

Cardiovascular Effects of 1 Year of Progressive and Vigorous Exercise Training in Previously Sedentary Individuals Older Than 65 Years of Age

Naoki Fujimoto, MD, PhD; Anand Prasad, MD; Jeffrey L. Hastings, MD; Armin Arbab-Zadeh, MD; Paul S. Bhella, MD; Shigeki Shibata, MD, PhD; Dean Palmer, MS; Benjamin D. Levine, MD

Background—Healthy but sedentary aging leads to cardiovascular stiffening, whereas life-long endurance training preserves left ventricular (LV) compliance. However, it is unknown whether exercise training started later in life can reverse the effects of sedentary behavior on the heart.

Methods and Results—Twelve sedentary seniors and 12 Masters athletes were thoroughly screened for comorbidities. Subjects underwent invasive hemodynamic measurements with pulmonary artery catheterization to define Starling and LV pressure-volume curves; secondary functional outcomes included Doppler echocardiography, magnetic resonance imaging assessment of cardiac morphology, arterial stiffness (total aortic compliance and arterial elastance), and maximal exercise testing. Nine of 12 sedentary seniors (70.6 ± 3 years; 6 male, 3 female) completed 1 year of endurance training followed by repeat measurements. Pulmonary capillary wedge pressures and LV end-diastolic volumes were measured at baseline, during decreased cardiac filling with lower-body negative pressure, and increased filling with saline infusion. LV compliance was assessed by the slope of the pressure-volume curve. Before training, $\dot{V}_{O_2\max}$, LV mass, LV end-diastolic volume, and stroke volume were significantly smaller and the LV was less compliant in sedentary seniors than Masters athletes. One year of exercise training had little effect on cardiac compliance. However, it reduced arterial elastance and improved $\dot{V}_{O_2\max}$ by 19% (22.8 ± 3.4 versus 27.2 ± 4.3 mL/kg/mL; $P < 0.001$). LV mass increased (10%, 64.5 ± 7.9 versus 71.2 ± 12.3 g/m²; $P = 0.037$) with no change in the mass-volume ratio.

Conclusions—Although 1 year of vigorous exercise training did not appear to favorably reverse cardiac stiffening in sedentary seniors, it nonetheless induced physiological LV remodeling and imparted favorable effects on arterial function and aerobic exercise capacity. (*Circulation*. 2010;122:1797-1805.)

Key Words: diastole ■ exercise ■ aging ■ heart diseases ■ hemodynamics

Cardiovascular stiffening develops during the aging process.^{1,2} For example, previous studies from this laboratory have shown that healthy but sedentary aging leads to left ventricular (LV) atrophy and prominent increases in LV stiffness.³ These age-related changes may provide the substrate for heart failure with a preserved ejection fraction (HFpEF), a disease of the elderly characterized by increased LV stiffness.^{4,5} Indeed, recent work has raised the possibility that especially in women, this stiffening in patients with HFpEF may not be much worse than that observed with sedentary aging.^{6,7}

Clinical Perspective on p 1805

In contrast to cardiovascular deconditioning induced by sedentary behavior,⁸ young endurance-trained athletes have markedly enhanced LV compliance.⁹ Moreover, Masters athletes who have trained virtually their whole adult lives

have LV compliance that is indistinguishable from healthy young controls.³ This prevention of cardiovascular stiffening in vigorously active seniors emphasizes the critical role physical activity plays in the aging cardiovascular system.

However, whether stiffening of the heart in sedentary seniors can be reversed by endurance exercise training started later in life is unknown. This knowledge would be essential to develop lifestyle strategies that might forestall age-related cardiovascular diseases such as HFpEF. The purpose of the present study was therefore to perform a comprehensive and detailed measurement of hemodynamics and LV structure and function in healthy sedentary seniors before and after 1 year of endurance exercise training. We hypothesized that 1 year of progressive and vigorous training would improve functional capacity, increase LV mass, and restore cardiac compliance to the levels observed in Masters athletes and young individuals.

Received January 19, 2010; accepted August 24, 2010.

From the University of Texas Southwestern Medical Center at Dallas (N.F., A.P., J.L.H., A.A.-Z., P.S.B., S.S., B.D.L.), and Institute for Exercise and Environmental Medicine (N.F., A.P., J.L.H., A.A.-Z., P.S.B., S.S., D.P., B.D.L.), Texas Health Presbyterian Hospital Dallas, Dallas, Tex.

Correspondence to Dr Benjamin D. Levine, Institute for Exercise and Environmental Medicine, 7232 Greenville Ave, Suite 435, Dallas, TX 75231. E-mail BenjaminLevine@TexasHealth.org

© 2010 American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.110.973784

Methods

Subject Population

Twelve healthy adults older than 65 years of age (6 men, 6 women; mean age 69.8 ± 3 years) and 12 age-matched Masters athletes (6 men, 6 women; mean age 67.8 ± 3 years) were enrolled in the present study. Sedentary subjects were excluded if they were exercising for ≥ 30 minutes 3 times a week. All subjects were rigorously screened for comorbidities, including obesity, lung disease, hypertension, coronary artery disease, or structural heart disease at baseline and after exercise testing as previously reported.³ Body fat content and lean body mass were measured by underwater weighing.¹⁰ Baseline data from this patient population have been published,^{3,11,12} and this study now reports the effects of 1 year of vigorous endurance exercise training on cardiac remodeling and mechanics in the sedentary subjects. All subjects signed an informed consent form, which was approved by the institutional review boards of the University of Texas Southwestern Medical Center at Dallas and Texas Health Presbyterian Hospital Dallas.

Exercise Testing

A modified Astrand-Saltin incremental treadmill protocol was used to determine peak exercise capacity.¹³ Measures of ventilatory gas exchange were made by use of the Douglas bag technique. Gas fractions were analyzed by mass spectrometry (Marquette MGA 1100), and ventilatory volumes were measured with a Tissot spirometer. $\dot{V}O_2$ max was defined as the highest oxygen uptake measured from at least a 40-second Douglas bag. Cardiac output was measured with a modification of the acetylene rebreathing method, with acetylene as the soluble gas and helium as the insoluble gas.¹⁴ Measurement of cardiac output by acetylene rebreathing has been validated at rest and maximal exercise.^{14–17} This method assumes that cardiac output is equal to effective pulmonary blood flow to ventilated lung, which can be assessed by the rate of decay of acetylene concentration during rebreathing.¹⁵ Adequate mixing of the rebreathing gas in the lung was confirmed by a constant level of helium in all cases. Arterial-venous oxygen difference ($a-v\text{Do}_2$) was calculated by the Fick equation. The ventilatory threshold was determined by commercial software (First Breath, Marquette). The heart rate at the work rate that elicited the ventilatory threshold was defined as the heart rate at maximal steady state (MSS), which was generally equivalent to $\approx 85\%$ to 90% of the maximal heart rate.

Exercise Training

The sedentary subjects participated in a 1-year training program with the goal of increasing duration and intensity as previously reported; a detailed day-by-day training plan has been published online (<http://jap.physiology.org/cgi/content/full/99/3/1041>).¹⁸ Initially, the sedentary subjects walked or jogged 3 times per week for 25 minutes/session, at the “base pace” in which target heart rates were equivalent to $\approx 75\%$ to 85% of the maximal heart rates at just below the ventilatory threshold. At the third month, a 30 minutes/session of MSS was added monthly, and the frequency of MSS was increased to twice per month from the fifth month. At the seventh month, 30 seconds/session of “intervals,” with target heart rates within 5 to 10 bpm of the maximal heart rate, were added, and the duration of each interval session was gradually prolonged. A 45 minutes/session of “long slow distance” was then added at the eighth month, and the duration was prolonged to 60 minutes/session by the end of the training program.

Cardiac Catheterization and Experimental Protocol

Right heart catheterizations were performed at baseline and were repeated only in sedentary subjects after training. A 6-Fr Swan-Ganz catheter was placed from a peripheral antecubital vein under fluoroscopic guidance to measure pulmonary capillary wedge pressure (PCWP) and right atrial pressure. Correct position of the Swan-Ganz catheter was confirmed by fluoroscopy and by the presence of characteristic pressure waveforms. After the baseline measurements, lower-body negative pressure (LBNP) was used to decrease cardiac filling.^{3,9} Measurements, including heart rate, PCWP, blood pres-

sure, LV end-diastolic volume (LVEDV), and cardiac output by acetylene rebreathing (and therefore stroke volume), were performed after 5 minutes each of -15 and -30 mm Hg LBNP. The LBNP was then released. After repeat measurements confirmed a return to a steady state, cardiac filling was increased by rapid infusion (100 to 200 mL/min) of warm isotonic saline. Measurements were repeated after 10 to 15 and 20 to 30 mL/kg of saline infusion. Total arterial compliance was determined by the ratio of stroke volume and pulse pressure to evaluate central aortic function.¹⁹ Effective arterial elastance was defined as end-systolic pressure divided by stroke volume,²⁰ where end-systolic pressure was calculated as brachial systolic pressure $\times 0.9$.²¹

Assessment of Cardiac Catheterization Data

Hemodynamic data were used to construct Starling (stroke volume index/PCWP) and pressure-volume (LVEDV index/PCWP) curves. To characterize LV pressure-volume curves, we modeled the data according to an exponential equation²²: $P = P_{\infty}(\exp^{a(V-V_0)} - 1)$, where P is PCWP, P_{∞} is pressure asymptote of the curve, V is LVEDV index, and V_0 is equilibrium volume or the volume at which $P = 0$ mm Hg pressure. Overall LV chamber stiffness (or its inverse, compliance) was assessed from the LV stiffness constant “ a .” Because external constraints influence LV volumes and pressures,²³ LV end-diastolic transmural filling pressure was calculated as PCWP–right atrial pressure and used to construct transmural pressure-volume curves.²⁴ Preload recruitable stroke work was assessed by relating LVEDV to stroke work, which was calculated by the product of stroke volume and mean arterial pressure. LV contractility was assessed by the slopes of the stroke work–LVEDV relationship.²⁵

Echocardiography

At all levels of LV filling, LV images were obtained and LVEDV was determined from the apical 4-chamber view by modified Simpson’s method of disks that was used in our previous studies.^{3,6} Great attention was paid to ensure that the images were not foreshortened.

LV early (E) and late (A) filling peak velocities were recorded, and the ratio of E to A (E/A ratio) was used to assess global LV diastolic function.¹¹ The peak early diastolic mitral annular velocity was measured in both septal and lateral sides of the mitral annulus,²⁶ and values were averaged to obtain tissue Doppler imaging (TDI) E mean.¹¹ Color M-mode Doppler was obtained, and the mitral inflow propagation velocity (V_p) was measured by the slope along the aliasing isovelocity line.¹² Isovolumic relaxation time (IVRT) was also determined.

Cardiac Magnetic Resonance Imaging Image Acquisition

Cardiac magnetic resonance imaging images were obtained using a 1.5-tesla Philips NT scanner mainly to observe the effects of exercise on cardiac morphology: LV mass, volume, and LV mass-volume ratio.²⁷ LVEDV and mass were measured as previously reported²⁸ using a steady-state free-precession imaging sequence.²⁹ All analysis was performed by 1 physician who was blinded to the protocol and results.

Assessment of Overall Cardiovascular Function

The primary outcome variables in the present study included (1) LV stiffness assessed from the pressure-volume curves, which reflects LV static diastolic function; and (2) global LV performance as assessed from Starling curves and preload-recruitable stroke work. Secondary outcomes included (1) functional responses during exercise as assessed by $\dot{V}O_2$ max and exercise hemodynamics; (2) LV morphology by cardiac magnetic resonance imaging to document the cardiac adaptation to the exercise training; (3) LV dynamic diastolic function and relaxation by echo Doppler variables (TDI E mean, V_p , and IVRT); and (4) arterial function as assessed by total aortic compliance and arterial elastance.

Table 1. Subject Characteristics

	Masters Athletes (n=12)	Sedentary Seniors (n=9)		<i>P</i> Value (Pre-Post)
		Before Training	After Training	
Age, y	68±3	71±3*		
Height, cm	170±11	171±9		
Weight, kg	64.6±13.5	76.0±9.2*	72.4±8.8	0.001
Body surface area, m ²	1.74±0.24	1.90±0.16	1.85±0.15	0.001
Body fat, %	17.7±5.7	28.5±5.8*	27.0±6.3*	0.096
Heart rate, beats/min	53±6	66±11*	59±10	0.003
Systolic blood pressure, mm Hg	118±11	130±7*	134±11*	0.297
Diastolic blood pressure, mm Hg	71±8	75±6	74±7	0.527
Hematocrit, %	41.5±1.6	41.8±2.2	40.3±2.2	0.292

Values are mean±SD. Systolic and diastolic blood pressures were obtained from 24-hour blood pressure monitoring.

**P*<0.05 for sedentary seniors vs Masters athletes, and *P* values for sedentary seniors after training vs before training.

Statistical Analysis

Statistical analyses were performed using commercially available software. Continuous data were expressed as mean±SD except for graphics, in which SEM was used. Data in Masters athletes and sedentary seniors before training were compared by using an unpaired *t* test or nonparametric Man-Whitney rank sum test, depending on the outcome of tests for normality. For data obtained during cardiac catheterization, 2-way repeated ANOVA with post hoc testing was applied to evaluate the differences between the groups. To evaluate the effects of training, paired *t* test and 2-way repeated measures ANOVA with post hoc testing were used. For pressure-volume curves, a multivariate regression analysis was conducted on the repeated measures data, modeling pressure by use of the covariates volume and subject group. A *P* value <0.05 was considered significant.

Results

Subject Characteristics

Ten of 12 previously sedentary seniors completed a year of training; 2 women felt that the training was too burdensome and dropped out. One of these 10 developed a left bundle branch block during training, and therefore was excluded from the study. Hemodynamic data were analyzed in the remaining 9 sedentary seniors (6 men, 3 women; mean age 70.6±3 years) before and after training and were compared with those of 12 Masters athletes. Table 1 shows subject characteristics before and after training. Body weight and heart rate were significantly decreased after a year of exercise training, whereas no differences were observed in systolic and diastolic blood pressures. By the end of the 1 year of training, the exercise duration was about 200 minutes/wk.¹⁸

Effects of Exercise Training on Exercise Capacity

Before training, sedentary seniors had smaller cardiac and stroke volume indices and larger arterial elastance than Masters athletes at peak exercise (Table 2). The magnitude of the increase in stroke volume index at peak exercise was 66% (34.4±5.6 to 56.1±10.3 mL/m²) in sedentary seniors, significantly less than that observed in Masters athletes (104%; 39.8±7.0 to 79.7±16.1 mL/m²; *P*=0.045). A year of exercise training significantly increased $\dot{V}O_{2\max}$ by 19% (22.8±3.4 to 27.2±4.3 mL/kg/mL; *P*<0.001). Although baseline cardiac output and stroke volume were unaffected by exercise train-

ing, there were significant increases in cardiac output by 11% and stroke volume by 13% at peak exercise.

Cardiac Size and Vascular Function

As shown in Table 3, sedentary seniors had smaller LVEDV and stroke volume indexes and LV mass than Masters athletes before training.³ After training, a 22% increase in stroke volume and a decrease in heart rate by 9% were observed in the supine position, with no changes in cardiac output. LV mass index increased 10% (64.5±7.9 to 71.2±12.3 g/m²; *P*=0.037), with no change in LV mass-volume ratio. These morphological adaptations were consistent with predominantly eccentric LV remodeling. Arterial function was significantly improved by exercise training, with an increased total aortic compliance by 24% (*P*=0.026) and a decreased arterial elastance (1.7±0.5 versus 1.3±0.4 mm Hg/mL; *P*<0.001).

Catheterization Data

As reported previously, the Starling curve in sedentary seniors before training showed a smaller stroke volume for any given PCWP than those in Masters athletes, with no difference in cardiac contractility (Figure 1A and B).³ Before training, the baseline PCWP was 11.4±1.7 mm Hg, whereas after training it was 12.5±2.8 mm Hg (*P*=0.304). Although there was some variability in the response, PCWP after training seemed to be slightly higher than before training by ≈1 mm Hg across all loading conditions (*P*=0.209), consistent with a possible plasma volume expansion. After training, Starling curves shifted upward substantially with a larger stroke volume for any given PCWP. Stroke work was increased after training across all loading conditions, mainly due to increased stroke volume (*P*=0.002); however, the slopes of the individual stroke work–LVEDV relation were unchanged (*P*=0.817). Heart rates were decreased in all loading conditions by 7 to 11 bpm after training.

LV Pressure-Volume Curves

The LV pressure-volume curves constructed from group mean data in Masters athletes and sedentary seniors are shown in Figure 2A. The pressure-volume curve in the sedentary seniors before training was steeper than that in Masters athletes, as previously reported.³ In contrast to our

Table 2. Subject Characteristics During Exercise Test at Upright Position

	Masters Athletes (n=12)	Sedentary Seniors (n=9)		P Value (Pre-Post)
		Before Training	After Training	
Heart rate, bpm				
Baseline	69±6	79±11*	76±9	0.406
Peak exercise	161±10	163±14	160±14	0.265
Systolic blood pressure, mm Hg				
Baseline	135±18	152±20	143±18	0.117
Peak exercise	189±29	222±14*	208±23	0.098
Cardiac output (reb), L/min				
Baseline	4.82±1.23	5.10±0.74	5.14±0.84	0.817
Peak exercise	22.66±6.35	17.46±4.11*	19.23±4.72	0.030
Cardiac index (reb), L · min ⁻¹ · m ⁻²				
Baseline	2.72±0.41	2.68±0.28	2.70±0.33	0.808
Peak exercise	12.81±2.63	9.14±1.69*	10.05±1.89*	0.033
Stroke volume index (reb), mL/m ²				
Baseline	39.8±7.0	34.4±5.6	36.3±5.6	0.397
Peak exercise	79.7±16.1	56.1±10.3*	62.9±9.1*	0.010
Arterial elastance, mm Hg/mL				
Baseline	1.8±0.5	2.2±0.6	1.9±0.5	0.052
Peak exercise	1.3±0.3	2.0±0.6*	1.6±0.3	0.017
a-vDO ₂ , vol%				
Baseline	4.8±1.1	4.6±0.8	4.5±0.6	0.677
Peak exercise	11.0±1.4	10.1±1.4	10.4±1.0	0.373
VO ₂ max, mL · kg ⁻¹ · min ⁻¹	38.3±5.9	22.8±3.4*	27.2±4.3*	<0.001
Normalized VO ₂ max, mL · kg LBM ⁻¹ · min ⁻¹	46.7±8.0	32.2±5.3*	36.6±5.9*	<0.001

Values are mean±SD. LBM indicates lean body mass; reb, acetylene rebreathing technique.

**P*<0.05 compared with Masters athletes, and *P* values for sedentary seniors after training vs before training.

hypothesis, no significant changes in pressure-volume curves were observed in sedentary seniors after training (Figure 2A). The stiffness constant “a” for the group mean data before and after training was 0.089 and 0.075, and equilibrium volume was 16.0 and 12.1 mL, respectively. LV pressure-volume curves constructed using transmural pressure, which minimizes the effects of external constraints on the LV and is

more specific for myocardial (as opposed to chamber) compliance, also demonstrated no significant shift of the pressure-volume curves after training, Figure 2B.

When analyzed individually and statistically, LV stiffness constant “a” was unaffected by a year of exercise training (0.062±0.030 versus 0.058±0.031, *P*=0.451; difference, 0.0044; SD, 0.0167; 95% confidence interval, -0.0088 to

Table 3. Baseline Ventricular-Vascular Function

	Masters Athletes (n=12)	Sedentary Seniors (n=9)		P (Pre-Post)
		Before Training	After Training	
Ventricular function				
LVEDV index, mL/m ²	81.8±8.0	64.7±9.3*	67.8±13.1*	0.511
LV mass index, g/m ²	78.9±17.7	64.5±7.9*	71.2±12.3	0.037
LV mass-volume ratio, g/mL	0.97±0.20	1.01±0.14	1.07±0.22	0.412
Cardiac output (reb), L/min	5.57±1.12	5.20±0.52	5.50±0.58	0.261
Cardiac index (reb), L · min ⁻¹ · m ⁻²	3.20±0.51	2.74±0.25*	2.91±0.39	0.225
Stroke volume index (reb), mL/m ²	54.7±6.8	41.0±9.0*	49.9±9.0	0.009
LV stiffness constant	0.024±0.017	0.062±0.030*	0.058±0.031	0.452
LV equilibrium volume, mL	19.5±15.6	19.0±7.5	10.6±7.3	0.018
Pressure asymptote, mm Hg	6.2±4.5	5.3±6.0	3.5±3.0	0.261
Vascular function				
Total arterial compliance, mL/mm Hg	1.77±0.40	1.35±0.48*	1.72±0.63	0.026
Arterial elastance, mm Hg/mL	1.2±0.3	1.7±0.5*	1.3±0.4	0.001

Values are mean±SD. LV volumes and mass obtained by cardiac magnetic resonance imaging. reb indicates acetylene rebreathing technique.

**P*<0.05 for sedentary seniors vs Masters athletes, and *P* values for sedentary seniors after training vs before training.

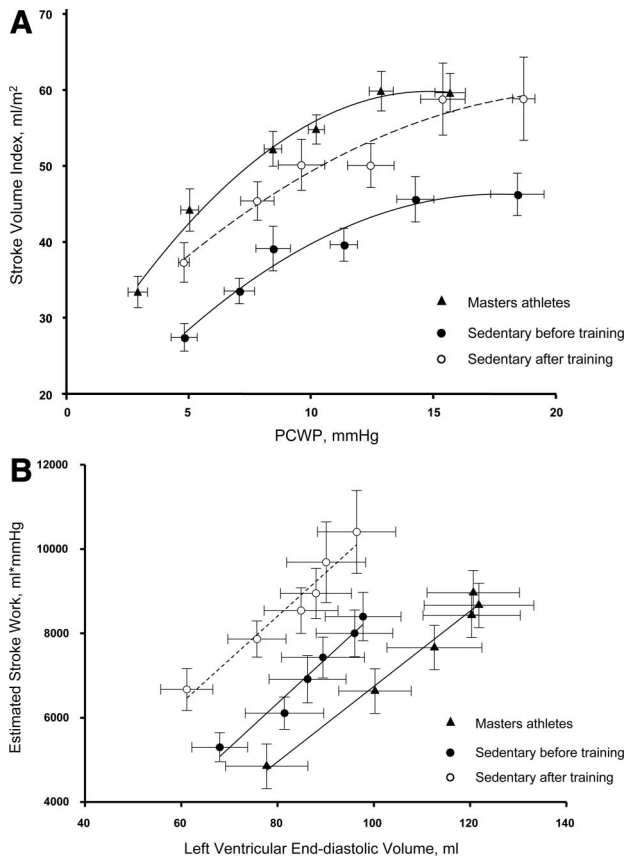


Figure 1. A, Frank Starling relationship. Systolic ventricular performance for sedentary seniors before and after exercise training and Masters athletes. Lines represent results of second linear regression analyses for sedentary seniors before ($r=0.98$) and after ($r=0.97$) training and Masters athletes ($r=0.99$). Note lower stroke volume index for any given PCWP in sedentary seniors before training compared with those in Masters athletes and substantially upward shift of Starling curve after training. B, Preload recruitable stroke work. Lines represent results of linear regression analyses for sedentary seniors before ($r=0.98$) and after ($r=0.97$) training and Masters athletes ($r=0.99$). No differences were noted in stroke work between sedentary seniors and Masters athletes before training across all loading conditions ($P=0.513$). However, stroke work was increased across all loading conditions in sedentary seniors after training ($P=0.002$).

0.01684) and a slight decrease in equilibrium volume after training was observed (19.0 ± 7.5 versus 10.6 ± 7.3 ; $P=0.018$). These findings indicated that a year of exercise had no major effects on LV stiffness in sedentary seniors.

Doppler Measures of Diastolic Function

Doppler data before training have also been reported.¹¹ Briefly, as shown in Figure 3, sedentary seniors had smaller E/A ratios than Masters athletes at baseline and during saline infusion. TDI E mean in sedentary seniors were slower than those in Master athletes at baseline and during LBNP, but not during saline infusion ($P=0.103$). No differences were observed in IVRT or V_p across all loading conditions.

Transmitral Flow Velocities After Training

In sedentary seniors, there was an increase in E/A ratio after training at baseline (0.83 ± 0.17 versus 0.97 ± 0.23 ; $P=0.052$) and during saline infusion (0.96 ± 0.18 versus 1.16 ± 0.18 ; $P=0.009$) (Figure 3A).

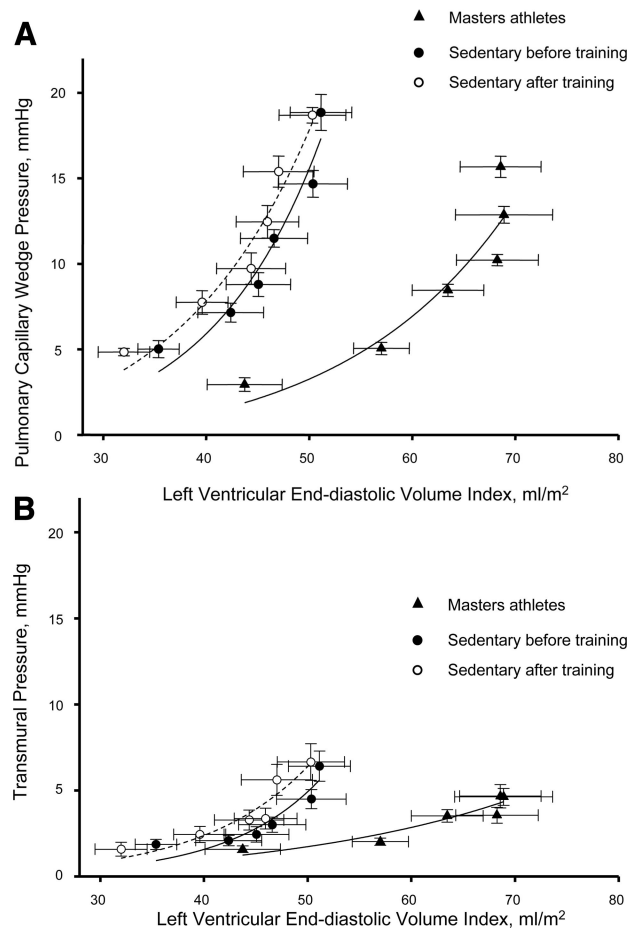


Figure 2. Diastolic pressure volume relationships. A, Pressure-volume curves for sedentary seniors before ($r=0.97$) and after ($r=0.98$) training and Masters athletes ($r=0.93$). Note leftward shift and steeper slope of curve for sedentary seniors before training compared with Masters athletes, suggesting a stiffer ventricle. No significant changes in pressure-volume curves were observed after training. B, Transmural pressures (PCWP–right atrial pressure) are used instead of PCWP for sedentary seniors before ($r=0.94$) and after ($r=0.94$) training and Masters athletes ($r=0.94$) to minimize the effects of external constraints on LV compliance. No significant changes were observed in pressure-volume curves after training. Note that the same scale is used for both panels A and B to emphasize the very small transmural pressure gradients that actually influence LV distension.

Peak Early Diastolic Mitral Annular Velocity (TDI) After Training

The baseline TDI E mean velocities after training were significantly slower compared with those before training (9.31 ± 1.42 versus 8.09 ± 1.34 cm/s; $P<0.001$). This difference was also observed during saline infusion (10.76 ± 1.82 versus 9.77 ± 1.41 cm/s; $P<0.001$), but not during LBNP (7.53 ± 1.25 versus 7.34 ± 1.12 cm/s; $P=0.326$) (Figure 3B).

IVRT After Training

Baseline IVRT after training was shorter than that before training (145.5 ± 17.8 versus 120.3 ± 15.2 ms; $P=0.002$). This difference was present across all loading conditions ($P<0.001$) (Figure 3C).

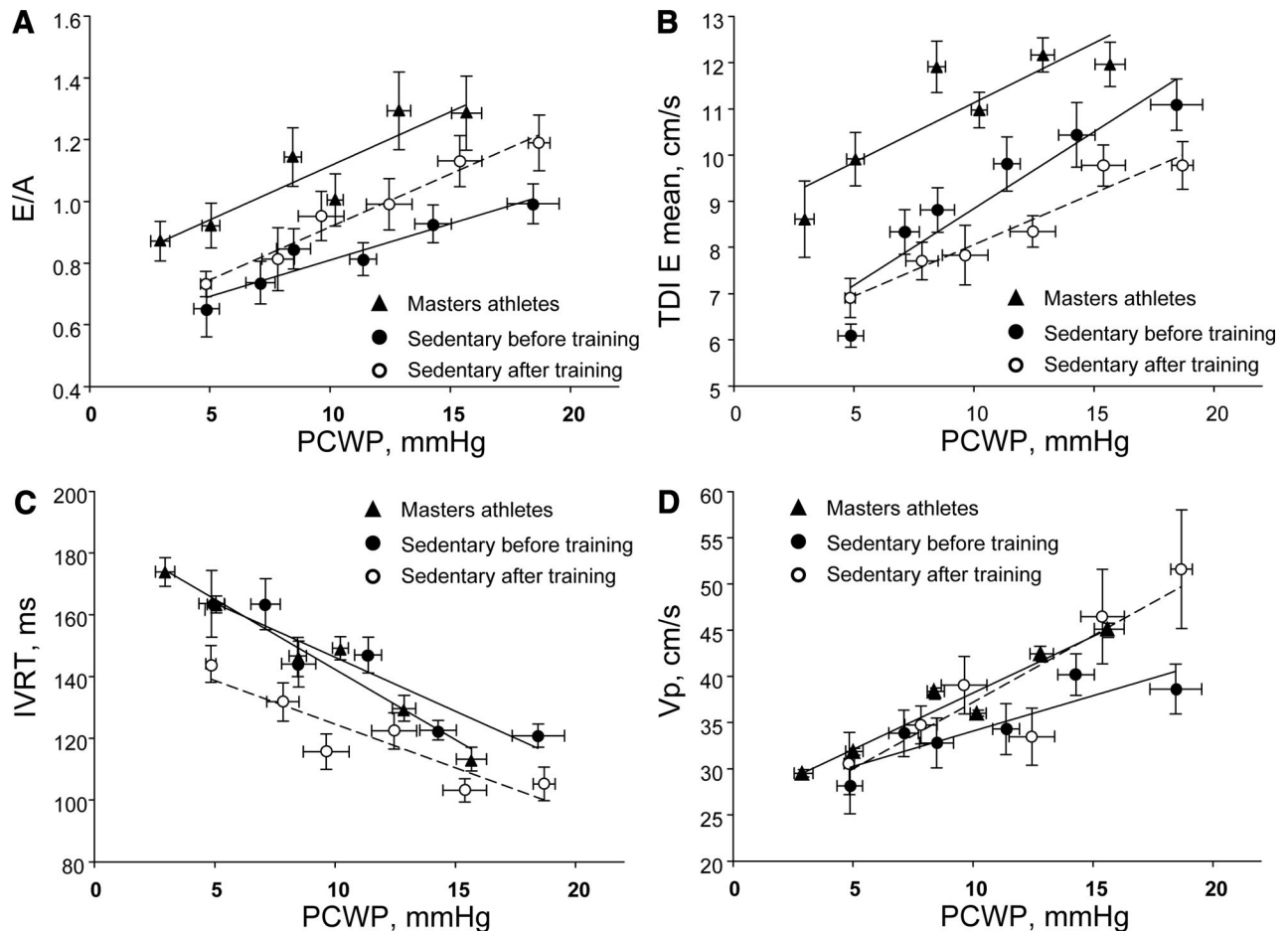


Figure 3. Doppler measures of LV diastolic function. ▲ indicates Masters athletes; ●, sedentary subjects before training; ○, sedentary subjects after training. A, Ratio of early and late mitral inflow velocities (E/A). After exercise training, E/A ratio were increased at baseline ($P=0.052$) and during saline infusion ($P=0.009$). (B) Doppler mitral annular velocities (TDI E mean). The resting baseline TDI E mean velocities were slower after training ($P<0.001$). This difference was observed during saline infusion ($P<0.001$), but not during LBNP. C, Isovolumic relaxation time (IVRT). After training, baseline IVRT was shorter than those before training ($P=0.002$). This difference was present across all loading conditions ($P<0.001$). D, Propagation velocity of early mitral inflow (V_p). After training, V_p was increased during saline infusion, especially at maximal dose of saline infusion ($P=0.003$), but unaffected at baseline and during LBNP.

Mitral Inflow V_p After Training

After training, there were no differences in V_p at baseline (33.5 ± 7.6 versus 36.3 ± 8.8 cm/s; $P=0.465$) or during LBNP (32.8 ± 8.9 versus 32.8 ± 7.4 cm/s; $P=0.850$). In contrast, V_p during saline infusion was increased, especially at maximal dose of saline infusion (38.6 ± 8.1 versus 51.6 ± 19.3 cm/s; $P=0.003$). There was a significant difference in the overall relationship between PCWP and V_p before and after training ($P=0.007$) (Figure 3D).

Discussion

In the present study, we demonstrated that 1 year of progressive and vigorous exercise training failed to reverse cardiac stiffening in previously sedentary seniors. However, this “dose” of exercise training extending over 1 year, encompassing 200 minutes per week and incorporating both low- and high-intensity training, did clearly induce physiological LV remodeling and improve such predictors for cardiovascular morbidity and mortality as aerobic power and arterial function.^{30,31}

Effects of Aging on LV Diastolic Function

Aging induces structural and functional alterations in the cardiovascular system. For example, cardiac myocytes are reduced in

number, with slight increases in the size of residual cells. Moreover, there is an increase in connective tissue volume, partly due to degeneration of matrix proteins, which results in impaired LV diastolic function.⁴ Previous findings that the LV of Masters athletes was as compliant as that of the young demonstrated the efficacy of life-long endurance exercise training on LV stiffness.³ In contrast, life-long endurance exercise training had only minimal effects on Doppler measures of LV dynamic diastolic function in seniors.¹¹ To our knowledge, there are no reports that investigate the effects of exercise training on LV stiffness in normal sedentary seniors.

Effects of a Year of Endurance Exercise Training on LV Size and Hemodynamics

A year of vigorous endurance training increased $\dot{V}O_{2\max}$ by 19% in our previously sedentary seniors. This improvement in aerobic power was mediated primarily through an increase in cardiac output without any change in $a-v\text{Do}_2$ at peak exercise. We also observed an increase in LV mass by 10% with no change in LV mass-volume ratio, suggesting physiological LV remodeling. This increase in LV mass was similar to that in

previous studies evaluating the effects of moderate to vigorous endurance training on LV mass (8% to 15%).^{32–34}

Aging also increases peripheral resistance and stiffens the aorta. These functional alterations in arteries was normalized in some previous studies by less than 3 months of training, which enhances endothelial function and endothelium-dependent vasodilation.^{35,36} Consistent with these studies, we observed improvements of arterial function: an increase in total arterial compliance and a decrease in arterial elastance. These improvements in arterial function from training may have played an important role in the increased stroke volume by improving ventricular-arterial coupling.

LV Stiffness Was Not Improved by a Year of Exercise Training

Contrary to our hypothesis, neither grouped LV pressure-volume curves nor individual LV stiffness constants showed significant improvements after training. There are several possibilities why a year of training failed to improve LV compliance in sedentary seniors. First, the age at which exercise was started may have been too late. Cardiovascular aging is in part characterized by cross-linked advanced glycation end products in vascular and LV walls along with changes in the number and the volume of cardiac myocytes.^{37,38} Because these proteins are pathologically irreversible once formed, any improvements in LV compliance from increases in protein content could have been constrained by cross-linked collagen. A phase II drug, alagebrium, is a cross-link breaker and has been shown to improve LV and arterial stiffness in animals.³⁹ This drug has the potential to reverse cardiovascular stiffening in the elderly, and a trial of an adjunct therapy with exercise training is now underway in healthy elderly subjects (NIH clinicaltrials.gov identifier NCT01014572). Caloric restriction has also been reported to decrease LV stiffness in middle-aged men without obesity.⁴⁰ How the stiffening of the cardiovascular system can be reversed, thereby preventing age-related diseases such as HFpEF, is a compelling area of ongoing research.

Second, the period of training may be insufficient to reverse the stiffening of the heart. Improvements in LV compliance related to training may require longer periods in seniors than the young. Pericardial remodeling may also take many years or require exercise training while young (ie, during growth) to stretch the pericardium. Results may also differ if exercise training is prescribed at very high intensity.⁴¹ The present results could constitute an important step for future optimal training programs or adjunctive therapies in seniors with and without cardiovascular diseases.

Effects of a Year of Exercise Training on Doppler Measure of LV Diastolic Function

We previously reported that the Doppler variables (E/A, Vp, and IVRT) of Masters athletes were similar to those of sedentary elderly subjects, suggesting that life-long exercise training did not prevent the age-related decline in LV relaxation.¹¹ The present results of a modest increase in E/A ratio and Vp, with a small decrease in IVRT, which are consistent with an improvement in LV relaxation after a year of training, seem to be discordant with the previous findings. More

importantly however, E', which is perhaps a more specific measure of LV relaxation, did not change, similar to the pressure-volume curves and even appeared to decrease slightly after training. We speculate that these results are not actually contradictory and may be due to 2 key factors: (1) the difference in the left atrial size and compliance between populations; and (2) mild increases in plasma volume⁴² and thereby left atrial driving pressure with training.

We observed a slightly higher PCWP after exercise training in all loading conditions, although the probability value did not achieve conventional levels of statistical significance. We speculate that the Doppler results after a year of exercise (a shortened IVRT and increases in Vp and E/A ratio) resulted from an increase in left atrial driving pressure, but not from a decrease in LV minimal pressure due to an improvement in LV relaxation. A decreased heart rate and a possible increase in blood volume due to exercise training⁴² may have caused this small elevation of left atrial pressure. The fact that the Vp during high-volume saline infusion after training was higher than that in Masters athletes seems to support this speculation because pseudonormalization of Vp (high Vp) is observed when there is a high atrioventricular pressure gradient between the left atrium and the LV.⁴³ Shortened IVRT in all conditions after training may also reflect the small increase in left atrial pressure as measured from PCWP.

After training, baseline TDI E mean was decreased. LV relaxation can be affected by cardiac contractility and heart rate.^{44,45} Because no changes in LV contractility were observed after training, a slight decrease in heart rate may partly have contributed to the reduction in TDI E mean. Our results suggest that the effects of training on LV diastolic parameters are quite different in Masters athletes with life-long training and sedentary subjects with short-term training.

Effects of a Year of Exercise Training on Exercise Performance

After training, sedentary seniors demonstrated significant improvements in $\dot{V}O_2$ max by 19% through an increase in maximal cardiac output by 10% with minimal change in a-vDo₂. Although neither LV compliance nor relaxation were improved after training at supine rest, cardiac reserve during exercise could be improved partly by a decreased afterload, an improved LV-arterial coupling, and an increased stroke volume at maximal load.

Peripheral alterations with sedentary aging may include loss of skeletal muscle and impaired muscle oxidative capacity.^{46,47} Previous studies reported that exercise training increased peak a-vDo₂ both in sedentary and trained subjects.^{48,49} Contrary to previous studies, no improvement was observed in the a-vDo₂ in the present study. The average age of our subjects was 71 years, which was higher than those in previous studies that showed an increase in a-vDo₂. These results may suggest that the effects of training on oxygen utilization at the periphery may diminish along with aging. Seals et al⁴⁹ also reported that a-vDo₂ was increased after high-intensity exercise training, but not after low-intensity training. More intense exercise training may be required to increase peripheral oxygen extraction in subjects like those reported here.

Study Limitations

There are several limitations. First, the number of sedentary participants was relatively small, primarily because of the comprehensive and invasive nature of the instrumentation and the very long period of controlled training. However, power analysis showed that the sample size in the present study ($n=9$, difference 0.0044; SD, 0.0167; 95% confidence interval, -0.0088 to 0.01684) was sufficient to detect a true difference in the mean change of LV stiffness of -0.018 or 0.018 with a probability of type II error at less than 20% (power 0.8). This minimal detectable difference is more than twice the difference between the mean baseline stiffness constant in these subjects (0.062 ± 0.030) and the stiffness constant for the Masters athletes (0.024 ± 0.017), thus giving us adequate power to detect at least 50% of the difference between Masters athletes and sedentary subjects. Therefore, it is possible but unlikely that a physiologically meaningful difference was missed due to a type II error; however, owing to the small number size, these data should be regarded as preliminary. Second, all comparisons between the older sedentary subjects and the Masters athletes are cross-sectional, and Masters athletes may have been genetically fitter and more predisposed to pursue athletics throughout their life. Thus differences between these groups may be due to more than training status. There also may be sex differences in the effects of exercise training on LV stiffness that could not be detected given the small number of women who completed the training program.

Third, LV pressure-volume curves were evaluated by use of mean PCWP as a surrogate for LV end-diastolic pressure. However, none of our patients had valvular abnormalities or pulmonary disease, which might alter this relationship. Moreover, the development of pressure-volume curves using effective transmural pressure (difference between left atrial [from PCWP] and right atrial pressures) as the independent variable showed exactly the same outcome, increasing confidence in the results. Finally, there was a difference in heart rates before and after training. Although this difference could affect LV relaxation, its influence on LV filling time was small, and LV relaxation was complete before atrial contraction (ie, diastasis was present) in all subjects at all time points. Therefore, this small difference was unlikely to alter LV pressure-volume curves.

Conclusions

The hypothesized improvement in LV compliance with training was not observed in this small but carefully studied sample. Nonetheless, this “dose” of exercise training did induce physiological LV remodeling and imparted favorable effects on arterial function and aerobic exercise capacity, which may have beneficial effects for cardiovascular morbidity and mortality.

Sources of Funding

This study was supported by the National Institutes of Health grant AG17479-02 and an American Heart Association Postdoctoral Fellowship grant 09POST2050083.

Disclosures

None.

References

- Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: part II: the aging heart in health: links to heart disease. *Circulation*. 2003;107:346–354.
- Chen CH, Nakayama M, Nevo E, Fetich BJ, Maughan WL, Kass DA. Coupled systolic-ventricular and vascular stiffening with age: implications for pressure regulation and cardiac reserve in the elderly. *J Am Coll Cardiol*. 1998;32:1221–1227.
- Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, Thomas JD, Palmer D, Levine BD. Effect of aging and physical activity on left ventricular compliance. *Circulation*. 2004;110:1799–1805.
- Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure: abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med*. 2004;350:1953–1959.
- Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. *Circulation*. 2000;101:2118–2121.
- Prasad A, Hastings JL, Shibata S, Popovic ZB, Arbab-Zadeh A, Bhella PS, Okazaki K, Berk M, Palmer D, Greenberg NL, Garcia MJ, Thomas JD, Levine BD. Characterization of static and dynamic left ventricular diastolic function in patients with heart failure and a preserved ejection fraction. *Circ Heart Fail*. 2010;3:617–626.
- Prasad A, Levine BD. Aging and diastolic heart failure. In: Klein A, Garcia M, eds. *Diastology*. Philadelphia, Pa: Elsevier; 2008:385–400.
- Levine BD, Zuckerman JH, Pawelczyk JA. Cardiac atrophy after bed-rest deconditioning: a nonneural mechanism for orthostatic intolerance. *Circulation*. 1997;96:517–525.
- Levine BD, Lane LD, Buckley JC, Friedman DB, Blomqvist CG. Left ventricular pressure-volume and Frank-Starling relations in endurance athletes: implications for orthostatic tolerance and exercise performance. *Circulation*. 1991;84:1016–1023.
- Roche AF, Heymsfield SB, Lohman TG. *Human Body Composition*. Champaign, Ill: Human Kinetics; 1996.
- Prasad A, Popovic ZB, Arbab-Zadeh A, Fu Q, Palmer D, Dijk E, Greenberg NL, Garcia MJ, Thomas JD, Levine BD. The effects of aging and physical activity on Doppler measures of diastolic function. *Am J Cardiol*. 2007;99:1629–1636.
- Popovic ZB, Prasad A, Garcia MJ, Arbab-Zadeh A, Borowski A, Dijk E, Greenberg NL, Levine BD, Thomas JD. Relationship among diastolic intraventricular pressure gradients, relaxation, and preload: impact of age and fitness. *Am J Physiol Heart Circ Physiol*. 2006;290:H1454–H1459.
- Balke B, Nagle FJ, Daniels J. Altitude and maximum performance in work and sports activity. *JAMA*. 1965;194:646–649.
- Triebwasser JH, Johnson RL, Burpo RP, Campbell JC, Reardon WC, Blomqvist CG. Noninvasive determination of cardiac output by a modified acetylene rebreathing procedure utilizing mass spectrometer measurements. *Aviat Space Environ Med*. 1977;48:203–209.
- Laszlo G. Respiratory measurements of cardiac output: from elegant idea to useful test. *J Appl Physiol*. 2004;96:428–437.
- Jarvis SS, Levine BD, Prisk GK, Shykoff BE, Elliott AR, Rosow E, Blomqvist CG, Pawelczyk JA. Simultaneous determination of the accuracy and precision of closed-circuit cardiac output rebreathing techniques. *J Appl Physiol*. 2007;103:867–874.
- Liu Y, Menold E, Dullenkopf A, Reissnecker S, Lormes W, Lehmann M, Steinacker JM. Validation of the acetylene rebreathing method for measurement of cardiac output at rest and during high-intensity exercise. *Clin Physiol*. 1997;17:171–182.
- Okazaki K, Iwasaki K, Prasad A, Palmer MD, Martini ER, Fu Q, Arbab-Zadeh A, Zhang R, Levine BD. Dose-response relationship of endurance training for autonomic circulatory control in healthy seniors. *J Appl Physiol*. 2005;99:1041–1049.
- Chemla D, Hébert JL, Coirault C, Zamani K, Suard I, Colin P, Lecarpentier Y. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. *Am J Physiol*. 1998;274:H500–H505.
- Kelly RP, Ting CT, Yang TM, Liu CP, Maughan WL, Chang MS, Kass DA. Effective arterial elastance as index of arterial vascular load in humans. *Circulation*. 1992;86:513–521.
- Chen CH, Fetich B, Nevo E, Rochitte CE, Chiou KR, Ding PA, Kawaguchi M, Kass DA. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. *J Am Coll Cardiol*. 2001;38:2028–2034.
- Mirsky I. Assessment of diastolic function: suggested methods and future considerations. *Circulation*. 1984;69:836–841.
- Dauterman K, Pak PH, Maughan WL, Nussbacher A, Ariè S, Liu CP, Kass DA. Contribution of external forces to left ventricular diastolic

- pressure: implications for the clinical use of the Starling law. *Ann Intern Med.* 1995;122:737–742.
24. Belenkie I, Kieser TM, Sas R, Smith ER, Tyberg JV. Evidence for left ventricular constraint during open heart surgery. *Can J Cardiol.* 2002;18:951–959.
 25. Glower DD, Spratt JA, Snow ND, Kabas JS, Davis JW, Olsen CO, Tyson GS, Sabiston DC Jr, Rankin JS. Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work. *Circulation.* 1985;71:994–1009.
 26. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, Lee MM, Park YB, Choi YS, Seo JD, Lee YW. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. *J Am Coll Cardiol.* 1997;30:474–480.
 27. Hundley WG, Li HF, Willard JE, Landau C, Lange RA, Meshack BM, Hillis LD, Peshock RM. Magnetic resonance imaging assessment of the severity of mitral regurgitation: comparison with invasive techniques. *Circulation.* 1995;92:1151–1158.
 28. Katz J, Milliken MC, Stray-Gundersen J, Buja LM, Parkey RW, Mitchell JH, Peshock RM. Estimation of human myocardial mass with MR imaging. *Radiology.* 1988;169:495–498.
 29. Plein S, Bloomer TN, Ridgway JP, Jones TR, Bainbridge GJ, Sivanathan MU. Steady-state free precession magnetic resonance imaging of the heart: comparison with segmented k-space gradient-echo imaging. *J Magn Reson Imaging.* 2001;14:230–236.
 30. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation.* 1991;83:778–786.
 31. Halsuka BA, Jeffries L, Carlier S, Marwick TH. Measurement of arterial distensibility and compliance to assess prognosis. *Atherosclerosis.* 2010;209:474–480.
 32. Baggish AL, Wang F, Weiner RB, Elinoff JM, Tournoux F, Boland A, Picard MH, Hutter AM Jr, Wood MJ. Training-specific changes in cardiac structure and function: a prospective and longitudinal assessment of competitive athletes. *J Appl Physiol.* 2008;104:1121–1128.
 33. Rodrigues AC, de Melo Costa J, Alves GB, Ferreira da Silva D, Picard MH, Andrade JL, Mathias W Jr, Negrão CE. Left ventricular function after exercise training in young men. *Am J Cardiol.* 2006;97:1089–1092.
 34. Spina RJ, Turner MJ, Ehsani AA. Beta-adrenergic-mediated improvement in left ventricular function by exercise training in older men. *Am J Physiol.* 1998;274:H397–404.
 35. Desouza CA, Shapiro LF, Clevenger CM, Dinunno FA, Monahan KD, Tanaka H, Seals DR. Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. *Circulation.* 2000;102:1351–1357.
 36. Clarkson P, Montgomery HE, Mullen MJ, Donald AE, Powe AJ, Bull T, Jubb M, World M, Deanfield JE. Exercise training enhances endothelial function in young men. *J Am Coll Cardiol.* 1999;33:1379–1385.
 37. Aronson D. Cross-linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of aging and diabetes. *J Hypertens.* 2003;21:3–12.
 38. Kass DA. Getting better without AGE: new insights into the diabetic heart. *Circ Res.* 2003;92:704–706.
 39. Asif M, Egan J, Vasani S, Jyothirmayi GN, Masurekar MR, Lopez S, Williams C, Torres RL, Wagle D, Ulrich P, Cerami A, Brines M, Regan TJ. An advanced glycation endproduct cross-link breaker can reverse age-related increases in myocardial stiffness. *Proc Natl Acad Sci U S A.* 2000;97:2809–2813.
 40. Riordan MM, Weiss EP, Meyer TE, Ehsani AA, Racette SB, Villareal DT, Fontana L, Holloszy JO, Kovács SJ. The effects of caloric restriction and exercise-induced weight loss on left ventricular diastolic function. *Am J Physiol Heart Circ Physiol.* 2008;294:H1174–H1182.
 41. Wisløff U, Støylen A, Loennechen JP, Bruvold M, Rognum Ø, Haram PM, Tjønnå AE, Helgerud J, Slørdahl SA, Lee SJ, Videm V, Bye A, Smith GL, Najjar SM, Ellingsen Ø, Skjaerpe T. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation.* 2007;115:3086–3094.
 42. Convertino VA. Blood volume response to physical activity and inactivity. *Am J Med Sci.* 2007;334:72–79.
 43. De Boeck BW, Oh JK, Vandervoort PM, Vierendeels JA, van der Aa RP, Cramer MJ. Colour M-mode velocity propagation: a glance at intra-ventricular pressure gradients and early diastolic ventricular performance. *Eur J Heart Fail.* 2005;7:19–28.
 44. Eichhorn EJ, Willard JE, Alvarez L, Kim AS, Glamann DB, Risser RC, Grayburn PA. Are contraction and relaxation coupled in patients with and without congestive heart failure? *Circulation.* 1992;85:2132–2139.
 45. Freeman GL, Little WC, O'Rourke RA. Influence of heart rate on left ventricular performance in conscious dogs. *Circ Res.* 1987;61:455–464.
 46. Fleg JL, Lakatta EG. Role of muscle loss in the age-associated reduction in VO₂ max. *J Appl Physiol.* 1988;65:1147–1151.
 47. Conley KE, Esselman PC, Jubrias SA, Cress ME, Inglin B, Mogadam C, Schoene RB. Ageing, muscle properties and maximal O₂ uptake rate in humans. *J Physiol.* 2000;526:211–217.
 48. McGuire DK, Levine BD, Williamson JW, Snell PG, Blomqvist CG, Saltin B, Mitchell JH. A 30-year follow-up of the Dallas bedrest and training study: II. Effect of age on cardiovascular adaptation to exercise training. *Circulation.* 2001;104:1358–1366.
 49. Seals DR, Hagberg JM, Hurley BF, Ehsani AA, Holloszy JO. Endurance training in older men and women. I. Cardiovascular responses to exercise. *J Appl Physiol.* 1984;57:1024–1029.

CLINICAL PERSPECTIVE

Healthy but sedentary aging leads to the stiffening of the heart. For example, the left ventricle (LV) becomes less compliant and LV early diastolic function (relaxation and filling) becomes impaired with aging. Life-long endurance training as seen in Masters athletes can prevent this age-related change in the LV compliance, but only minimally influences age-related impairments in dynamic LV relaxation and filling. In the present study, we prescribed a year of progressive and vigorous exercise training to 9 sedentary individuals older than 65 years of age and evaluated overall cardiac function by use of several modalities, including invasive pressure-volume measurements, exercise testing, cardiac echo-Doppler, and cardiac magnetic resonance imaging before and after the training. To our knowledge, this is the first study to evaluate the effect of exercise training on the LV compliance in sedentary individuals. Unfortunately the hypothesized improvement in LV compliance with training was not observed in this small but carefully studied sample. Nonetheless, the dose of exercise training prescribed induced physiological LV remodeling and imparted favorable effects on arterial function and aerobic exercise capacity, which may have beneficial effects for cardiovascular morbidity and mortality. Further research will elucidate at which age exercise training should be started or how much exercise training (volume and intensity) per week is needed to prevent the age-related change in LV compliance. The present results could constitute an important step for the development of optimal training programs or adjunctive therapies in seniors with and without cardiovascular diseases.

Cardiovascular Effects of 1 Year of Progressive and Vigorous Exercise Training in Previously Sedentary Individuals Older Than 65 Years of Age

Naoki Fujimoto, Anand Prasad, Jeffrey L. Hastings, Armin Arbab-Zadeh, Paul S. Bhella, Shigeki Shibata, Dean Palmer and Benjamin D. Levine

Circulation. 2010;122:1797-1805; originally published online October 18, 2010;
doi: 10.1161/CIRCULATIONAHA.110.973784

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:

<http://circ.ahajournals.org/content/122/18/1797>

Data Supplement (unedited) at:

<http://circ.ahajournals.org/content/suppl/2013/10/17/CIRCULATIONAHA.110.973784.DC1>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation* is online at:
<http://circ.ahajournals.org/subscriptions/>



accidents coronaires majeurs définissant l'événement cible composite ; nous avons également effectué une analyse pour savoir si, administré à la posologie de 0,5 mg/jour, le lasofoxifène exerçait le même effet quelle que soit l'importance du risque coronaire.

Méthodes et résultats—Dans cette étude, 8 556 femmes âgées de 59 à 80 ans et atteintes d'ostéoporose ont reçu pendant 5 ans du lasofoxifène à la dose journalière de 0,25 mg ou de 0,5 mg ou un placebo. Les taux d'événements cardiovasculaires, notamment à type d'accident coronaire majeur, ont été retenus comme critères de jugement secondaires. Par rapport au placebo, le traitement par le lasofoxifène à la posologie de 0,5 mg/jour a diminué le risque d'événement coronaire majeur de 32 % (rapport des risques : 0,68 ; intervalle de confiance [IC] à 95 % : 0,50 à 0,93), cela ayant inclus le risque de revascularisation coronaire (rapport des risques : 0,56 ; IC à 95 % : 0,32 à 0,98). Les réductions du risque d'hospitalisation pour angor instable (rapport des risques : 0,55 ; IC à 95 % : 0,29 à 1,04) et du risque d'apparition d'une cardiopathie ischémique jusqu'alors absente (rapport des risques : 0,52 ; IC à 95 % : 0,26 à 1,04) ont presque atteint le seuil de significativité ($p = 0,06$ pour les deux comparaisons). Bien que le rapport des risques ait été inférieur à 1,0 dans les deux cas, l'administration de lasofoxifène à la dose de 0,5 mg/jour n'a pas eu d'effet significatif sur la mortalité de cause coronaire ni sur le risque d'infarctus du myocarde non fatal. Administré à raison de 0,25 mg/jour, le lasofoxifène n'a pas entraîné de diminution significative du taux d'événements coronaires (rapport des risques : 0,76 ; IC à 95 % : 0,56 à 1,03 ; $p = 0,08$). L'efficacité dont a fait preuve le lasofoxifène à la dose de 0,5 mg/jour en termes de réduction des événements coronaires a été similaire quelle qu'ait été l'importance des facteurs de risque cardiovasculaire majeur.

Conclusions—Chez la femme ménopausée ostéoporotique, l'administration journalière de 0,5 mg de lasofoxifène pendant 5 ans a diminué le risque d'événement coronaire et ce, que des facteurs de risque cardiovasculaire aient été ou non présents. La réduction significative du risque d'événement coronaire engendrée par le médicament à la posologie considérée a essentiellement découlé de la diminution des risques d'intervention de revascularisation coronaire, d'hospitalisation pour angor instable et de développement d'une cardiopathie ischémique.

Registre américain des Essais cliniques—URL : <http://www.clinicaltrials.gov>. Identifiant unique : NCT00141323. (Traduit de l'anglais : Lasofoxifene and Cardiovascular Events in Postmenopausal Women With Osteoporosis; Five-Year Results From the Postmenopausal Evaluation and Risk Reduction With Lasofoxifene (PEARL) Trial. *Circulation*. 2010;122:1716-1724.)

Mots clés : essai clinique ■ maladie coronaire ■ modulateur sélectif des récepteurs œstrogéniques ■
accident vasculaire cérébral

Effets cardiovasculaires à un an de la pratique progressive d'un entraînement physique énergique chez des sujets de plus de 65 ans jusqu'alors sédentaires

Naoki Fujimoto, MD, PhD ; Anand Prasad, MD ; Jeffrey L. Hastings, MD ; Armin Arbab-Zadeh, MD ;
Paul S. Bhella, MD ; Shigeki Shibata, MD, PhD ; Dean Palmer, MS ; Benjamin D. Levine, MD

Contexte—Même lorsque le vieillissement va de pair avec la conservation d'un bon état de santé, la sédentarité contribue à rigidifier les structures cardiovasculaires ; en revanche, la pratique d'exercices d'endurance tout au long de la vie préserve la compliance ventriculaire gauche (VG). On ignore toutefois si un entraînement physique entrepris à un âge plus avancé est à même de corriger les effets exercés par la sédentarité sur le cœur.

Méthodes et résultats—Douze séniors sédentaires et 12 autres s'adonnant à un entraînement physique régulier ont fait l'objet d'un examen approfondi à la recherche d'éventuelles pathologies sous-jacentes. Des mesures hémodynamiques invasives avec cathétérisme de l'artère pulmonaire ont été pratiquées chez chacun d'eux afin d'établir leurs courbes de Starling et de pression-volume VG ; les explorations fonctionnelles secondaires ont consisté en une échocardiographie Doppler, en une évaluation de la morphologie cardiaque et de la rigidité artérielle (compliance aortique totale et élastance artérielle) par imagerie par résonance magnétique et en une épreuve d'effort d'intensité maximale. Pendant un an, 9 des 12 sujets sédentaires ($70,6 \pm 3$ ans ; 6 hommes et 3 femmes) ont effectué des exercices d'endurance suivis de mesures répétées. La pression capillaire pulmonaire bloquée et le volume télédiastolique VG ont été mesurés à l'état basal, pendant la phase de diminution du remplissage cardiaque engendrée en induisant une pression négative au niveau des membres inférieurs et au cours de l'augmentation du remplissage réalisée au moyen d'une perfusion de sérum physiologique. La compliance VG a été estimée d'après la pente de la courbe de pression-volume. Avant le programme d'entraînement, les séniors sédentaires présentaient une Vo_{2max} , une masse VG, un volume télédiastolique VG et un volume d'éjection significativement inférieurs à ceux de leurs homologues qui s'entraînaient régulièrement ; leur compliance VG était également plus faible. La période d'un an d'entraînement physique n'a pratiquement pas eu d'impact sur la compliance cardiaque. En revanche, elle a eu pour effet de diminuer l'élastance artérielle et d'améliorer la Vo_{2max} de 19 % ($22,8 \pm 3,4$ ml/kg/ml contre $27,2 \pm 4,3$; $p < 0,001$). La masse VG a également augmenté de 10 % ($64,5 \pm 7,9$ g/m² contre $71,2 \pm 12,3$; $p = 0,037$) sans modification du rapport masse/volume.





Conclusions—Bien qu'un an d'entraînement physique intense n'ait pas semblé avoir d'influence bénéfique sur la rigidité cardiaque des séniors sédentaires, cela a néanmoins induit un remodelage VG physiologique et a amélioré la fonction artérielle et la capacité d'effort aérobie. (Traduit de l'anglais : Cardiovascular Effects of 1 Year of Progressive and Vigorous Exercise Training in Previously Sedentary Individuals Older Than 65 Years of Age. *Circulation*. 2010;122:1797–1805.)

Mots clés : diastole ■ activité physique ■ vieillissement ■ maladies cardiaques ■ hémodynamique

Dysfonction vasculaire chez la femme ayant des antécédents de prééclampsie et de retard de croissance intra-utérin

Eléments d'appréciation du risque vasculaire à venir

Yoav Yinon, MD ; John C.P. Kingdom, MD ; Ayodele Odutayo, BSc ; Rahim Moineddin, PhD ; Sascha Drewlo, PhD ; Vesta Lai, RN ; David Z.I. Cherney, MD, PhD ; Michelle A. Hladunewich, MD

Contexte—Les femmes ayant présenté une maladie placentaire sont exposées à un risque accru de développement d'une affection vasculaire. On ignore toutefois si la préexistence d'une dysfonction endothéliale intervient dans la prédisposition aux pathologies placentaires et dans la survenue ultérieure d'un trouble vasculaire. Cette étude avait donc pour objet d'évaluer la fonction vasculaire chez des femmes en période de postpartum et d'établir si son altération différait selon le type d'affection placentaire.

Méthodes et résultats—Des patientes qui avaient respectivement des antécédents de prééclampsie de début précoce (n = 15), de prééclampsie de survenue tardive (n = 9) et de retard de croissance intra-utérin sans prééclampsie (n = 9) ont été suivies pendant une durée de 6 à 24 mois après leur accouchement parallèlement à des femmes dont la grossesse s'était déroulée normalement (n = 16). La vasodilatation médiée par le flux sanguin et celle indépendante de celui-ci (induite par la trinitrine) ont été étudiées au niveau de l'artère humérale par écho-Doppler de haute résolution. La rigidité artérielle a été appréciée par analyse de l'onde de pouls (indice d'augmentation). Le bilan biologique a porté sur les taux de facteurs angiogéniques circulants (facteur de croissance de l'endothélium vasculaire, fms-like tyrosine kinase 1 soluble, facteur de croissance placentaire et endogline soluble). La vasodilatation dépendante du flux est apparue significativement plus faible chez les femmes qui avaient des antécédents de prééclampsie de début précoce et de retard de croissance intra-utérin que chez celles ayant antérieurement présenté une prééclampsie de survenue tardive et que chez les témoins (respectivement, $3,2 \pm 2,7\%$ et $2,1 \pm 1,2\%$ contre $7,9 \pm 3,8\%$ et $9,1 \pm 3,5\%$; $p < 0,0001$). La vasodilatation indépendante du flux a été comparable dans tous les groupes. De même, l'indice d'augmentation de la pression artérielle radiale s'est révélé significativement majoré chez les femmes ayant des antécédents de prééclampsie de début précoce et de retard de croissance intra-utérin, alors qu'il a été normal chez celles ayant présenté une prééclampsie tardive et chez les témoins ($p = 0,0105$). Les taux de facteurs angiogéniques circulants ont été similaires dans tous les groupes.

Conclusions—Seules les femmes ayant des antécédents de prééclampsie de survenue précoce et de retard de croissance intra-utérin sans prééclampsie sont sujettes à une altération de leur fonction vasculaire, ce qui pourrait expliquer leur prédisposition aux pathologies placentaires et leur propension supérieure à développer secondairement une affection vasculaire. (Traduit de l'anglais : Vascular Dysfunction in Women With a History of Preeclampsia and Intrauterine Growth Restriction; Insights Into Future Vascular Risk. *Circulation*. 2010;122:1846–1853.)

Mots clés : endothélium ■ prééclampsie ■ vasodilatation ■ femmes ■ maladies vasculaires ■ pathologies placentaires ■ femme en postpartum

Activation de la voie intrinsèque de la coagulation et risque de thrombose artérielle chez la femme jeune

Résultats de l'étude cas-témoin Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO)

B. Siegerink, MSc ; J.W.P. Govers-Riemslog, PhD ; F.R. Rosendaal, MD, PhD ; H. ten Cate, MD, PhD ; A. Algra, MD, PhD

Contexte—L'opinion qui prévaut est que les protéines de la voie intrinsèque de la coagulation jouent un rôle mineur dans l'hémostase. De récentes données suggèrent toutefois que ces protéines, et plus particulièrement le facteur XII, seraient des acteurs clés dans la pathogenèse des thromboses artérielles. La présente étude a donc été entreprise pour évaluer les risques

