[47]

We have previously shown that 1 year of exercise training in patients with HFpEF and sedentary seniors has little effect on LV stiffness,[9,48] suggesting an inadequate exercise training stimulus or that older seniors and patients with HFpEF may have limited cardiac plasticity, which inhibits their capacity to respond to exercise training. Previous work from our group demonstrated a proportional relationship between

cardiac compliance and sedentary aging that rapidly accelerated after age 65.[11] Subjects who were middle aged, between 45 and 64 years, had cardiac compliance scores between those of younger (<35 years) and senior (>65 years) controls, suggesting a transition phase, or sweet spot in which potential plasticity to reverse age-related stiffening may still be present. Follow-up work from our group showed healthy seniors who exercised habitually for >25 years had cardiac compliance similar to young controls, essentially forestalling age-related changes.

We demonstrate for the first time that exercise training, predominantly endurance in nature, improves LV and myocardial stiffness in sedentary, but otherwise healthy middle-aged adults. Our findings suggest that intervening earlier in the aging process is necessary to preserve and possibly enhance ventricular compliance. ExT improved both global cardiac compliance in addition to myocardial compliance estimated from the end-diastolic pressure-volume relationship derived from transmural pressure. Improvements in cardiac compliance were thus likely driven by 2 independent but cumulative processes, namely attenuated pericardial constraint in addition to myocardial remodeling.

## Exercise Is Medicine

Studies investigating the chronic effects of exercise training have been limited by study design, where retrospective cross-sectional studies typically characterize exercise history over years to differentiate between trained and untrained individuals,[4,49] or supervised training studies are performed for relatively short periods of time, typically 12 to 16 weeks.[12] These study designs limit the ability to provide specific exercise prescriptions for particular outcomes, because the effects of intensity are typically difficult to quantify in cross-sectional studies and the long-term effects are unclear in short training studies. Our exercise prescription, which was evidence based, proved to be highly effective in enhancing cardiovascular structure and function. The periodized design of the training program permitted participants to become accustomed to the frequency of training gradually. In addition, by varying the duration, intensity, and type of training over the course of the week, the training was not onerous and was feasible with excellent adherence to prescribed sessions. The exercise prescription used in this study closely reflects the current population-based exercise/physical activity recommendations of 150 minutes per week of physical activity,[31] albeit with the addition of high intensity interval training. Moreover, a growing body of epidemiological evidence supports the beneficial impact of regularly exercising 4 days per week.[50,51] We provide contemporary, prospective evidence for the efficacy of this type of exercise training.

## Limitations

A limitation of our study is that we evaluated LV pressure curves by using mean PCWP as a surrogate for LV end-diastolic pressure. However, we performed rigorous screening for cardiovascular disease and excluded participants who had valvular abnormalities such as mitral valve regurgitation or pulmonary disease, which might alter the relationship between PCWP and LV end-diastolic pressure. We selected volunteers who were willing and able to participate in an intensive exercise regimen; therefore, these results may not necessarily apply to the general adult population. Moreover, our subjects were predominantly white, which may limit the generalizability of our findings to other racial groups. Indeed, the effects of race on the response to ExT are controversial, with some studies demonstrating racial differences,[52] whereas others do not.[53] The long-term goal is to establish whether this model of ExT is effective in preventing the development of HFpEF and reducing mortality in this population. This goal is especially relevant in at-risk populations, including women who are disproportionately affected by HFpEF, because the present study was not adequately powered to address this distinction. Future studies will also need to address whether this intervention is efficacious in other populations at increased risk of developing heart failure; for example, those who are sedentary plus have evidence of LV hypertrophy or abnormal cardiac biomarkers (troponin and N-terminal fragment of the prohormone of B-type natriuretic peptide).[54]

# CONCLUSIONS

In conclusion, we demonstrate that 2 years of intensive ExT, at levels consistent with current public health recommendations, increases maximal oxygen uptake and decreases cardiac stiffness in previously sedentary but otherwise healthy middle-aged adults. Regular ExT may provide protection against the future risk of HFpEF by preventing the increase in cardiac stiffness attributable to sedentary aging.

## ARTICLE INFORMATION

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## Correspondence

Benjamin D. Levine, MD, Institute for Exercise and Environmental Medicine, 7232 Greenville Avenue, Suite 435, Dallas, TX 75231. E-mail benjaminlevine@texashealth.org

## Affiliations

Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital, Dallas (E.J.H., S.S., J.S.L., M.O., W.C., D.S., M.A.U., B.D.L.). University of Texas Southwestern Medical Center, Dallas (E.J.H., S.S., J.S.L., D.S., M.A.U., B.A.-H., B.D.L.). The Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia (E.J.H.). Stanford University, CA (M.O.). University of Colorado Anschutz Medical Campus, Aurora (W.C.).

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## Disclosures

None.

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# Reversing the Cardiac Effects of Sedentary Aging in Middle Age—A Randomized Controlled Trial: Implications For Heart Failure Prevention

Erin J. Howden, Satyam Sarma, Justin S. Lawley, Mildred Opondo, William Cornwell, Douglas Stoller, Marcus A. Urey, Beverley Adams-Huet and Benjamin D. Levine

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# SUPPLEMENTAL MATERIAL

## Reversing the Cardiac Effects of Sedentary Aging in Middle Age, A Randomized Controlled Trial: Implications For Heart Failure Prevention

**Authors:** Erin J. Howden, PhD[1,2,3], Satyam Sarma, MD[1,2], Justin S. Lawley, PhD[1,2], Mildred Opondo, MD[1,4], William Cornwell, MD[1,5], Douglas Stoller, MD, PhD[1,2], Marcus A. Urey, MD[1,2], Beverley Adams-Huet, MS[2], Benjamin D. Levine, MD[1,2]

[1] Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital, Dallas TX 75231, United States

[2] University of Texas Southwestern Medical Center, Dallas, TX 75390, United States

[3] The Baker Heart and Diabetes Institute, Melbourne VIC 3004, Australia

[4] Stanford University, Stanford CA 94305, United States

[5] University of Colorado Anschutz Medical Campus, Aurora, CO 80045, United States

### Supplemental Methods

### Measurements

**Exercise Testing.** Measurements of maximal oxygen uptake were performed at baseline, 10 months (after the peak training phase, described in detail above) and two years. At each testing session, $VO_2$, hemodynamics and blood pressures were determined at the following treadmill conditions: 1) quiet standing rest, 2) low-intensity (≈30—45% of $VO_2$max; SS1) steady-state submaximal exercise, 3) moderate-intensity (≈60—75% of $VO_2$max; SS2) steady-state

submaximal exercise, and 4) maximal exercise. Two participants were tested on an upright cycle at the same conditions because of orthopedic limitations. Gas fractions were analyzed by mass spectrometry and ventilatory volumes by a Tissot spirometer, as previously reported.[1] Maximal oxygen uptake ($VO_2$max) was defined as the highest oxygen uptake measured from at least a 30 second Douglas bag.

**Total blood volume.** Total blood volume (TBV) was measured using the carbon monoxide rebreathing method, modified from that described by Burge and Skinner,[2] and has been reported in detail previously.[3] The typical error of this measurement expressed as a coefficient of variation (%) for test-retest reproducibility for hemoglobin mass, the primary calculation derived from the carbon monoxide distribution, is ≈3% for repeated measures in our laboratory.[3] To reduce the confounding effect of body size and composition on TBV, absolute values were scaled relative to total body mass (ml/kg).

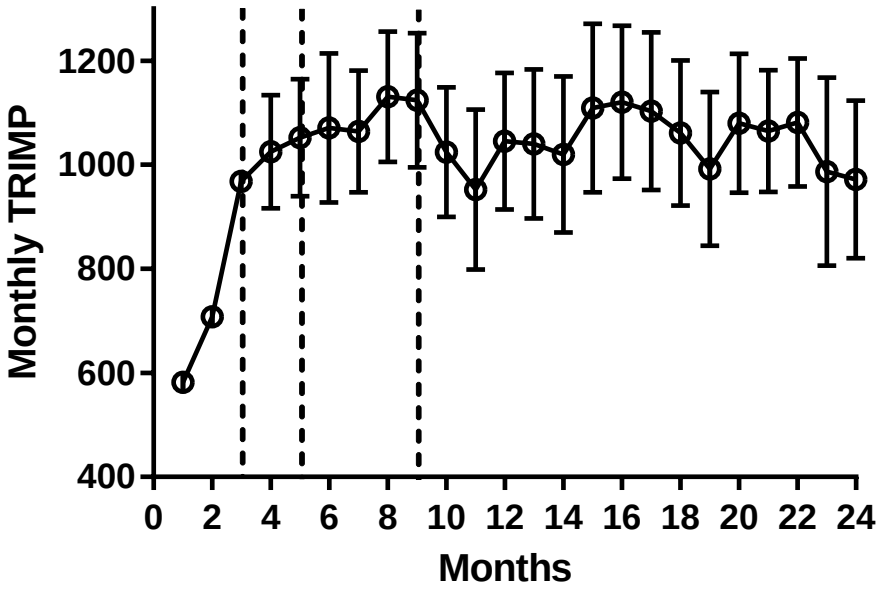
## Supplemental Results

### Compliance with Prescribed Exercise Training

Participants in the ExT group maintained excellent compliance with the two-year exercise intervention (mean 88±11%). Six participants maintained almost perfect compliance to the prescribed training (completing ≥97% of prescribed sessions). Supplemental Figure 1 depicts the average monthly training load over the course of the study. As expected, TRIMPs increased in response to the progressive increase in training volume from month 1 – 6, before remaining relatively stable during the peak training phase (months 6 - 9). After completion of the peak phase, participants maintained a relatively constant training load, which equated to approximately 3 hours/week of aerobic exercise.

**Supplemental Table 1. Effect of Exercise Training on Hemodynamic Response to Preload Manipulation**

| | HR bpm | | MAP mmHg | | SV mL | | PCWP mmHg | |
|---|---|---|---|---|---|---|---|---|
| | **Pre** | **Post** | **Pre** | **Post** | **Pre** | **Post** | **Pre** | **Post** |
| **Control Group** | | | | | | | | |
| Baseline | 63 (60 -66) | 62 (59-64) | 83 (80 -85) | 82 (79 -85) | 76 (71 – 80) | 78 (73 -83) | 12.0 (11.2 – 12.8) | 11.8 (10.9-12.6) |
| LBNP - 15mmHg | 64 (61 -67) | 64 (61-68) | 80 (77-83) | 84 (82-86) | 67 (61 – 73) | 68 (62 -74) | 7.4 (6.8 -8.0) | 7.8 (7.1 – 8.5) |
| LBNP - 30mmHg | 72 (67-76) | 71 (66-76) | 82 (79 -85) | 82 (78 -85) | 54 (49-60) | 60 (54 – 66) | 5.3 (4.7 – 6.0) | 5.7 (5.1 – 6.3) |
| Baseline | 68 (65 – 70) | 68 (64-72) | 78 (76-80) | 79 (76-82) | 78 (72-84) | 80 (74 – 86) | 10.5 (9.7 -11.3) | 10.1 (9.4 – 10.8) |
| NS 15 ml/kg | 756 (72 – 79) | 76 (71-80) | 80 (77-83) | 81 (78-83) | 87 (81 -95) | 91 (84 -97) | 16.2 (15.4 – 16.9) | 15.9 (15.1 – 16.7) |
| NS 30 ml/kg | 81 (76 – 85) | 79 (74-83) | 84 (80-88) | 83 (81-86) | 91 (84 -99) | 93 (86 101) | 19.6 (19.0 – 20.3) | 19.3 (18.5 – 20.2) |
| **ExT Group** | | | | | | | | |
| Baseline | 61 (58 – 64) | 56 (53-59) | 80 (78-83) | 80 (77-83) | 78 (72 -85) | 84 (76 -92) | 11.6 (11.1 -12.2) | 11.8 (11.2 – 12.5) |
| LBNP - 15mmHg | 63 (60-66) | 59 (55-62) | 80 (79-82) | 79 (76-81) | 70 (64 – 76) | 74 (66 -82) | 7.1 (6.5 – 7.7) | 7.3 (6.5 – 8.1) |
| LBNP - 30mmHg | 71 (68-75) | 65 (61-68) | 79 (76-81) | 80 (77-82) | 59 (52 -65) | 62 (54 – 69) | 5.0 (4.6 – 5.5) | 5.0 (4.4 – 5.6) |
| Baseline | 67 (63-70) | 63 (59-66) | 78 (76-79) | 76 (73-78) | 79 (73 -85) | 90 (82 -99) | 10.4 (9.8 – 10.9) | 10.5 (10.0 – 11.0) |
| NS 15 ml/kg | 75 (71 – 79) | 69 (64-74) | 80 (77-82) | 76 (73-79) | 91 (84 -97) | 102(93– 111) | 15.8 (15.3 – 16.3) | 15.9 (15.3 – 16.5) |
| NS 30 ml/kg | 76 (71-81) | 72 (67-77) | 81 (79-84) | 80 (77-82) | 91 (85 – 98) | 104 (95 -114) | 19.6 (19.0 – 20.2) | 18.9 (18.2 -19.7) |




**Supplemental Figure 1.** Training impulse (mean 95% CI). Mean monthly training load recorded in ExT participants over the two-years. Note the progressive increase in training volume over the first 6 months of the study, before participants completed a 4 month peak phase (6-9months), followed by 14 months of "maintenance training" were training load was kept constant.

## References

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