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Impact of Lifelong Exercise "Dose" on Left Ventricular Compliance and Distensibility

Paul S. Bhella, MD,*† Jeffrey L. Hastings, MD,* Naoki Fujimoto, MD,* Shigeki Shibata, MD, PhD,* Graeme Carrick-Ranson, PhD,* M. Dean Palmer, MS,* Kara N. Boyd, MS,* Beverley Adams-Huet, MS,‡ Benjamin D. Levine, MD*‡

ABSTRACT

BACKGROUND Sedentary aging has deleterious effects on the cardiovascular system, including decreased left ventricular compliance and distensibility (LVCD). Conversely, Masters level athletes, who train intensively throughout adulthood, retain youthful LVCD.

OBJECTIVES The purpose of this study was to test the hypothesis that preservation of LVCD may be possible with moderate lifelong exercise training.

METHODS Healthy seniors (n = 102) were recruited from predefined populations, screened for lifelong patterns of exercise training, and stratified into 4 groups: "sedentary" (<2 sessions/week); "casual" (2 to 3 sessions/week); "committed" (4 to 5 sessions/week); and "competitive" Masters level athletes (6 to 7 sessions/week). Right heart catheterization and echocardiography were performed while preload was manipulated using lower body negative pressure and rapid saline infusion to define LV pressure–volume relationships and Frank-Starling curves.

RESULTS Peak oxygen uptake and LV mass increased with escalating doses of lifelong exercise, with little change in systolic function. At baseline, LV distensibility was greater in committed (21%) and competitive (36%) exercisers than in sedentary subjects. Group LV stiffness constants (sedentary: 0.062 ± 0.039; casual: 0.079 ± 0.052; committed: 0.055 ± 0.033; and competitive: 0.035 ± 0.033) revealed: 1) increased stiffness in sedentary subjects compared to competitive athletes, whereas lifelong casual exercise had no effect; and 2) greater compliance in committed exercisers than in sedentary or casual exercisers.

CONCLUSIONS Low doses of casual, lifelong exercise do not prevent the decreased compliance and distensibility observed with healthy, sedentary aging. In contrast, 4 to 5 exercise sessions/week throughout adulthood prevent most of these age-related changes. As LV stiffening has been implicated in the pathophysiology of many cardiovascular conditions affecting the elderly, this "dose" of exercise training may have important implications for prevention of cardiovascular disease. (J Am Coll Cardiol 2014;64:1257–66) © 2014 by the American College of Cardiology Foundation.

Sedentary but healthy aging has been shown to have deleterious effects on the cardiovascular (CV) system, including stiffening of the vasculature and left ventricle (1–3). This stiffening plays a key role in the pathophysiology of many common CV conditions affecting the elderly, including hypertension, left ventricular (LV) hypertrophy, atrial fibrillation, and heart failure with preserved ejection fraction (HFpEF) (2). With an aging population, the development of strategies to prevent these common CV conditions is imperative.

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Lifelong exercise training appears to be one such preventative strategy. Masters level athletes, defined as highly competitive seniors with a lifelong history

From the *Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital, Dallas, Texas; †John Peter Smith Health Network, Fort Worth, Texas; and the ‡University of Texas-Southwestern Medical Center at Dallas, Dallas, Texas. This project was supported by the National Institutes of Health grant RO1 AG17479. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

CV = cardiovascular

HFpEF = heart failure with preserved ejection fraction

LBNP = lower body negative pressure

LV = left ventricular

LVEDV = left ventricular end-diastolic volume

MRI = magnetic resonance imaging

PCWP = pulmonary capillary wedge pressure

SV = stroke volume

VO_2 = oxygen uptake

of vigorous exercise training, maintained youthful LV compliance and distensibility compared to healthy sedentary seniors (3). These same healthy seniors were found to have an LV stiffness similar to that in a highly screened cohort of patients with HFpEF (4), furthering the notion that sedentary aging may set the stage for this increasingly recognized form of heart failure.

Although preservation of youthful LV compliance and distensibility is almost certainly advantageous, engaging in 6 to 7 exercise sessions per week at a competitive level may not be practical or feasible for the general population. We hypothesized that a lower, less frequent "dose" of exercise training might still confer similar benefits in regard to LV compliance and distensibility when continued over a lifetime. To test this hypothesis, we invasively assessed LV compliance and distensibility in a cohort of healthy subjects with well-defined, graded, lifelong histories of dynamic exercise training.

METHODS

SUBJECTS. Healthy seniors (n = 102, >64 years of age) were recruited from pre-identified populations, screened for lifelong patterns of exercise training, and stratified into 1 of 4 groups based on their lifelong histories of endurance exercise training. "Sedentary" subjects (n = 27) exercised no more than once per week during the previous 25 years; "casual" exercisers (n = 25) engaged in 2 to 3 sessions per week during the previous 25 years; "committed" exercisers (n = 25) performed 4 to 5 sessions per week during the previous 25 years; and "competitive" Masters level athletes (n = 25) trained 6 to 7 times per week and participated in regular competitions sponsored by U.S. Masters organizations during the previous 25 years. Exercise sessions were defined as periods of dynamic activity lasting at least 30 minutes.

Subjects were recruited primarily from the CCLS (Cooper Center Longitudinal Study) (5), a cohort of more than 80,000 individuals in whom physical activity and CV risk factors have been quantified and followed for >40 years. Using the CCLS database, investigators identified healthy subjects who had consistently reported the same level of regular exercise on clinic questionnaires over multiple visits spanning at least 20 years. Interested subjects underwent a comprehensive exercise history examination conducted by an experienced exercise physiologist and assisted by family members when possible. If exercise histories could be corroborated, subjects were invited to participate in the next phase of screening. The sedentary population was enriched with subjects recruited from local senior groups such as bingo, gardening, volunteer groups, and health fairs (most subjects in this group came from non-Cooper Clinic sources). The Masters athlete population was enriched by direct recruitment from the top performers (10% to 15%) at regional and national endurance events (3) with most selected from race results. Regardless of the source of referral, however, all subjects were equally well vetted and rigorously screened in terms of medical history, physical examination, and detailed exercise training history.

All recruited subjects underwent the following screening protocol. First, study physicians and nurses obtained a medical history and performed a physical examination. Subjects were excluded if they had major chronic illnesses such as obesity (body mass index [BMI] >30 kg/m^2), regular tobacco use within the previous 10 years, hypertension, diabetes, chronic obstructive pulmonary disease, atrial fibrillation, coronary artery disease requiring treatment (medical therapy, percutaneous coronary intervention, or surgical intervention), or significant valvular disease (defined as greater than "mild"). To ensure the absence of hypertension, 24-h ambulatory blood pressure monitoring was performed, and subjects with a mean ambulatory blood pressure of >135/85 mm Hg were excluded. Subjects with an estimated glomerular filtration rate of <45 ml/min/1.73 m^2 also were excluded. Exercise treadmill stress echocardiography was performed, and those subjects with resting or exercise stress-induced wall motion abnormalities were excluded. All subjects signed an informed consent form approved by the institutional review boards of the University of Texas-Southwestern and Texas Health Resources Presbyterian Hospital of Dallas.

CARDIOPULMONARY STRESS TESTING. An individualized, modified Astrand-Saltin incremental treadmill protocol was used to determine peak exercise capacity. As previously described (6), measurements of ventilatory gas exchange were made using the Douglas bag technique. Gas fractions were analyzed by mass spectrometry, and ventilatory volume was measured with a Tissot spirometer. Peak oxygen uptake (VO_2) was defined as the highest oxygen uptake measured from at least a 40-second Douglas bag collection. Resting blood pressure, assessed in the standing position, was measured in the arm by electrosphygmomanometry (Tango+, Suntech, Morrisville, North Carolina) with a microphone over the brachial artery and the detection of Korotkoff sounds gated to the electrocardiograph (ECG). Heart rate (HR)

was monitored continuously by ECG (Schiller AT-10 model, Welch Allyn, Inc., Skaneateles Falls, New York).

CARDIAC MAGNETIC RESONANCE IMAGING. Resting cardiac magnetic resonance imaging (MRI) was performed using a 1.5-T scanner (NT model; Philips Corp., Amsterdam, the Netherlands). Short-axis, gradient-echo, cine MRI sequences with a temporal resolution of approximately 40 ms were obtained to calculate LV masses and volumes as previously described (7). Left ventricular mass was computed as the differences between epicardial and endocardial areas (with the inclusion of papillary muscles and large trabeculations) multiplied by the density of heart muscle, 1.05 g/ml. For LV volumes, the endocardial border of each slice was identified manually at end-diastole and end-systole, and volumes were calculated by summation. LV volumes were calculated using the Simpson rule technique. Left ventricular EF was computed according to the formula: (LV end-diastolic volume [LVEDV] − LV end-systolic volume)/LVEDV.

CARDIAC CATHETERIZATION AND EXPERIMENTAL PROTOCOL. To determine LV compliance and distensibility, we studied subjects in the resting supine position. A 6-F balloon-tipped fluid-filled catheter (Edwards Lifesciences, Irvine, California) was placed using fluoroscopic guidance through the median antecubital vein into the pulmonary artery. The catheter was connected to a physiologic pressure transducer with the zero reference point set at 5.0 cm, below the sternal angle. The wedge position of the catheter tip was confirmed using fluoroscopy and by the presence of an appropriate pulmonary capillary wedge pressure (PCWP) waveform.

After 30 minutes of quiet supine rest, baseline data were collected. Cardiac filling was then decreased by 2 sequential levels, using lower body negative pressures (LBNP) of −15 and −30 mm Hg as previously described (8). Five minutes into each level of cardiac unloading, 3 measurements of the mean PCWP were obtained at end-expiration; these measurements were then averaged. After release of the LBNP and confirmation of return to hemodynamic baseline with repeat measurements, cardiac filling was increased by 2 sequential levels through a rapid infusion of 15 and 30 ml/kg warm (37°C) isotonic saline solution at ~ 200 ml/min.

ECHOCARDIOGRAPHY. At each level of cardiac loading and unloading, a transthoracic echocardiogram was obtained using an iE33 model ultrasound machine (Philips Healthcare, Bothell, Washington). Images were obtained in the apical 4-chamber view, with great care taken to avoid foreshortening and to ensure maximal endocardial definition. Images were stored digitally for offline analysis by an experienced cardiologist who was unaware of the resultant changes in PCWP associated with preload manipulation. LVEDV was measured using the modified Simpson rule (3). Because 2-dimensional (2D) echocardiography has been reported to underestimate LV volumes compared to cardiac MRI, due to limitations in image position, boundary tracing, and geometric assumption (9), a correction factor was calculated for each subject (ratio of the baseline 2D echocardiographic LVEDV to the cardiac MRI-derived LVEDV). This correction factor was then applied to each stage of cardiac manipulation to construct LV pressure-volume relationships. All end-diastolic volumes were also indexed to body surface area. Pulsed wave Doppler was used to assess select indices of diastolic filling at baseline. In the apical 4-chamber view, a 2-mm sample volume was placed at the tips of the mitral valve leaflets to determine peak velocities of mitral inflow. Isovolumic relaxation time, the interval between aortic valve closure and mitral valve opening, was assessed in the apical 5-chamber view with a 4-mm sample volume (10). Tissue Doppler imaging was performed at baseline in the apical 4-chamber view by placing a 2-mm sample volume on the septal and lateral sides of the mitral annulus; and septal and lateral values were averaged to obtain a mean tissue Doppler imaging value (11). Color M-mode imaging was used to measure the velocity of propagation (Vp) of early mitral inflow at baseline. Using this mode in the apical 4-chamber view, LV inflow was recorded using a sample area that extended from mid-atrium to the LV apex. The scale was reduced to produce a clear aliasing within the early portion of the mitral inflow. The slope of first aliasing velocity from the mitral plane to 4 cm into the left ventricle was used to measure Vp (12).

DATA ANALYSIS. In each subject, an LV end-diastolic pressure-volume relationship was constructed using the PCWP and corrected left ventricular end-diastolic index (LVEDVi) obtained at each stage of preload manipulation. As previously reported (1,3,4), a constant for LV chamber stiffness (stiffness being the inverse of compliance) was modeled using commercially available software (SigmaPlot version 11.0, Systat Software Inc., Chicago, Illinois), which uses an iterative technique to solve the following exponential equation: $P = P_{\infty}(\exp^{a[V - V0]} - 1)$, where P is PCWP, P_{∞} is pressure asymptote of the curve, V is LVEDVi, V0 is equilibrium volume (or the volume at which P = 0 mm Hg), and "a" is the constant that characterizes the chamber stiffness. LV distensibility was defined as the absolute LVEDVi at the baseline PCWP (1).

TABLE 1 Baseline Characteristics

Group	Sedentary Subjects (n = 27)	Casual Exercisers (n = 25)	Committed Exercisers (n = 25)	Competitive Exercisers (n = 25)	ANOVA
Age, yrs	68.8 ± 5.1	71.0 ± 5.7	68.9 ± 5.5	67.8 ± 2.9	0.191*
Female, %	44	28	20	32	
Height, cm	169.5 ± 10.3	173.7 ± 10.0	173.5 ± 7.7	171.1 ± 9.8	0.327
Weight, kg	74.7 ± 11.2	75.8 ± 14.1	73.5 ± 11.1	65.6 ± 12.1	0.015
BMI, kg/m^2	25.9 ± 2.5	25.0 ± 2.9	24.3 ± 1.9	22.2 ± 2.4	<0.001
BSA, m^2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	0.058
ABPM SBP, mm Hg	125 ± 8	124 ± 7	125 ± 8	114 ± 27	0.295*
ABPM DBP, mm Hg	73 ± 6	71 ± 6	74 ± 7	74 ± 6	0.406
% Hct	41 ± 3	40 ± 3	41 ± 3	41 ± 2	0.118
Peak VO_2, ml/kg/min	23.7 ± 4.9	25.8 ± 4.8	32.0 ± 5.8	39.5 ± 5.3	<0.001

Values are mean ± SD or %. *Nonparametric analyses were used.

ABPM = ambulatory blood pressure monitoring; ANOVA = analysis of variance; BMI = body mass index; BSA = body surface area; DBP = diastolic blood pressure; Hct = hematocrit; SBP = systolic blood pressure.

Modeling was performed for each individual subject. The averages of the individual LV chamber stiffness constants for all of the subjects within each group are reported throughout, denoted as "individual LV stiffness." There is inherent noise in each measure of our dependent and independent variables (pressure and volume). Therefore, to best characterize our groups in terms of pressure-volume curves for a visual comparison in the figures, we also fit a single curve to the data that was derived from the means of each loading condition, which we refer to as "group" curves. Because external constraints influence ventricular volumes and pressures, LV end-diastolic transmural pressure-volume relationships were constructed using estimated transmural pressure (PCWP - right atrial pressure) (13). Transmural stiffness constants were modeled as described above. PCWP and stroke volume data were used to construct Frank-Starling relationships. The stroke volume (SV), mean arterial pressure (MAP), and MRI-corrected LVEDV data were used to construct preload recruitable stroke work relationships: (PRSW = [SV × MAP]/LVEDV). The slope of this relationship was used as an index of global LV systolic function (14).

STATISTICAL ANALYSIS. Numerical data are mean ± SD in tables and mean ± SEM in figures. Commercially available software was used to perform all analyses. Parametric data were analyzed by one-way analysis of variance (ANOVA) with post-hoc analysis (Bonferroni correction). Nonparametric data were analyzed using Kruskal-Wallis ANOVA, with pairwise Wilcoxon rank sum tests for multiple comparisons. No adjustments for multiple ordinal comparisons were performed. A p value of <0.05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS. The baseline characteristics of the 4 groups are presented in Table 1. The groups were well-matched for age, height, hematocrit, and 24-h ambulatory blood pressure. Normalized peak VO_2 rose with increasing doses of lifelong exercise training ($p < 0.001$) (Figure 1). Body mass and BMI decreased with increasing doses of lifelong exercise training.

RESTING HEMODYNAMICS. Resting cardiac indexes and PCWP values were similar among groups, whereas resting HR decreased with increased doses of lifelong exercise training (Table 2). Doppler measurements of diastolic filling also were similar among groups, with no effect of fitness, as we have reported previously in other groups of sedentary seniors and Masters athletes (10). Resting stroke volume index increased with increasing doses of lifelong exercise training. Group-averaged Frank-Starling relationships are presented in Figure 2.

LEFT VENTRICULAR MORPHOLOGY AND SYSTOLIC FUNCTION. MRI-derived LV mass index, resting LVEDVi (indexed to body surface area), and resting LVEDVi increased with increasing doses of lifelong exercise training (Table 2). Resting EF and preload recruitable stroke work slopes were similar among groups. Group-averaged preload recruitable stroke work is plotted in Figure 3.

LEFT VENTRICULAR COMPLIANCE AND DISTENSIBILITY. Individual and group LV chamber stiffness constants

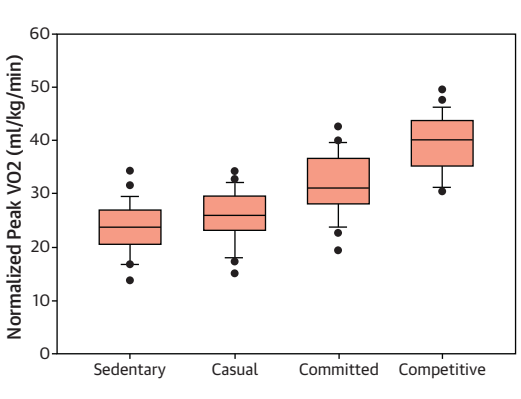


FIGURE 1 Normalized Peak VO_2 by Group

Peak VO_2 increased with increasing doses of lifelong exercise.

were modeled as described above; these data are presented in Table 3. Group LV pressure-volume relationships are plotted in the Central Illustration. As shown by higher stiffness constants, sedentary subjects and casual exercisers exhibited stiffer ventricles (0.062 ± 0.039 and 0.079 ± 0.052, respectively) than committed (0.055 ± 0.033) and competitive exercisers (0.035 ± 0.033). Post-hoc analysis revealed that competitive Masters athletes' hearts were more compliant than those of both sedentary and casual exercisers, with those of committed exercisers falling in between, that is, more compliant than casual exercisers but less than Masters athletes (Table 3). Individual and group transmural stiffness constants were also modeled as described above, following the trend in LV chamber stiffness constants (Table 3, Figure 4). Because PCWPs were similar among the groups at baseline, LV distensibility was assessed by comparing LVEDVi among groups at this stage (Table 3). Compared to the LVEDVi in sedentary subjects, the LVEDVi was 21% greater in committed and 36% greater in competitive exercisers at the same filling pressure, demonstrating a significant increase in baseline distensibility with at least 4 to 5 sessions/week of exercise training. As with the compliance data, sedentary subjects and casual exercisers were indistinguishable.

TABLE 2 Baseline Hemodynamics, Left Ventricular Morphology, and Function

Group	Sedentary Subjects (n = 27)	Casual Exercisers (n = 25)	Committed Exercisers (n = 25)	Competitive Exercisers (n = 25)	ANOVA
Resting HR (beats/min)	66 ± 11	62 ± 7	58 ± 9	56 ± 7	0.001*
Resting CI (l/min/m^2)	2.6 ± 0.5	2.6 ± 0.4	2.6 ± 0.5	2.8 ± 0.6	0.171
Resting SVI (ml/m^2)	40.1 ± 10.3	41.9 ± 6.9	45.3 ± 8.7	50.5 ± 8.1	<0.001*
Resting RAP (mm Hg)	7.3 ± 1.9	7.4 ± 1.7	7.0 ± 1.5	6.8 ± 1.4	0.564
Resting PCWP (mm Hg)	10.9 ± 2.0	10.8 ± 1.9	10.6 ± 1.9	9.9 ± 1.7	0.132
Resting LVEDVi (ml/m^2)	56.5 ± 11.3	59.9 ± 11.8	67.1 ± 12.8	75.4 ± 13.7	<0.001
Resting LVESVi (ml/m^2)	16.4 ± 5.1	18.9 ± 7.2	21.2 ± 6.2	25.0 ± 7.1	<0.001
Resting LVMi (g/m^2)	49.9 ± 8.1	52.1 ± 7.9	61.7 ± 11.1	67.2 ± 11.8	<0.001
LV mass-to-volume ratio (g/ml)	0.90 ± 0.16	0.89 ± 0.15	0.94 ± 0.22	0.90 ± 0.13	0.911*
Resting EF (%)	72 ± 5	69 ± 7	68 ± 7	67 ± 6	0.09
Preload recruitable stroke work slope	107 ± 64	95 ± 66	97 ± 49	72 ± 26	0.168*
E (cm/s)	65 ± 13	75 ± 16	71 ± 12	70 ± 11	0.072
A (cm/s)	69 ± 15	75 ± 18	66 ± 17	66 ± 18	0.213*
E/A	0.97 ± 0.24	1.02 ± 0.20	1.14 ± 0.32	1.10 ± 0.24	0.097*
Em (cm/s)	9.2 ± 1.8	9.0 ± 1.4	9.4 ± 1.3	10.4 ± 2.2	0.043*
IVRT (ms)	122 ± 27	108 ± 17	117 ± 25	126 ± 27	0.058*
Vp (cm/s)	43.3 ± 8.5	44.2 ± 10.1	45.2 ± 9.1	38.5 ± 5.7	0.032

Values are mean ± SD. *Nonparametric analyses were used.

A = late peak mitral inflow velocity; CI = cardiac index; E = early peak mitral inflow velocity; E/A = the ratio of E/A; EF = ejection fraction; Em = mean tissue Doppler imaging mitral annular velocity; HR = heart rate; IVRT = Isovolumic relaxation time; LV = left ventricular; LVEDVi = LV end-diastolic index; LVESVi = left ventricular end-systolic volume index; LVMi = left ventricular mass index; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; SVI = stroke volume index; Vp = velocity of propagation.

DISCUSSION

This study's key finding is the novel observation that at least 30 min of dynamic exercise per session for 4 to 5 days per week over a lifetime can sufficiently prevent most of the decreases in LV compliance and distensibility observed with sedentary aging. This finding holds important implications for global health as ventricular stiffening has been implicated in the pathophysiology of many common CV conditions affecting the elderly.

AGING, EXERCISE, AND CARDIAC MORPHOLOGY. In healthy subjects, sedentary aging leads to deleterious changes in cardiac morphology and function. These changes result in decreased exercise capacity, an observation reinforced by the relatively low peak VO_2 in our sedentary subjects that was only modestly higher in the casual exercisers. Cardiac atrophy, described as an age-associated decrease in LV mass and end-diastolic volume with little change in mass-to-volume ratio (1,3), was apparent in sedentary subjects and casual exercisers, contributing to diminished stroke volume at each stage of preload manipulation (Figure 2). Lifelong exercise training at a dose of >3 days per week mitigated this atrophy, with committed exercisers increasing LV mass to levels equivalent to those previously observed in healthy young subjects (21 to 34 years of age) studied in our laboratory, using similar techniques (1). This trend continued in competitive Masters athletes, with additional increases in LV mass and LVEDV driving increases in peak VO_2 by mechanisms such as a

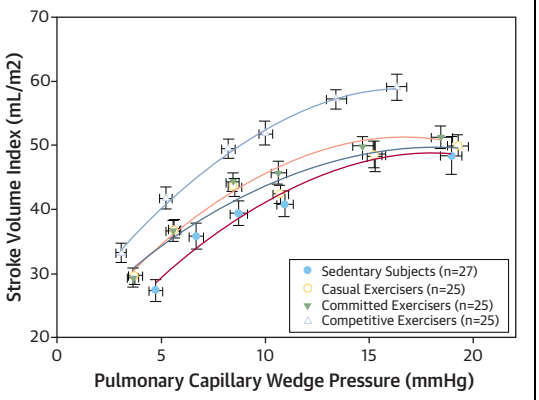


FIGURE 2 Group-Averaged Frank-Starling Relationships

Competitive exercisers showed a statistically significant increase in stroke volume index at baseline compared to sedentary subjects and casual exercisers. **Solid circles** = sedentary subjects; **open circles** = casual exercisers; **solid triangles** = committed exercisers; **open triangles** = competitive exercisers.

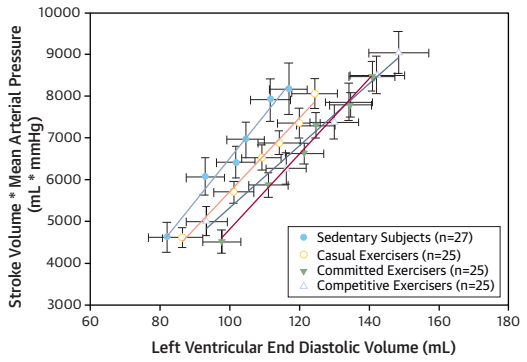


FIGURE 3 Group-Averaged Pre-Load Recruitable Stroke Work

This index of left ventricular systolic function was similar among groups. **Solid circles** = sedentary subjects; **open circles** = casual exercisers; **solid triangles** = committed exercisers; **open triangles** = competitive exercisers.

leftward and upward shift in the Frank-Starling relationship. No group presented obvious differences in LV compliance by gender (Online Table 1), although the relatively small numbers of subjects, when broken down by gender (low statistical power), precluded formal analysis.

In contrast to LV morphology, LV systolic function remained relatively unaffected by lifelong exercise dose. Ejection fraction and preload recruitable stroke work were similar among the 4 groups. The results support the notions that global LV systolic function is preserved with healthy aging (2,15), is not a significant correlate of functional capacity in healthy subjects without LV dysfunction (16), and remains relatively unaffected by exercise training (15,17,18). These findings also couple the increases in functional capacity in healthy subjects to improvements in diastolic function (15), heightening the importance of LV compliance and distensibility.

AGING, EXERCISE, AND LV COMPLIANCE AND DISTENSIBILITY. Previously, we showed that healthy but sedentary aging leads to diminished LV compliance and distensibility; conversely, vigorous lifelong exercise training, encompassing 6 to 7 exercise sessions per week in Masters athletes, preserves youthful levels of these important indices of diastolic function (3). Our current work extends these findings, confirming our hypothesis that a less rigorous level of lifelong exercise training, specifically, 4 to 5 sessions per week, can prevent most of the decrease in LV compliance and distensibility observed with sedentary aging. Because we saw a similar pattern in pressure-volume relationships derived from estimated

TABLE 3 Left Ventricular Compliance and Distensibility

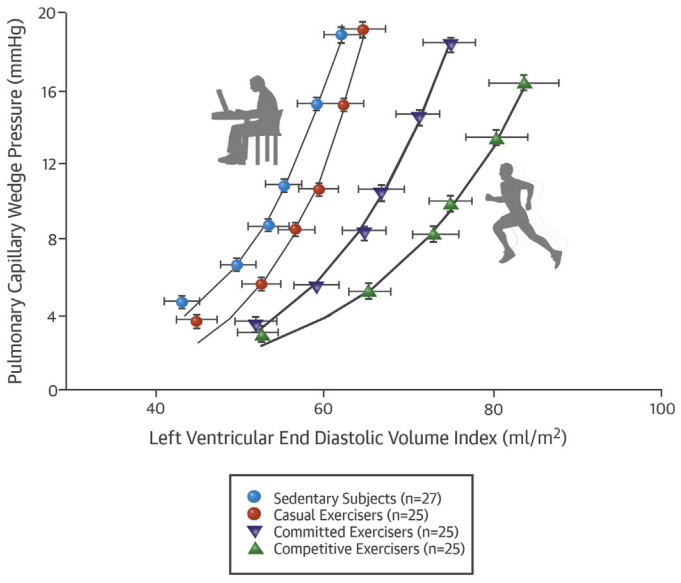
Group	Sedentary Subjects (n = 27)	Casual Exercisers (n = 25)	Committed Exercisers (n = 25)	Competitive Exercisers (n = 25)	ANOVA	Post-Hoc Analysis					
						Sedentary vs. Casual	Sedentary vs. Committed	Sedentary vs. Competitive	Casual vs. Committed	Casual vs. Competitive	Committed vs. Competitive
Individual LV stiffness	0.062 ± 0.039	0.079 ± 0.052	0.055 ± 0.033	0.035 ± 0.023	<0.001*	0.1967	0.7678	0.0039	0.0750	0.0014	0.0400
Individual TM stiffness	0.067 ± 0.062	0.070 ± 0.070	0.043 ± 0.028	0.027 ± 0.017	<0.001*	0.8664	0.1184	0.0041	0.0753	0.0006	0.0464
Distensibility (ml/m^2)	55.3 ± 11.5	59.5 ± 11.9	66.9 ± 13.6	75.1 ± 12.6	<0.001	1.000	0.007	<0.001	0.236	<0.001	0.123

Values are mean ± SD. *Nonparametric analyses were used.
ANOVA = analysis of variance; LV = left ventricular; TM = transmural.

transmural pressure, this difference is likely due to direct effects of lifelong exercise training on myocardial properties, rather than extra-cardiac factors such as pericardial constraint.

POTENTIAL UNDERLYING MECHANISMS. In addition to the well-described phenotype of an athlete's heart, namely a mildly enlarged LV chamber with wall thickness ranging from slightly increased to the upper limits of normal (19), changes in myocardial properties attributable to prolonged exercise training have been observed on a cellular and molecular level. In the rat heart, prolonged exercise training maintained youthful sarcomeric mass with little increase in the mass of surrounding connective tissue (20). This increase in mass is marked primarily by myocyte elongation, forming the foundation of a heart with an enlarged chamber with minimal hypertrophy. Furthermore, increases in the expression of mRNA encoding sarcoendoplasmic reticulum calcium transport ATPase (SERCA) have been noted in the setting of physiologic hypertrophy (21). During cellular relaxation, SERCA-mediated resequestration of calcium is augmented, improving relaxation rates (22). Myofilament responsiveness to calcium, particularly at submaximal exercise, has also been shown to increase in response to exercise training (22). These pathways serve as potential mechanisms by which LV compliance and distensibility are favorably impacted in committed and competitive exercisers.

Additional mechanisms may contribute to the increases in compliance and distensibility noted with prolonged exercise training. Alterations in myocardial energetics secondary to increased mitochondrial mass (23) and the expression of genes involved in fatty acid oxidation have been noted (24) in response to exercise training in animal models. In this regard, exercise training may limit the accumulation of myocardial triglyceride, thereby avoiding the negative effects of lipotoxicity (25). In the swine model, low-intensity interval exercise training prevented increases in myocardial fibrosis in response to pressure overload, normalizing matrix metalloproteinase/tissue inhibitor of metalloproteinases expression and altering collagen isoform composition toward more compliant variants (26). The latter mechanism has also been demonstrated in the rat heart, with exercise-trained rats exhibiting greater proportions of collagen III and I than hypertensive ones (27). Alternatively, several large clinical trials have demonstrated decreases in circulating levels of C-reactive protein with exercise training (28–30), furthering the notion that mitigation of inflammation-mediated myocardial fibrosis may serve as an important mechanism in the preserving youthful LV compliance and distensibility.



CENTRAL ILLUSTRATION Group-Averaged Left Ventricular Pressure-Volume Relationships

Left ventricular end-diastolic pressure-volume relationships are shown as determined by right heart catheterization (pulmonary capillary wedge pressure) and echocardiography (left ventricular volume) for sedentary subjects **(blue circles)**, casual exercisers **(red circles)**, committed exercisers **(purple triangles)**, and competitive exercisers **(green triangles)**. Data are mean group SEM (**horizontal bars** = volume; **vertical bars** = pressure), with best curve fit through these data points as described in the text. Data points correspond to 2 levels of lower body negative pressure (LBNP) (i.e., lowest pressure and volume), 2 baseline data points (third and fourth data points from below), and 2 saline infusions (2 highest pressures and volumes). Note the leftward shift and steeper slope of curve for the sedentary and casual exercisers, reflecting a stiffer, less distensible ventricle in comparison to the rightward shift and flatter slope of curve for the committed and competitive exercisers, reflecting a more distensible and compliant ventricle. Committed exercisers demonstrated improved ventricular compliance and distensibility compared to that in casual exercisers and sedentary subjects, almost matching those achieved by competitive exercisers.

IMPLICATIONS FOR CV DISEASE. LV compliance and distensibility are diminished in patients with HFpEF (4,31,32). In recent work from our laboratory, the LV compliance of 13 outpatients with adjudicated diagnoses of HFpEF was similar to that of sedentary but otherwise healthy seniors (4). These findings suggest sedentary aging, as well as the changes in LV morphology and diastolic function that accompany it, may set the stage for this increasingly recognized form of heart failure. With a high prevalence of HFpEF in the elderly (33) and an aging global population, developing strategies to prevent HFpEF is imperative. Given its ability to mitigate decreases in LV mass, end-diastolic volume, compliance and distensibility associated with

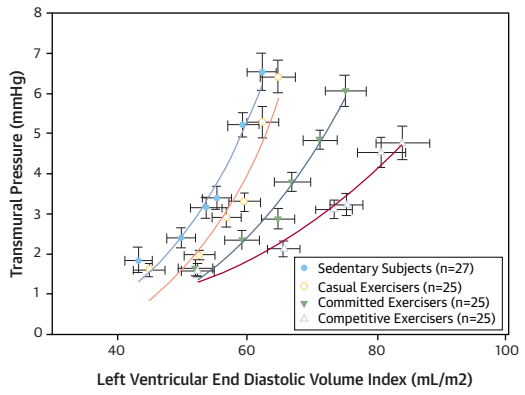


FIGURE 4 Group-Averaged Transmural Pressure–Volume Relationships

Transmural end-diastolic pressure–volume relationships as determined by right heart catheterization (pulmonary capillary wedge pressure–right atrial pressure) and echocardiography (left ventricular volume) for sedentary subjects **(solid circles)**, casual exercisers **(open circles)**, committed exercisers **(solid triangles)**, and competitive exercisers **(open triangles)**. Data are mean group ± SEM (**horizontal bars** = volume; **vertical bars** = pressure) with best curve fit as described in the text. The disparities among groups persisted with the use of transmural pressures, confirming that differences in compliance and distensibility noted in the group-averaged left ventricular pressure volume relationships were attributable to myocardial properties rather than extracardiac factors such as pericardial constraint.

sedentary aging, lifelong exercise training appears to be one such strategy. The observation that 4 to 5 dynamic exercise sessions per week, a less rigorous routine than has been previously recognized, sufficiently averts the decreases in LV compliance and distensibility associated with sedentary aging is compelling. This novel finding adds additional strength to the 2008 Physical Activity Guidelines reported by the U.S. Department of Health and Human Services, which recommends at least 150 minutes a week of moderate-intensity physical activity, a dose similar to that of our committed exercisers.

QUANTIFICATION OF THE EXERCISE DOSE AND POTENTIAL BIAS. Exercise dose in this study was quantified by lifelong exercise frequency: the average number of dynamic exercise sessions per week, performed over the subject's adult life. This somewhat simple classification scheme featured several key strengths and weaknesses. Strengths included: 1) a simple and robust search criteria to identify potential subjects within the Aerobics Center Longitudinal Study database; 2) a reproducible means by which subjects and their family members could recall lifelong exercise histories; and 3) a framework to provide a straightforward recommendation regarding a lifelong exercise dose based on the study's findings. Furthermore, this scheme did yield a progressively increasing normalized peak VO_2 by group (**Figure 1**), suggesting utility in differentiating meaningful increments in training stimulus.

STUDY LIMITATIONS. A key weakness of this scheme, however, was its inability to account for the intensity, duration, or mode of a subject's exercise session, factors that may have an important impact on the training response. For example, Wisloff et al. (22) demonstrated a substantial influence of relatively short, high-intensity bouts of aerobic exercise training on physiologic remodeling (22). Intensity, in particular, may serve as an important differentiator between the committed and competitive exercisers examined in our study. Although committed exercisers were participating in 4 to 5 exercise sessions per week, just 1 to 2 sessions less than the competitive exercisers, they may not have achieved the same levels of intensity as competitive athletes, who consistently performed in the top 10% to 15% of their age group in sanctioned competitions. This heighted intensity may be necessary to elicit the greater increases in compliance and distensibility observed in Masters athletes, providing an important avenue of future investigation.

Finally, this study was a cross-sectional evaluation of exercise dose on LV compliance and distensibility and, as such, was subject to the inherent limitations of that approach. For example, it is conceivable that in earlier decades of life, subjects with greater LV compliance and distensibility were more drawn to high-frequency exercise than subjects with inherently diminished LV compliance and distensibility, predestining them to become Masters level athletes. In addition, increases in LV compliance and distensibility in the committed and competitive subjects may have resulted from physiologic changes in the early decades of adulthood rather than simply reflecting the subjects' lifelong exercise routines; however, this hypothesis was not tested. Furthermore, although great care was taken to accurately quantify the lifelong exercise dose, the potential for recall bias could not be excluded. To obviate such concerns, one would need to perform a longitudinal study of similar subjects, a study that would require >20 years of surveillance and testing. Given the prohibitive nature of such an approach, a cross-sectional approach was selected, coupled with great effort to minimize bias. Last, subjects who were enrolled in this study were recruited primarily (although not exclusively) from the CCLS. The CCLS cohort is mostly Caucasian (>95%), well educated (approximately 80% are

college graduates), and from middle to upper socioeconomic strata. The CCLS population is similar to other large, well-characterized cohorts in regard to exercise habits, fitness, chronic disease, and several clinical variables (34–36). This database's strength, the homogeneity of our sample on socioeconomic variables, reduces the likelihood of confounding by race/ethnicity, education, occupation, income, and other sociodemographic variables known to influence health separately from fitness. Thus, the internal validity of this sample is very high, similar to other databases investigating CV health such as Harvard Alumni (37), U.S. nurses (38), or physicians (39).

CONCLUSIONS

Left ventricular stiffening has been implicated in the pathophysiology of many common CV conditions affecting the elderly including atrial fibrillation and HFpEF. Sedentary aging, and the decreases in LV compliance and distensibility that accompany it, may set the stage for these conditions. In an attempt to identify the minimal exercise dose necessary to preserve more youthful LV compliance and distensibility, we observed that at least 30-min exercise sessions 4 to 5 times/week are sufficient to prevent the decreases in LV compliance and distensibility associated with sedentary aging regardless of duration, intensity, or mode of exercise. With an aging global population, this observation has important implications for the prevention of CV disease.

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. Benjamin D. Levine, Institute for Exercise and Environmental Medicine, 7232 Greenville Ave, Suite 435, Dallas, Texas 7523. E-mail: BenjaminLevine@TexasHealth.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Sedentary aging is associated with reduced diastolic LV compliance that contributes to common CV conditions including atrial fibrillation and HFpEF. Daily dynamic exercise for >30 minutes 4 or 5 times weekly over the course of a lifetime preserves LV diastolic function.

COMPETENCY IN PATIENT CARE: Physical activity should be assessed routinely, and the benefits of lifelong exercise on CV health should be discussed with those who are sedentary. An individualized exercise prescription that addresses pertinent comorbidities should be part of a CV disease prevention program.

TRANSLATIONAL OUTLOOK: Further studies are needed to explore the mechanisms by which lifelong exercise training mitigates LV diastolic dysfunction, including myocardial remodeling, calcium transport, and mitochondrial conditioning or modification of inflammatory factors that influence myocardial cell metabolism.

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KEY WORDS aging, diastolic function, distensibility, exercise training, hemodynamics, ventricular compliance

APPENDIX For a supplemental table, please see the online version of this article.