

# Effect of Aging and Physical Activity on Left Ventricular Compliance

Armin Arbab-Zadeh, MD; Erika Dijk, BS; Anand Prasad, MD; Qi Fu, MD, PhD; Pilar Torres, MD; Rong Zhang, PhD; James D. Thomas, MD; Dean Palmer, MS; Benjamin D. Levine, MD

**Background**—Left ventricular compliance appears to decrease with aging, which may contribute to the high incidence of heart failure in the elderly. However, whether this change is an inevitable consequence of senescence or rather secondary to reduced physical activity is unknown.

**Methods and Results**—Twelve healthy sedentary seniors (69.8±3 years old; 6 women, 6 men) and 12 Masters athletes (67.8±3 years old; 6 women, 6 men) underwent pulmonary artery catheterization to define Starling and left ventricular pressure-volume curves. Data were compared with those obtained in 14 young but sedentary control subjects (28.9±5 years old; 7 women, 7 men). Pulmonary capillary wedge pressures and left ventricular end-diastolic volumes by use of echocardiography were measured at baseline, during decreased cardiac filling by use of lower-body negative pressure (−15 and −30 mm Hg), and after saline infusion (15 and 30 mL/kg). Stroke volume for any given filling pressure was greater in Masters athletes compared with the age-matched sedentary subjects, whereas contractility, as assessed by preload recruitable stroke work, was similar. There was substantially decreased left ventricular compliance in healthy but sedentary seniors compared with the young control subjects, which resulted in higher cardiac pressures for a given filling volume and higher myocardial wall stress for a given strain. The pressure-volume curve for the Masters athletes was indistinguishable from that of the young, sedentary control subjects.

**Conclusions**—A sedentary lifestyle during healthy aging is associated with decreased left ventricular compliance, leading to diminished diastolic performance. Prolonged, sustained endurance training preserves ventricular compliance with aging and may help to prevent heart failure in the elderly. (*Circulation*. 2004;110:1805-1811.)

**Key Words:** aging ■ diastole ■ exercise ■ hemodynamics ■ myocardium

Heart failure is the leading cause of hospitalizations for patients over the age of 65 years, resulting in substantial morbidity, mortality, and cost.<sup>1</sup> Although coronary artery disease and other comorbid conditions often lead to impaired ventricular function in this population, up to 50% of elderly heart failure patients have a normal ejection fraction.<sup>2-4</sup> In such patients, reduced left ventricular (LV) compliance, or “diastolic dysfunction,” is presumed to play a significant role.<sup>5</sup> Drawing primarily from animal studies, recent reviews have suggested that diastolic function deteriorates with age.<sup>6,7</sup> Moreover, indirect measures of “diastolic function,” such as mitral filling velocities, have been reported to decline with age in population-based studies, suggesting that the human heart may also stiffen during aging.<sup>8-10</sup>

However, cardiac compliance has never been measured directly in completely healthy, asymptomatic elderly volunteers. Furthermore, recent work suggests that bed rest deconditioning impairs<sup>11</sup> and endurance training improves cardiac compliance.<sup>12</sup> Therefore, we hypothesized that sedentary

aging results in decreased LV compliance, whereas endurance training during healthy aging preserves ventricular compliance.

## Methods

### Subject Population

Twelve healthy adults older than 65 years of age (6 female, 6 male; mean age, 69.8±3 years; all white) formed the sedentary seniors group, and 12 age-matched Masters athletes (6 female, 6 male; mean age, 67.8±3 years; all white) represented the athletic group. All subjects were rigorously screened for the presence of arterial hypertension, obstructive coronary artery disease, or structural heart disease by use of 24-hour blood pressure recordings, baseline and exercise ECGs, and echocardiograms. Body fat content and lean body mass were measured by underwater weighing.<sup>13</sup> Masters athletes were recruited from race records derived from United States Masters Athletes-sanctioned events demonstrating consistent age-group place winners at regional and national endurance races for at least 10 years. The athletic subjects ultimately recruited had participated in regular endurance competitions for 23±8 years, with a weekly running mileage of 32±10 miles or equivalent swimming or

Received October 7, 2003; revision received May 20, 2004; accepted June 2, 2004.

From the Institute for Exercise and Environmental Medicine, Presbyterian Hospital, and University of Texas Southwestern Medical Center, Dallas, Tex (A.A.-Z., A.P., Q.F., P.T., R.Z., D.P., B.D.L.); University Medical Center, Nijmegen, Netherlands (E.D.); and Cleveland Clinic Foundation, Cleveland, Ohio (J.D.T.).

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

© 2004 American Heart Association, Inc.

*Circulation* is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000142863.71285.74

cycling. Six of the Masters athletes were nationally ranked competitors, and 6 were regional champions. Sedentary participants, conversely, were excluded if they engaged in endurance exercise for more than 30 minutes 3 times a week.

Subjects of either group were excluded if one of the following was present: mean daytime blood pressure greater than 140/90 mm Hg, ECG changes suggestive of ischemic heart disease, left bundle-branch block, atrial flutter/fibrillation, atrioventricular block greater than first degree, baseline or exercise-induced wall motion abnormalities, valvular heart disease other than mild valvular insufficiency, right or LV hypertrophy (by ECG or echocardiogram, only in sedentary subjects), untreated thyroid disorders, chronic lung disease, regular cigarette smoking within the previous 10 years, body mass index of 30 or greater, cardiovascular medication, or warfarin use. In addition, 14 healthy, sedentary young subjects (7 female, 7 male; mean age,  $28.9 \pm 5$  years) who were studied before this investigation in our laboratory according to the same standards and criteria were used for comparison. All subjects signed an informed consent approved by the institutional review boards of the University of Texas Southwestern Medical Center at Dallas and Presbyterian Hospital of Dallas.

### Echocardiography

Baseline and exercise echocardiographic evaluations were performed to detect structural or ischemic heart disease (HDI 5000, ATL). In addition, LV end-diastolic volumes and end-systolic volumes were measured by use of the modified Simpson's rule method during altered loading conditions of the experimental protocol as described below. Great care was taken to avoid foreshortening of image views and to record images with optimal endocardial definition.<sup>14</sup> All images were stored digitally for offline analysis. Echocardiographic images were analyzed locally by an unblinded investigator and by an independent core laboratory, whose analysts were blinded to the study protocol and results. Results from both analyses were compared for variation. In addition, echocardiographic assessment of LV end-diastolic volume was compared with analysis by MRI.

### Peak Oxygen Consumption

A modified Astrand-Saltin incremental treadmill protocol was used to determine peak exercise capacity.<sup>15</sup> Measures of ventilatory gas exchange were made by use of the Douglas bag technique. Gas fractions were analyzed by mass spectrometry, and ventilatory volume was measured by use of a Tissot spirometer. Maximum oxygen uptake was defined as the highest oxygen uptake measured from at least a 40s Douglas bag. Heart rate was monitored continuously via ECG, and cardiac output was measured by use of a modification of the acetylene rebreathing technique<sup>16</sup> at baseline, steady state 1 ( $\approx 30\%$  maximum oxygen uptake), steady state 2 ( $\approx 60\%$  maximum oxygen uptake), and at peak exercise.

### Cardiac Catheterization and Experimental Protocol

A 6F balloon-tipped fluid-filled catheter was placed under fluoroscopic guidance through an antecubital vein 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 and right atrial pressures were determined visually at the end of expiration. Cardiac output was measured by use of the acetylene rebreathing technique with acetylene as the soluble and helium as the insoluble gas. Stroke volume was calculated from cardiac output and heart rate measured during rebreathing. Effective arterial elastance (or arterial stiffness) was defined as the ratio of end-systolic pressure over stroke volume,<sup>17</sup> with end-systolic pressure estimated by use of the single-beat method as previously described and validated.<sup>18</sup>

### Testing Protocols

Cardiac filling was decreased by applying lower-body negative pressure as previously reported.<sup>12</sup> Briefly, lower-body negative pressure was achieved by placing the subject in a Plexiglas box sealed at the level of the iliac crest. The suction was provided by use

of a vacuum pump with a variable autotransformer. Measurements of pulmonary capillary wedge pressure, cardiac output (and therefore stroke volume), LV end-diastolic volume, heart rate, and blood pressure were made after 5 minutes each of  $-15$  mm Hg and  $-30$  mm Hg lower-body negative pressure. Blood samples were obtained at baseline and at each stage of lower-body negative pressure for the measurement of plasma norepinephrine levels by a reference laboratory (Arup Laboratories). The negative pressure was then released. After repeat baseline measurements to confirm a return to hemodynamic steady state, cardiac filling was increased by rapid infusion (100 mL/min) of warm ( $37^\circ\text{C}$ ), isotonic saline. Measurements were repeated after 10 to 15 mL/kg and 20 to 30 mL/kg had been infused.

Data were used to construct Starling (stroke volume/pulmonary capillary wedge pressure) and pressure/volume (pulmonary capillary wedge pressure/LV end-diastolic volume) curves. Preload recruitable stroke work was assessed by relating LV end-diastolic volumes to stroke work, which was calculated by the product of stroke volume and mean arterial pressure.<sup>19</sup> For the purposes of the present study, we characterized and defined explicitly 3 different but related mechanical properties of the heart during diastole: (1) operating stiffness (or its inverse, compliance) is used to mean the instantaneous change in pressure for a change in volume ( $dP/dV$ ) at a specific LV end-diastolic volume; (2) overall chamber stiffness (or its inverse, compliance) refers to the stiffness constant "a" of the exponential equation describing the pressure/volume curve (see below); and (3) distensibility is used to mean the absolute LV end-diastolic volume at a given distending pressure. To characterize LV pressure/volume relations, we modeled the data in the present experiment according to an exponential equation<sup>20</sup>:

$$P = P_\infty (\exp^{a(V-V_0)} - 1),$$

where  $P$  is pulmonary capillary wedge pressure,  $P_\infty$  is pressure asymptote of the curve,  $V$  is LV end-diastolic volume,  $V_0$  is equilibrium volume or the volume at which  $P=0$  mm Hg, and "a" is a constant that characterizes the chamber stiffness.

### LV End-Diastolic Stress-Strain Relationship

For the fit and sedentary elderly subjects, circumferential LV wall stress ( $\sigma_c$ ) and strain were determined.<sup>21</sup> For each individual, at each loading/unloading condition,  $\sigma_c$  was calculated by use of the modified Laplace relation:

$$\sigma_c = Pb/h[1 - (h/2b)][1 - (hb/2a^2)],$$

where  $P$  is estimated transmural pressure,  $h$  is LV midwall thickness,  $a$  is major semiaxis, and  $b$  is minor semiaxis. Transmural pressure was estimated by subtracting mean right atrial pressure from mean pulmonary capillary wedge pressure. The LV midwall thickness and semiaxis measurements were calculated from the transthoracic echocardiographic images. The smallest end-diastolic volume measured during cardiac unloading ( $V_{\min}$ ) was determined. This value was subtracted from the end-diastolic volume at each loading/unloading condition ( $V - V_{\min}$ ). Ventricular strain was calculated as

$$\text{Strain} = (V - V_{\min}) / V_{\min}.$$

The resulting data were used to construct stress-strain plots, which were modeled by an exponential equation ( $y = ae^{bx}$ ).

### Cardiac MRI Measurements

MRI was performed on a 1.5-T Philips NT MRI scanner. Short-axis, gradient-echo, cine MRI sequences with a temporal resolution of 39 ms were obtained to calculate LV masses and volumes as previously described.<sup>22</sup> LV mass was computed as the difference between epicardial and endocardial areas multiplied by the density of heart muscle, 1.05 g/mL.<sup>23</sup> For LV volume determination, the endocardial border of each slice was identified manually at end diastole and end systole, and volumes were calculated by summation. End diastole was defined as the first frame in each sequence and end systole as the frame with smallest endocardial area. LV volumes were calculated by use of the Simpson's rule technique as previously described.<sup>24</sup> LV ejection fraction was computed according to the formula (end-dia-

TABLE 1. Subject Characteristics

Variable	Sedentary Seniors	Masters Athletes	Young Controls
Age, y	69.8±3	67.8±3	28.9±5*†
Height, cm	168.3±10.1	170.0±11.3	173.7±5.8
Weight, kg	73.3±10.6	64.6±13.5*	71.2±4.4
Body surface area, m <sup>2</sup>	1.87±0.16	1.78±0.23	1.83±0.16
% Body fat	28.7±7.2	17.6±5.8*	22.5±4.3*
Heart rate, bpm	66±9	52±6*‡	66±2
Systolic blood pressure, mm Hg	123±10	117±12	121±8
Diastolic blood pressure, mm Hg	73±6	69±7	72±5
Cardiac output, L/min	4.85±0.63	5.57±1.21	6.66±1.31*†
Cardiac index, L·min <sup>-1</sup> ·m <sup>-2</sup>	2.63±0.31	3.22±0.61*	3.50±0.49*
Stroke volume, mL	70.8±14	95.8±21*	98.7±19*
Stroke volume index, mL/m <sup>2</sup>	38.2±6	54.8±8*	52.7±8*
VO <sub>2</sub> max, mL·kg <sup>-1</sup> ·min <sup>-1</sup>	21.6±2.8	38.6±6.1*	39.5±4.9*
Arterial elastance, mm Hg/mL	1.82±0.45	1.21±0.27*	1.07±0.20*
Relative LV mass, g/m <sup>2</sup>	69.2±11	82.9±18*	90.6±16*
LV end-diastolic volume, mL	104±24	140±33*	119±19
LV end-diastolic volume index, mL/m <sup>2</sup>	56±10	80±12*‡	63±6
Mass-to-volume ratio	1.27±0.31	1.08±0.26‡	1.40±0.24
Ejection fraction, %	70.0±3.3	71.7±5.1	74.3±4.2

Values are given as mean±SD.

\*Statistically significant difference from sedentary seniors; †statistically significant difference from Masters athletes; ‡statistically significant difference from young controls. Blood pressure values were obtained from 24-hour blood pressure monitoring; stroke volume was calculated from heart rate and cardiac output obtained from acetylene rebreathing technique; LV mass, volume, and ejection fraction were derived from MRI data. VO<sub>2</sub>max indicates maximum oxygen uptake; EDV, end-diastolic volume.

stolic volume—end-systolic volume)/end-diastolic volume. All analysis was performed by one physician who was blinded to the study protocol and results.

### Statistical Analysis and Interobserver Variability

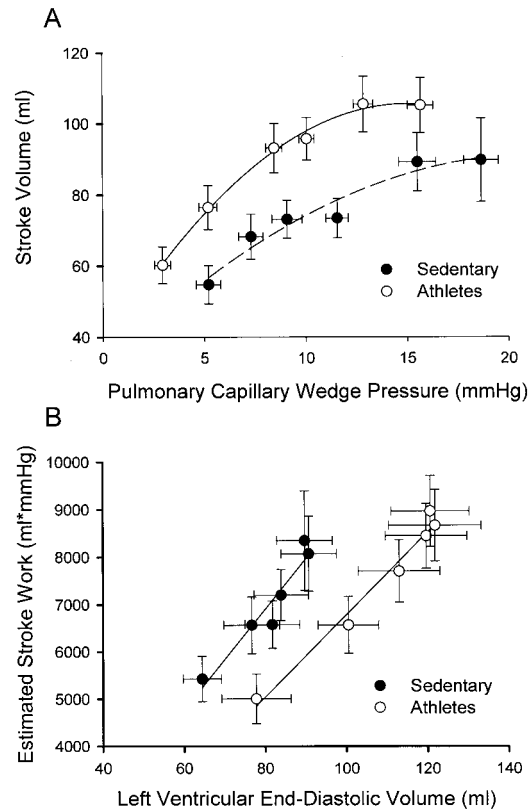
Numerical data are presented as mean±SD except for graphics, in which the SEM is used. Results for resting and exercise characteristics between sedentary and athletic subjects were compared by use of Student's *t* test. For pressure-volume curves, a multivariate regression analysis was conducted on the repeated measures data, modeling pressure by use of the covariates volume and subject group. Linear regression analysis was performed to assess the relationship between cardiac output and oxygen uptake as well as between stroke work and LV end-diastolic volume in both groups. All analyses were performed by use of commercial software. A probability value of  $P<0.05$  was considered statistically significant.

Analysis of interobserver variability between local and core laboratory assessment of LV volumes resulted in good correlation, with  $r=0.8$  and a typical error (SD of the differences divided by the square root of 2) of 15 mL (95% CI, 12 to 22 mL; coefficient of variation, 16%).

## Results

### Subject Characteristics

Baseline data are presented in Table 1. Sedentary seniors and athletic subjects were well matched for age. As expected,



**Figure 1.** Systolic ventricular performance for sedentary seniors ( $n=12$ ) and Masters athletes ( $n=12$ ). Shown are mean group data±SEM for stroke volumes at given pulmonary capillary wedge pressures (A) and for estimated stroke work at given LV end-diastolic volumes (B). Data points correspond to 2 degrees of lower-body negative pressure, 2 baselines, and 2 saline infusions. Lines represent results of second linear (A) and linear (B) regression analyses ( $r=0.97$  and  $0.95$  for sedentary subjects and  $0.99$  and  $0.99$  for athletes, respectively,  $P<0.01$  for all). Note substantially lower stroke volume for any given filling pressure in sedentary seniors, whereas their preload recruitable stroke work was similar compared with Masters athletes, indicating equivalent contractile function.

weight, body fat, and resting heart rate were lower in the Masters athletes, but stroke volume was greater compared with sedentary subjects, resulting in a similar cardiac output. Mean arterial stiffness (effective arterial elastance) was greater in the sedentary seniors than in both Masters athletes and young control subjects, indicating a higher arterial load, despite similar average 24-hour systolic and diastolic blood pressures. Baseline ejection fraction was not different between the groups. As expected, athletes achieved higher maximum oxygen uptakes compared with the age-matched sedentary subjects.

### Cardiac Remodeling

LV end-diastolic volume and mass were greater in the Masters athletes compared with the sedentary seniors (Table 1). Echocardiographic and MRI assessment of end-diastolic volume yielded excellent correlation ( $r=0.9$ ; slope 0.9;  $P<0.001$ ; 95% confidence limits, 9.2 to 15.0; coefficient of variation, 12.5%). There was a trend for a greater LV mass-to-volume ratio for the sedentary seniors, which did not reach statistical significance.

**TABLE 2. Hemodynamic and Sympathetic Response to Changes in Loading Conditions**

	Sedentary Seniors						Masters Athletes					
	LBNP -30	LBNP -15	Baseline 1	Baseline 2	Saline 1	Saline 2	LBNP -30	LBNP -15	Baseline 1	Baseline 2	Saline 1	Saline 2
Blood pressure, mm Hg	130/76 ±15/4	136/76 ±15/7	138/78 ±14/8	130/70 ±12/5	132/69 ±10/5	135/73 ±12/5	112/66 ±17/11	119/69 ±17/8	124/69 ±20/9	118/64 ±17/8	120/63 ±14/7	124/65 ±17/8
Heart rate, bpm	73±12	68±9	66±9	71±9	77±7	82±8	63±7	56±5	53±6	58±5	62±6	63±6
Norepinephrine, pg/mL	422±229	319±157	283±134	N/A	N/A	N/A	374±118	254±106	223±136	N/A	N/A	N/A

Values are the average values and SDs. LBNP indicates lower-body negative pressure. Other hemodynamic data (LV end-diastolic volume, stroke volume, and pulmonary capillary wedge pressure) are shown in the figures.

### Cardiac Mechanics

Elderly athletes were able to generate a higher stroke volume for any given filling pressure than sedentary seniors (Figure 1A). Importantly, this was achieved without evidence for better contractile function (Figure 1B). The preload recruitable stroke work for the sedentary seniors was not significantly different from that of the athletes, suggesting

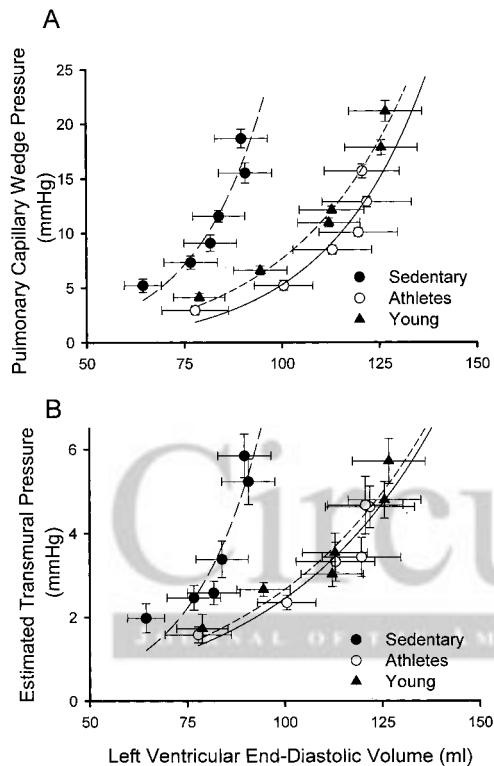
equivalent contractile function. The hemodynamic responses to changes in volume loading for both groups are given in Table 2. Norepinephrine release at baseline and during unloading was not different between the groups (Table 2), and changes in heart rate and blood pressure over the range of filling pressures were also similar, consistent with similar neurohumoral activation during the protocol.

The pressure-volume curves confirmed a substantially greater LV compliance for the Masters athletes compared with the sedentary seniors (Figure 2A). The constant “a,” which describes the chamber stiffness for the group mean data, was 0.039 for the athletes, compared with 0.055 for the sedentary seniors, suggesting greater ventricular stiffness for the latter. The curve for the young sedentary group was virtually identical to that of the elderly athletes and also revealed a more compliant ventricle ( $a=0.036$ ) compared with the elderly sedentary subjects. Individual comparisons of “a” confirmed the difference between the groups (average “a” was  $0.029\pm0.026$  and  $0.013\pm0.020$  for sedentary seniors and Masters athletes, respectively;  $P=0.05$ ). Multivariate analysis likewise confirmed that the pressure-volume curves for the Masters athletes were clearly different from those of the sedentary seniors ( $P<0.0001$ ), whereas there was no statistically significant difference between athletes and young control subjects. Equilibrium volumes for sedentary seniors, Masters athletes, and young control subjects were 12.3, 39.7, and 26.7 mL, respectively.

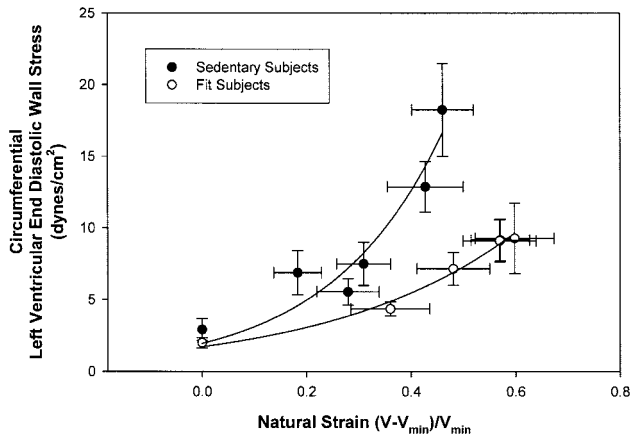
Because extraventricular forces influence resting ventricular volumes and pressures,<sup>25</sup> we also calculated the relationship between estimated transmural pressures (pulmonary capillary wedge pressure—right atrial pressure) and LV end-diastolic volume (Figure 2B). The difference between the groups persisted when estimated transmural pressures were used, supporting the validity of a true difference in ventricular compliance (Figure 2B). Finally, as derived from the LV end-diastolic stress-strain relationship (Figure 3), at any given degree of deformation, the ventricles of the sedentary subjects developed greater wall tension than those of the fit subjects. This relationship reached statistical significance during the 2 levels of saline infusion, with a rapid divergence of the stress-strain curves ( $P=0.002$ ).

### Discussion

The key new findings from the present study include the following. (1) Healthy but sedentary seniors exhibited substantially greater LV stiffness compared with healthy, sedentary young control subjects, providing evidence that cardiac



**Figure 2.** Diastolic pressure-volume curves. A, Pressure-volume curves for sedentary seniors ( $n=12$ ,  $r=0.95$ ), young control subjects ( $n=14$ ,  $r=0.98$ ), and Masters athletes ( $n=12$ ,  $r=0.94$ ). B, Same data when estimated transmural pressures (pulmonary capillary wedge pressure—right atrial pressure) are used instead of pulmonary capillary wedge pressures ( $r=0.93$  for sedentary seniors,  $r=0.95$  for young control subjects,  $r=0.94$  for athletes). Given are mean group data  $\pm$  SEM (horizontal bars, volume; vertical bars, pressure). Data points correspond to 2 degrees of lower-body negative pressure (LBNP, lower data points), baseline 2 and 1 (third and fourth data points from below), and 2 saline infusions (2 upper data points). Note left shift and steeper slope of curve for sedentary senior subjects compared with Masters athletes and young control subjects, suggesting a less distensible, stiffer ventricle (A). Disparity between sedentary seniors and 2 other groups persisted with use of estimated transmural pressures, confirming a difference in ventricular compliance (B).



**Figure 3.** LV end diastolic stress-strain relationship. End-diastolic circumferential wall stress-strain relationships for sedentary and fit elderly subjects are shown, calculated as described in text.  $V$ , ventricular volume;  $V_{min}$ , smallest volume measured during protocol, ie, at lower-body negative pressure  $-30$  mm Hg.

compliance decreases with aging. (2) Ventricles of Masters endurance athletes were much more compliant than those of the age-matched sedentary subjects and virtually identical to those of the young control subjects. Thus, prolonged and sustained endurance training seems to be an effective means of preserving cardiac compliance with aging.

Aging is associated with numerous changes and adaptations in the cardiovascular system. Vascular and ventricular wall thickness increase, whereas arterial compliance, endothelial function, and ventricular contractility decline.<sup>6,8,9</sup> Each of these changes is related to an increase in cardiovascular morbidity and mortality. There is controversy, however, about to what extent these adaptations are of intrinsic nature, ie, part of a “natural” aging process, or a response to environmental factors, such as accumulating toxins and/or an age-related change of behavior by the host organism. Because humans and animals alike adopt a more sedentary lifestyle with aging, it is conceivable that some of the observed cardiovascular adaptations are related to decreased physical activity. For example, bed rest deconditioning leads to many of the apparent manifestations of the aging process, such as decreased work capacity,<sup>26</sup> increased sympathetic nerve activity,<sup>27</sup> and muscle atrophy.<sup>28</sup> Furthermore, 2 weeks of bed rest results in decreased cardiac volume and distensibility, resulting in a diminished stroke volume, contributing, at least in part, to orthostatic intolerance.<sup>11</sup> More prolonged bed rest (6 to 12 weeks) leads to “physiological” atrophy of the heart of at least 10% to 15% of LV mass, which may further compromise diastolic function.<sup>29</sup> In fact, recent longitudinal data suggest that 3 weeks of bed rest causes a greater deterioration in maximal work capacity than 30 years of aging.<sup>30</sup> The results of the present study show that aging in healthy adults is associated with ventricular chamber and myocardial stiffening, which can be prevented with prolonged and sustained endurance exercise.

In addition to active ventricular relaxation during diastole, adequate ventricular compliance is essential for efficient cardiac filling. Ventricular chamber stiffness is determined primarily by the viscoelastic properties of the myocardium,

ventricular mass, chamber geometry, and pericardial constraint.<sup>4,31,32</sup> Aging is associated with alteration of size, number, and structure of cytoskeletal proteins and extracellular components,<sup>33</sup> which contributes to increased viscoelastic myocardial stiffness,<sup>6,7</sup> as demonstrated in our study. This alteration is assumed to be a response to increasing vascular load observed with aging,<sup>6</sup> similar to the more apparent changes in LV hypertrophy in response to arterial hypertension.<sup>34,35</sup> Chamber stiffness is increased in pathological concentric ventricular hypertrophy.<sup>36</sup> However, it appears that as long as the myocardial viscoelastic properties are maintained, ie, no fibrotic changes are present, this increased stiffness is rather the result of an altered mass-to-volume ratio than an increase in mass per se.<sup>31,36</sup> In the present study, the Masters athletes had considerably greater LV mass, as measured by MRI, than their sedentary counterparts, yet still had reduced LV stiffness and improved compliance. These results are similar to those reported by our group cross-sectionally in endurance athletes<sup>12</sup> and longitudinally with prolonged endurance training.<sup>37</sup>

It is important to note, however, that the relative LV mass of the Masters athletes was not significantly different from that of the young control subjects, arguing that LV mass was maintained during aging with lifelong exercise, rather than hypertrophied. However, their volume was somewhat larger, leading to the smallest mass/volume ratio of all 3 subject groups (Table 1). In contrast, the sedentary seniors had significantly smaller LV volumes, which has been observed by others.<sup>38</sup> The functional consequences of this difference in chamber geometry include increased chamber stiffness, reduced chamber distensibility, and diminished ventricular performance. Moreover, the analysis of the myocardial stress-strain relationship confirmed that intrinsic myocardial stiffness increases with aging, at least in part because of a sedentary lifestyle. Together, these results further suggest that the stiffening of the myocardium and the reduced chamber distensibility of sedentary aging can be effectively offset or prevented by favorable ventricular remodeling maintained by exercise training.

Adequate ventricular chamber compliance is important to allow cardiac filling at low pressures as well as to increase cardiac output via the Frank-Starling mechanism. In this study, lower LV compliance in healthy elderly subjects was associated with higher ventricular pressures after cardiac loading compared with age-matched athletic individuals or young control subjects. Such stiffening of the ventricle may decrease the threshold for dyspnea and heart failure in the setting of myocardial insults such as ischemia, hypertension, or metabolic derangement, all of which lead to further decrease of cardiac compliance.<sup>7,9</sup> Stiff ventricles in heart failure patients with preserved ejection fraction have been shown to induce high cardiac filling pressures and to impair augmentation of end-diastolic volume with exercise, leading to reduced exercise tolerance and dyspnea.<sup>39,40</sup> Preservation of ventricular compliance may therefore help to prevent this common type of heart failure.

The mechanisms leading to the demonstrated preservation of ventricular compliance with endurance training probably include preservation of viscoelastic myocardial properties

and pericardial size, as well as optimization of chamber geometry. Prolonged endurance exercise is known to result in eccentric ventricular hypertrophy, ie, a balanced enlargement of ventricular mass and dimensions. These adaptations lead to profoundly improved cardiac performance without apparent change in contractility, which thus is largely explained by enhanced diastolic function. In addition, prolonged exercise training may elicit its effect through maintenance of vascular elasticity and thus smaller arterial load. For example, in the present study, effective arterial elastance was greater in sedentary compared with fit elderly subjects. Arterial elastance is inversely related to vascular compliance and has been shown to be a more sensitive marker for arterial load than total peripheral resistance.<sup>17</sup> Decreased vascular compliance is associated with aging and hypertension<sup>41,42</sup> and recently has been related to heart failure with preserved ejection fraction<sup>43</sup> as well as to cerebrovascular events.<sup>44</sup> Endurance training preserves vascular elasticity with aging,<sup>45</sup> as confirmed in our study, and thereby may prevent cardiac adaptive changes, ie, alteration of myocyte morphology or focal proliferation of matrix, which lead to increasing myocardial stiffness.<sup>33,35</sup> Therefore, the present results support the concept that preserving ventricular-vascular coupling is a key component in the fight against hypertension and heart disease.<sup>6,43</sup>

One limitation of our investigation was the use of mean pulmonary capillary wedge pressure as a surrogate for LV end-diastolic pressure. In the absence of mitral valve disease, as ensured in our study, pulmonary capillary wedge pressure is a reasonable approximation of left atrial and ventricular end-diastolic pressure. However, mean wedge pressure may be affected by fluctuations of left atrial pressure, induced by variations of LV filling time, which are not necessarily reflected in LV end-diastolic pressure. Moreover, animal models have demonstrated slowing of myocardial relaxation with aging, which may be ameliorated by exercise training.<sup>46</sup> This delayed filling not only may distort the atrial pressure waveform during diastole but also may result in incomplete relaxation, leading to higher left atrial and LV filling pressures, particularly because heart rates were somewhat higher in the sedentary compared with the trained subjects.

However, arguing against this hypothesis is the fact that the primary differences between the young and older sedentary pressure-volume curves occurred during increases in LV filling from -30 mm Hg lower-body negative pressure (the smallest volume and lowest pressure) through baseline, when the heart rate was decreasing, rather than increasing (Table 2). Although we did indeed observe a typical Bainbridge reflex with a nonneural increase in heart rate at the highest-volume infusion level in all 3 groups, at this point, the curve is influenced predominantly by pericardial constraint, and the slope of all 3 curves is essentially vertical between these 2 points. Moreover, any increase in heart rate during the highest volume load was modest at best and was unlikely to alter the diastolic filling period substantially, with clear periods of diastasis in both Doppler and pressure waveforms observed at all points. Thus, it is very unlikely that the substantial differences among the curves could be a result of heart rate-mediated alterations in ventricular relaxation.

In conclusion, a sedentary lifestyle is associated with a decline of ventricular compliance, leading to higher cardiac filling pressures and lower stroke volumes for a given filling volume compared with age-matched athletes or young individuals. Prolonged, sustained endurance training preserves ventricular compliance with aging and may be an important approach to reduce the probability of heart failure with aging.

### Acknowledgments

This study was supported by National Institutes of Health grant AG17479-02. The authors thank Sarah Witkowski, MS, Julie H. Zuckerman, RN, Kimberly Williams, RN, and Marta Newby, RN, for their help with the data collection, and Tanja Taivassalo, PhD, for critical review of the manuscript (all at the Institute for Exercise and Environmental Medicine, Dallas, Tex); and Donna E. Levy, MS (Dana-Farber Cancer Institute, Boston, Mass), for her help with the statistical analysis. In addition, the authors thank Edward Yellin, PhD (Albert Einstein College of Medicine, Bronx, NY) for his critique of the manuscript and valuable suggestions.

### References

- Haldeman GA, Croft JB, Giles WH, et al. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. *Am Heart J*. 1999;137:352-360.
- Kitzman DW, Gardin JM, Gottdiener JS, et al. Cardiovascular Health Study Research Group. Importance of heart failure with preserved systolic function in patients > or =65 years of age: Cardiovascular Health Study. *Am J Cardiol*. 2001;87:413-419.
- Vasan RS, Larson MG, Benjamin EJ, et al. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol*. 1999;33:1948-1955.
- Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure, I: diagnosis, prognosis, and measurements of diastolic function. *Circulation*. 2002;105:1387-1393.
- Lakatta EG. Age-associated cardiovascular changes in health: impact on cardiovascular disease in older persons. *Heart Failure Rev*. 2002;7:29-49.
- Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises, I: aging arteries: a "set up" for vascular disease. *Circulation*. 2003;107:139-146.
- Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure, II: causal mechanisms and treatment. *Circulation*. 2002;105:1503-1508.
- Lakatta EG. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises, III: cellular and molecular clues to heart and arterial aging. *Circulation*. 2003;107:490-497.
- Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises, II: the aging heart in health: links to heart disease. *Circulation*. 2003;107:346-354.
- Kitzman DW. Diastolic dysfunction in the elderly: genesis and diagnostic and therapeutic implications. *Cardiol Clin*. 2000;18:597-617.
- 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, et al. 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.
- Vuille C, Weyman A. General considerations, assessment of chamber size and function. In: Weyman A, ed. *Principles and Practice of Echocardiography*. Philadelphia, Pa: Lea & Febiger; 1994:575-624.
- 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, et al. Noninvasive determination of cardiac output by a modified acetylene rebreathing procedure utilizing mass spectrometer measurements. *Aviat Space Environ Med*. 1977;48:203-209.
- Kelly RP, Ting CT, Yang TM, et al. Effective arterial elastance as index of arterial vascular load in humans. *Circulation*. 1992;86:513-521.

18. Chen CH, Fetits B, Nevo E, et al. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. *J Am Coll Cardiol*. 2001;38:2028–2034.
19. Glower DD, Spratt JA, Snow ND, et al. Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work. *Circulation*. 1985;71:994–1009.
20. Mirsky I. Assessment of diastolic function: suggested methods and future considerations. *Circulation*. 1984;69:836–841.
21. Fifer M, Grossman W. Measurement of ventricular volumes, ejection fraction, mass and wall stress. In: Grossman W, ed. *Cardiac Catheterization and Angiography*. Philadelphia, Pa: Lea & Febiger; 1986: 291–294.
22. Hundley WG, Li HF, Willard JE, et al. Magnetic resonance imaging assessment of the severity of mitral regurgitation: comparison with invasive techniques. *Circulation*. 1995;92:1151–1158.
23. Katz J, Milliken MC, Stray-Gundersen J, et al. Estimation of human myocardial mass with MR imaging. *Radiology*. 1988;169:495–498.
24. Peshock RM, Willett DL, Sayad DE, et al. Quantitative MR imaging of the heart. *Magn Reson Imaging Clin North Am*. 1996;4:287–305.
25. Dauterman K, Pak PH, Maughan WL, et al. 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.
26. Greenleaf JE, Bernauer EM, Ertl AC, et al. Work capacity during 30 days of bed rest with isotonic and isokinetic exercise training. *J Appl Physiol*. 1989;67:1820–1826.
27. Pawelczyk JA, Zuckerman JH, Blomqvist CG, et al. Regulation of muscle sympathetic nerve activity after bed rest deconditioning. *Am J Physiol*. 2001;280:H2230–H2239.
28. Watenpaugh DE, Ballard RE, Schneider SM, et al. Supine lower body negative pressure exercise during bed rest maintains upright exercise capacity. *J Appl Physiol*. 2000;89:218–227.
29. Perhonen MA, Franco F, Lane LD, et al. Cardiac atrophy after bed rest and spaceflight. *J Appl Physiol*. 2001;91:645–653.
30. McGuire DK, Levine BD, Williamson JW, et al. A 30-year follow-up of the Dallas Bedrest and Training Study, I: effect of age on the cardiovascular response to exercise. *Circulation*. 2001;104:1350–1357.
31. Gaasch WH, Levine HJ, Quinones MA, et al. Left ventricular compliance: mechanisms and clinical implications. *Am J Cardiol*. 1976;38: 645–653.
32. Traboulsi M, Scott-Douglas NW, Smith ER, et al. The right and left ventricular intracavitary and transmural pressure-strain relationships. *Am Heart J*. 1992;123:1279–1287.
33. Lakatta EG. Cardiovascular aging research: the next horizons. *J Am Geriatr Soc*. 1999;47:613–625.
34. Yang CM, Kandaswamy V, Young D, et al. Changes in collagen phenotypes during progression and regression of cardiac hypertrophy. *Cardiovasc Res*. 1997;36:236–245.
35. Harris TS, Baicu CF, Conrad CH, et al. Constitutive properties of hypertrophied myocardium: cellular contribution to changes in myocardial stiffness. *Am J Physiol*. 2002;282:H2173–H2182.
36. Peterson KL, Tsuji J, Johnson A, et al. Diastolic left ventricular pressure-volume and stress-strain relations in patients with valvular aortic stenosis and left ventricular hypertrophy. *Circulation*. 1978;58:77–89.
37. Arbab-Zadeh A, Zuckerman JH, Niemi HM, et al. Endurance training increases left ventricular distensibility in humans. *Med Sci Sports Exerc*. 2002;34(S7):38.
38. Slotwiner DJ, Devereux RB, Schwartz JE, et al. Relation of age to left ventricular function in clinically normal adults. *Am J Cardiol*. 1998;82: 621–626.
39. Grossman W. Diastolic dysfunction and congestive heart failure. *Circulation*. 1990;81(suppl III):III-1–III-7.
40. Kitzman DW, Higginbotham MB, Cobb FR, et al. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. *J Am Coll Cardiol*. 1991;17: 1065–1072.
41. McVeigh GE, Burns DE, Finkelstein SM, et al. Reduced vascular compliance as a marker for essential hypertension. *Am J Hypertens*. 1991;4: 245–251.
42. Rowe JW. Clinical consequences of age-related impairments in vascular compliance. *Am J Cardiol*. 1987;60:68G–71G.
43. Kawaguchi M, Hay I, Fetits B, et al. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation*. 2003;107:714–720.
44. Laurent S, Katsahian S, Fassot C, et al. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. *Stroke*. 2003;34: 1203–1206.
45. Vaitkevicius PV, Fleg JL, Engel JH, et al. Effects of age and aerobic capacity on arterial stiffness in healthy adults. *Circulation*. 1993;88: 1456–1462.
46. Spurgeon HA, Steinbach MF, Lakatta EG. Chronic exercise prevents characteristic age-related changes in rat cardiac contraction. *Am J Physiol*. 1983;244:H513–H518.

Fighting Heart Disease and Stroke

# Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION