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Impact of Lifelong Exercise Training Dose on Ventricular-Arterial Coupling

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BACKGROUND: The dynamic Starling mechanism, as assessed by beat-by-beat changes in stroke volume and left ventricular end-diastolic pressure, reflects ventricular-arterial coupling. It deteriorates with age, and is preserved in highly trained masters athletes. Currently, it remains unclear how much exercise over a lifetime is necessary to preserve efficient ventricular-arterial coupling. The purpose of this study was to assess the dose-dependent relationship between lifelong exercise training and the dynamic Starling mechanism in healthy seniors.

METHODS: One hundred two seniors were recruited and stratified into 4 groups based on 25 years of exercise training history: sedentary subjects (n=27, <2 sessions/week), casual exercisers (n=25, 2–3 sessions/week), committed exercisers (n=25, 4–5 sessions/week), and competitive Masters Athletes (n=25, 6–7 sessions/week). The dynamic Starling mechanism was estimated by transfer function gain between beat-by-beat changes in diastolic pulmonary artery pressure, a surrogate for left ventricular end-diastolic pressure, and stroke volume index.

RESULTS: The transfer function gain of pulmonary artery pressure–stroke volume index was markedly enhanced in committed and competitive exercisers compared with more sedentary seniors and correlated with higher peak oxygen uptake (Vo_2) and lower left ventricular stiffness. The power spectral density of pulmonary artery pressure was greater in sedentary adults than in committed and competitive exercisers, whereas the power spectral density of stroke volume index was greater in competitive exercisers than in the other groups.

CONCLUSIONS: There is a graded, dose-dependent improvement in ventricular-arterial coupling with increasing amounts of lifelong regular exercise in healthy older individuals. Our data suggest that the optimal dose of lifelong endurance exercise to preserve ventricular-arterial coupling with age appears to be at least 4 to 5 sessions per week.

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Clinical Perspective

What Is New?

- The optimal dose of lifelong endurance exercise appears to be ≥4– 5 sessions per week or more, which appears to prevent the impairment of the dynamic Starling mechanism with aging.
- The sufficient lifelong endurance exercise is effective for maintaining the normal dynamic Starling mechanism, left ventricular compliance, and arterial compliance with aging, which may lead to favorable effects on cardiovascular stiffness or function.

What Are the Clinical Implications?

- With a higher prevalence of heart failure with preserved ejection fraction in the elderly population, lifelong exercise training may represent an effective strategy for preventing heart failure with preserved ejection fraction pathogenesis by mitigating vascular stiffing, left ventricular compliance, and distensibility related with advanced aging.

Aging increases the risk of cardiovascular disease[1,2] and stiffens the left ventricle (LV) and central large arteries.[3,4] We have previously demonstrated in competitive Masters athletes that very high levels of exercise training preserves LV compliance and attenuates age-related arterial stiffening.[5,6] We have also shown recently that 4 to 5 sessions per week of exercise (1 session: ≥30 minutes) performed over a lifetime (eg, >25 years) prevents the age-related decrease in LV compliance and distensibility associated with sedentary aging in well-characterized healthy seniors.[7] However, 1 year of vigorous endurance training started later in life failed to improve LV or arterial compliance[8,9] or substantively improve ventricular-arterial coupling.[10,11] Therefore, these findings suggest that lifelong endurance training may be necessary to prevent a loss of LV compliance and distensibility as well as central arterial stiffening in older adults.[7,10,12]

The Starling mechanism represents the fundamental interaction between the LV and stroke volume (SV) in which changes in LV volume (or pressure) cause simultaneous alterations in SV.[13] Concurrent with respiration, beat-by-beat fluctuations in intrathoracic pressure and LV end-diastolic pressure (LVEDP) cause synchronous changes in SV. Using these respiratory-induced dynamic fluctuations in LVEDP and SV, we developed a novel method to assess the dynamic Starling mechanism using transfer function analysis[12] by which the linear relation between the beat-by-beat changes in LVEDP (input) and SV (output) can be determined during controlled breathing. Physiologically, the dynamic Starling mechanism estimated by transfer function gain and coherence reflects time-varying ventricular-arterial coupling which describes the integrated effect of increased LV diastolic stiffness and aortic stiffness.[10,12]

Using this technique to assess the dynamic Starling mechanism, our group reported that ventricular-arterial coupling is impaired by advancing age and preserved by lifelong competitive endurance training.[10] However, it remains unknown how much aerobic exercise training over a lifetime is sufficient to preserve this critical function. Therefore, the purpose of this study was to assess the dose–response relationship between lifelong exercise training and the dynamic Starling mechanism in older adults. We hypothesized that the dynamic Starling mechanism is improved with an increasing dose (frequency) of lifelong exercise training.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Subjects

Data for 102 subjects (>64 years of age) were obtained from Cooper Center Longitudinal Study (CCLS, Cooper Clinic, Dallas) which includes a cohort of >80 000 individuals who have a well-characterized history of physical activity and cardiovascular disease and risk factors for >40 years as previously reported.[7,11] Subjects were stratified into 1 of 4 groups based on their lifelong histories of endurance training.[7,11] Sedentary subjects (n = 27) exercised no more than once a week; casual exercisers (n = 25) engaged in 2 to 3 sessions per week; committed exercisers (n = 25) performed 4 to 5 sessions per week; and competitive Masters level athletes (n = 25) trained 6 to 7 times per week and participated in regular competitions sponsored by US Masters organizations during the previous 25 years. Exercise sessions were defined as periods of dynamic activity lasting ≥ 30 minutes.

The detailed patient characteristics, recruitment process, and demographics of this population have been described previously.[7,11,14] However, in brief, 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 ≥20 years. At each clinic examination participants were asked to report the average number of sessions per week and the average amount of time per session spent in brisk walking, jogging, or running activities during the 3 months preceding their clinic examination. The reliability and validity characteristics of this questionnaire is similar to other physical activity questionnaires used in epidemiological research.[15,16] 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[5] 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, a medical history and physical examination were recorded by a study physician or nurse. Obesity (body mass index >30 kg/m^2), regular tobacco use within the past 10 years, hypertension (24=hour ambulatory blood pressure >140/90 mm Hg), diabetes mellitus, chronic obstructive pulmonary disease, atrial fibrillation, obstructive coronary artery disease, or significant valvular disease were exclusion criteria. Second, an exercise stress test was performed on all subjects, with ECG or echocardiography changes suggestive of ischemia or abnormal wall motion criteria for exclusion.

The experimental procedures were explained to each subject, and informed consent was obtained as approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas. All procedures conformed to the standards set by the Declaration of Helsinki.

Peak Oxygen Uptake

A modified Astrand-Saltin incremental treadmill protocol was used to determine peak oxygen uptake (V_{O_2}) in all subjects.[7,17] 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. The mass spectrometer was calibrated against fixed gasses of known concentrations before every test. Peak V_{O_2} was defined as the highest V_{O_2} measured from a ≥ 40-second Douglas bag.

Static Hemodynamics

The subjects were asked to refrain from heavy exercise and caffeinated or alcoholic beverages for ≥24 hours before study visit. All experiments were performed in the morning ≥2 hours after a light breakfast in a quiet environmentally controlled laboratory with an ambient temperature of 25°C. A 6-F balloon-tipped, fluid filled catheter (Swan-Ganz catheter, Baxter) was placed through an antecubital vein into the pulmonary artery using fluoroscopic guidance. Pulmonary artery and right atrial pressures were referenced to atmospheric pressure, with the pressure transducer (Transpac IV, Abbott) zero reference point set at 5.0 cm below the sternal angle. The wedge position of the Swan-Ganz catheter tip was confirmed using fluoroscopy and by the presence of an appropriate pulmonary artery wedge pressure (PAWP) waveform. The static mean PAWP and right atrial pressure were determined from 3 measurements obtained visually at end expiration, as previously described.[7] Cardiac output was measured with the C_2H_2 rebreathing method.[18] Heart rate was monitored continuously via an ECG, and SV was calculated from the cardiac output divided by heart rate. Blood pressure was measured at the brachial artery by ECG-gated electrosphygmomanometry (Tango; SunTech Medical) during cardiac output measurements. For all subjects, a transthoracic echocardiogram was obtained using an iE33 echocardiograph (Philips Medical Systems, Andover, MA). Apical 4-chamber views were used to make each measurement. LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV mass were determined using a modified Simpson method. All images were evaluated off line by a blinded well-experienced sonographer as reported previously.[19,20]

Dynamic Hemodynamics

Pulmonary artery diastolic (PAD) pressure was used as a surrogate of LVEDP to avoid the risks associated with prolonged balloon inflation.[21] Finger photoplethysmography (Portapres, FMS, Amsterdam, The Netherlands) was used to measure arterial blood pressure continuously, with beat-to-beat SV calculated from the Model-flow method (Beat-Scope, FMS, Amsterdam, The Netherlands).[22] After confirmation of hemodynamic stability, subjects were asked to breathe at a controlled frequency (0.2 Hz: 12 breaths/min) by following a moving cursor displayed on a computer for 8 minutes while beat-to-beat PAD and SV index are collected. The last 6 minutes of data were used for the transfer function analysis.

Transfer Function Analysis

Pulmonary artery pressure and arterial pressure waveforms were digitized through 16-bit analog to digital conversion, and stored in a laboratory computer at 200 Hz. Beat-to-beat Model-flow SV was calculated from the finger arterial pressure waveform as previously described.[10,12] For transfer function analysis, beat-to-beat PAD and SV index were linearly interpolated and resampled at 2 Hz for spectral analysis. Fast Fourier transforms were implemented with each Hanning-windowed data segment. The minimal spectral resolution in the frequency domain is 0.0078125 Hz. Transfer function analysis between PAD and SV index, similar to the relation between input and output in a linear black-box model, was applied to obtain gain and coherence as previously described.[23,24]

The dynamic Starling mechanism gain reflects the amplitude relationship between the changes in PAD (input) and SV index (output). In other words, the dynamic Starling mechanism gain is similar conceptually to the slope of a linear regression.

The reliability of the linear transfer function was evaluated by estimates of coherence, which ranges between 0 and 1. The coherence quantifies the linearity of the linear relationship between the input and output at each frequency. The coherence is similar conceptually to the R^2 value in a linear regression. Mean values of the dynamic Starling mechanism gain and coherence were calculated in the respiratory range (0.188–0.211 Hz), and averaged for all subjects in each group.[10,12]

The power spectral density (PSD) of the input variable (PAD) and output variable (SV index) of the dynamic Starling mechanism was calculated by integrating the corresponding auto-spectra in respiratory range (0.188–0.211 Hz). The transfer function analysis was performed by computer software (DADiSP 6.0, DSP development Corporation, Newton, MA).

Pulse Wave Velocity

Carotid-femoral pulse wave velocity (cf-PWV) was measured using the SphygmoCor mm^3 system (AtCor Medical, Sydney, Australia) as reported previously.[11] The cf-PWV was determined by recording the pressure waveform at the carotid and femoral arteries using a high-fidelity micromanometer (Millar Instruments, Houston, TX) and calculating the distance between the recording sites divided by the time delay between the carotid and femoral pulse waves. The distance was measured on the body surface from the suprasternal notch to the carotid recording site and from the suprasternal notch to the femoral recording site.

Data Analysis

LVEDV, LVESV, LV mass, cardiac output, SV, and effective arterial elastance (Ea) were indexed to body surface area. As previously reported,[3,7,25] a constant for LV chamber stiffness (the stiffness being the inverse of compliance) was modeled using commercially statistical software (SigmaPlot version 11.0, Systat Software Inc, Chicago, IL), which uses an iterative technique to solve the following exponential equation: $P = s \cdot \{\exp [a (V - V0)] - 1\}$, where "P" is PAWP, "a" is the constant that characterizes the chamber stiffness, "s" is pressure asymptote of the curve, "V" is LVEDV index, "V0" is unstressed or equilibrium volume of LV (the LV assumption volume at which *P*=0 mm Hg).

Statistical Analysis

Numeric data are reported as mean±SD. Data were analyzed by Kruskal-Wallis analysis of variance (nonparametric ANOVA) with Wilcoxon signed ranks test for multiple comparisons. $P<0.05$ was considered statistically significant. Spearman's correlation was used to examine simple correlations. Statistical analysis was performed by computer software (JMP 11.0, SAS Institute Inc., Cary, NC).

RESULTS

Baseline Characteristics

The baseline characteristics are shown in Table 1 and have been reported previously for this cohort.[7] The groups were well-matched for age, sex, height, and hematocrit. The competitive exercisers had lower body mass index than all other groups and smaller body weight than the sedentary group and casual exercisers. There was a dose–response effect of regular exercise which yielded a progressively increasing peak Vo_2 by group, confirming the ability to differentiate meaningful increments in training stimulus.

Resting systolic and diastolic blood pressure, cardiac index, right atrial pressure, PAWP, and LVEF were similar among the 4 groups (Table 2). Heart rate at rest was lower in the committed and competitive exercisers than in the sedentary group and casual exercisers. LVEDV index, LVESV index, SV index, and SW index were greater in competitive exercisers than all other groups (Table 2). LV mass index was larger in competitive exercisers than sedentary subjects and casual exercisers.

Dynamic Starling Mechanism

Figure 1 shows transfer function gain and coherence as well as PSD of PAD and SV index over the entire frequency range. As intended by controlled breathing, the coherence peaked at the respiratory frequency of 0.2 Hz in all groups. The transfer function gain of PAD-SV index relation exhibited a dose-dependent association with exercise training levels: competitive > committed > casual exercisers > sedentary group (Figure 2A). The mean coherence was greater than 0.75 in all 4 groups (Figure 2B), confirming the validity of the transfer function gain estimation. PSD of PAD (the input signal of the dynamic Starling mechanism) was higher in the sedentary group than in the committed and competitive exercisers (Figure 3A). Conversely, PSD of SV index (the output signal of the dynamic Starling mechanism) was greater in competitive exercisers than in all other groups (Figure 3B).

Ventricular-Vascular Function

LV stiffness and transmural stiffness index in competitive exercisers were smaller than all other groups (Table 3), as previously reported.[7] There were no differences in car-

Table 1. Subject Characteristics

	Sedentary Subjects	Casual Exercisers	Committed Exercisers	Competitive Exercisers	*P* Value
N (% female)	27 (44)	25 (28)	25 (20)	25 (32)	0.29
Age, y	69±5.1	71±5.7	69±5.5	68±2.9	0.22
Height, cm	169.5±10.3	173.7±10.0	173.5±7.7	171.1±9.8	0.33
Weight, kg	74.7±11.2	75.8±14.1	73.5±11.1	65.6±12.1*†	0.02
Body mass index, kg/m^2	25.9±2.5	25.0±2.9	24.3±1.9	22.2±2.4*†‡	<0.001
Body surface area, m^2	1.9±0.2	1.9±0.3	1.9±0.3	1.8±0.2	0.06
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 means±SD.
*P<0.05 vs Q1.
†P<0.05 vs Q2.
‡P<0.05 vs Q3.

Table 2. Baseline Hemodynamics and Left Ventricular Function

	Sedentary Subjects (n=27)	Casual Exercisers (n=25)	Committed Exercisers (n=25)	Competitive Exercisers (n=25)	*P* Value
Systolic blood pressure, mm Hg	126±16	117±12*	118±13	121±15	0.11
Diastolic blood pressure, mm Hg	74±8	71±7	69±8	71±9	0.20
Heart rate, beats/min	66±11	62±7	58±9*†	56±7*†	0.0013
Cardiac index, L/min/m^2	2.6±0.5	2.6±0.4	2.6±0.5	2.8±0.6	0.17
Right atrial pressure measured at end expiration, mm Hg	7.3±1.9	7.4±1.7	7.0±1.5	6.8±1.4	0.56
Pulmonary artery wedge pressure measured at end expiration, mm Hg	10.9±2.0	10.8±1.9	10.6±1.9	9.9±1.7	0.13
Left ventricular end-diastolic volume index, mL/m^2	56.5±11.3	59.9±11.8	67.1±12.8*	75.4±13.7*†‡	<0.001
Left ventricular end-systolic volume index, mL/m^2	16.4±5.1	18.9±7.2	21.2±6.2*	25.0±7.1*†‡	<0.001
Let ventricular ejection fraction, %	58.7±5.5	55.4±6.3	56.6±7.6	59.1±8.7	0.28
Stroke volume index, mL/min/m^2	40.1±10.3	41.9±6.9	45.3±8.7*	50.5±8.1*†‡	0.0002
Stroke work index, mL·mm Hg/m^2	4558±1241	4415±912	4797±993	5503±1242*†‡	0.0074
Left ventricular mass index, g/m^2	49.9±8.1	52.1±7.9	61.7±11.1	67.2±11.8*†	<0.001

Values are means±SD.
*P<0.05 vs Q1.
†P<0.05 vs Q2.
‡P<0.05 vs Q3.

diac power output index and preload recruitable stroke work as an index of LV systolic function among the 4 groups (Table 3). The Ea and cf-PWV in committed and competitive exercisers were lower than the sedentary group (Table 3) as reported previously.[11,14] Systemic vascular resistance was similar among the 4 groups.

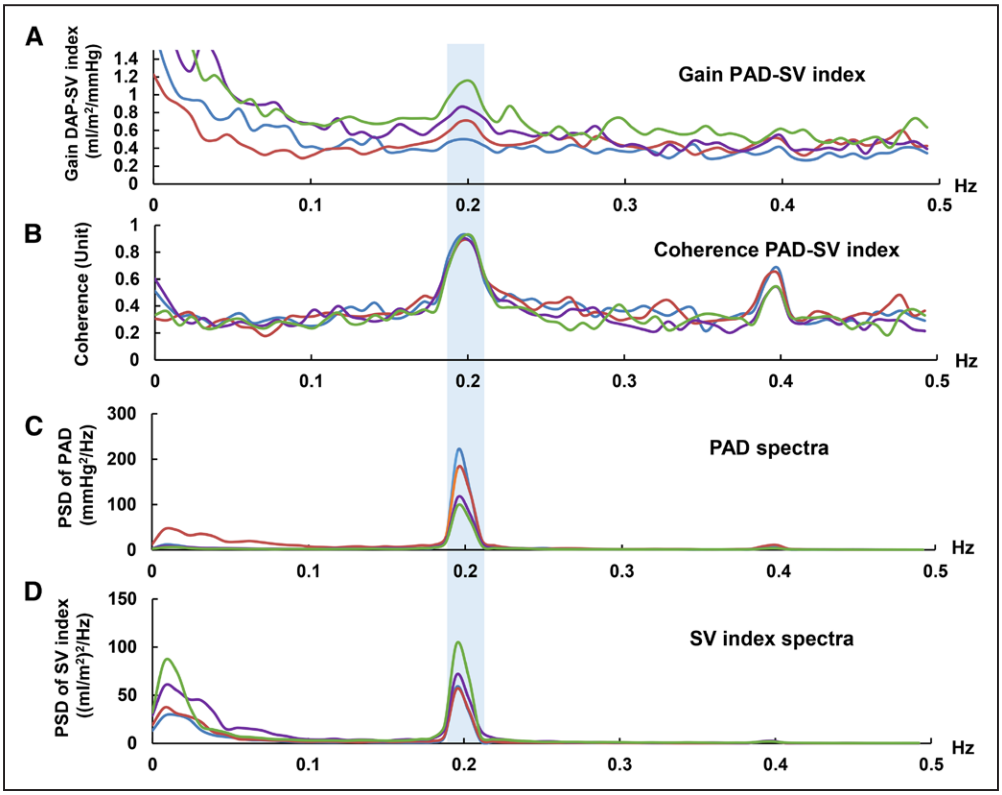

Figure 1. Transfer function analysis.
Transfer function gain (**A**) and coherence (**B**) of the dynamic Starling mechanism. Power spectral density of diastolic pulmonary artery pressure (PAD; **C**) and stroke volume (SV) index (**D**). Sky-blue bar highlights the frequency of 0.20 Hz (0.188–0.211 Hz) where the input and output signals were augmented by controlled breathing (12 breaths/min). Sedentary subjects = Blue line, Casual exercisers = Red line, Committed exercisers = Purple line, and Competitive exercisers = Green line. PSD indicates power spectoral density.

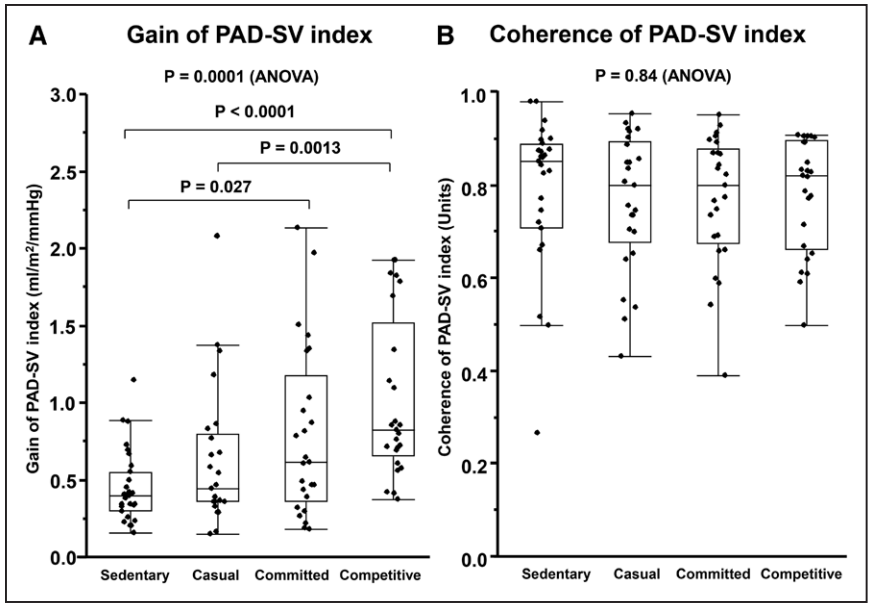

Figure 2. Transfer function gain (A) and coherence (B).
Transfer function gain (**A**) and coherence (**B**) extracted at the point frequency of 0.20 Hz (0.188–0.211 Hz). PAD indicates diastolic pulmonary artery pressure; SV, stroke volume.

DISCUSSION

The primary findings of the present study are 2-fold: (1) lifelong endurance training improves the dynamic Starling mechanism in a dose-dependent manner, as assessed by the time-varying relation between LV filling pressure and SV; (2) committed levels of aerobic activity (>4–5 sessions per week with each session lasting for >30 minutes) are required to prevent or slow age-related impairment of the dynamic Starling mechanism. These findings suggest that lifelong exercise training can prevent the deterioration of the dynamic Starling mechanism with aging. Therefore, the optimal dose of lifelong endurance exercise appears to be at least 4 to 5 sessions per week or more, which may prevent impairment of the ventricular-arterial coupling associated with advancing age.

Lifelong Exercise and Dynamic Starling Mechanism

To our knowledge, this is the first study to demonstrate the impact of lifelong exercise training on the dynamic Starling mechanism as assessed by transfer function analysis, a tool to quantify the time-varying hemodynamic relation between input and output signals using a linear model system. Because the end-diastolic pressure–volume relationship and the end-systolic pressure–volume relationship interact with each other within a cardiac cycle, it is difficult to calculate the beat-to-beat nature of ventricular-arterial coupling and to distinguish simultaneously the primary changes of either end-diastolic pressure–volume relationship or end-systolic pressure–volume relationship from the secondary changes that occur from their interdependence

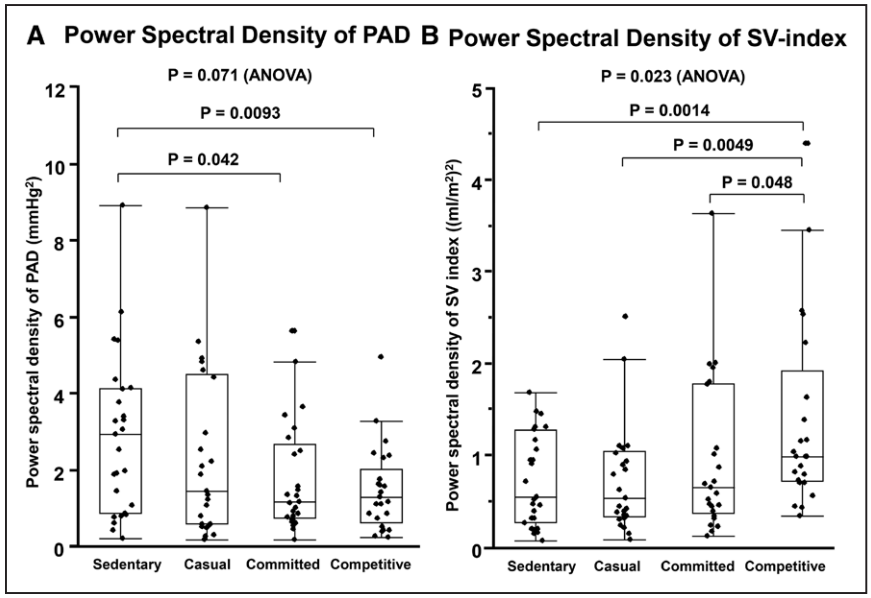

Figure 3. Power spectral density of diastolic pulmonary artery pressure (PAD; A) and stroke volume (SV) index (B).
Mean power spectral density of PAD (**A**) and SV index (**B**) extracted at the point frequency of 0.20 Hz (0.188–0.211 Hz).

Table 3. Ventricular-Vascular Function

	Sedentary Subjects (n=27)	Casual Exercisers (n=25)	Committed Exercisers (n=25)	Competitive Exercisers (n=25)	*P* Value
Cardiac power output index, mm Hg·L/min/m^2	238±56	223±38	224±45	249±61	0.53
Preload recruitable stroke work index	107±64	95±66	97±49	72±26	0.17
Systemic vascular resistance, dyne·sec/cm^5	1583±400	1445±265	1434±279	1457±326	0.73
Effective arterial elastance, mm Hg/mL	1.64±0.55	1.36±0.27	1.31±0.33*	1.26±0.29*	0.02
Carotid-femoral pulse wave velocity, cm/s	1056±359	917±221	841±177*	781±109*†	0.0034
Left ventricular stiffness	0.062±0.039	0.079±0.052	0.055±0.033	0.035±0.023*†‡	<0.001
Transmural stiffness	0.067±0.062	0.070±0.070	0.043±0.028	0.027±0.017*†‡	<0.001

Values are means±SD.
*P<0.05 vs Q1.
†P<0.05 vs Q2.
‡P<0.05 vs Q3.

in the static state and the time domain. However, transfer function analysis in the frequency domain, like this study, enables the quantification of dynamic changes in hemodynamics between PAD (input) and SV (output) on a beat-by-beat and breath-by-breath basis. Moreover, because the dynamic Starling mechanism reflects time-varying ventricular-arterial stiffness, this transfer function gain can provide an index of this integrated feature of ventricular-arterial coupling.

In the present study, transfer function gain of the PAD-SV index relation increased with cumulative dose of lifelong exercise training (Figure 2A). Intriguingly, the PSD of PAD (input variability of the dynamic Starling mechanism) was decreased with increasing training dose (Figure 3A), whereas the PSD of SV index (output variability of the dynamic Starling mechanism) was increased with exercise training (Figure 3B). The elevated PSD of PAD in the most sedentary group is consistent with the known decrease in LV compliance and distensibility in sedentary subjects. We have previously reported that 1 year of vigorous exercise training did not appear to favorably reverse LV stiffening in sedentary seniors.[9] However, in this study, vigorous lifelong exercise can prevent the decreasing dynamic Starling mechanism with ageing, representing the impairment of the ventricular-arterial coupling. Moreover, the PSD of SV index (output variability of the dynamic Starling mechanism) was increased with exercise training. The magnitude of beat-to-beat changes in SV in response to changes in LV preload is mainly determined by the relationship between aortic flow and pressure. Thus, the PSD of SV index in dynamic Starling mechanism conceptually reflects pulsatile loading. Central arterial stiffening and peripheral vascular resistance leading to increased risk of cardiovascular mortality and morbidity have been observed in sedentary elderly adults.[6] Regular exercise training is one favorable strategy to prevent arterial stiffening. We have previously shown that aortic stiffening with aging was not improved even after 1 year of progressive endurance exercise training in previously sedentary seniors.[6] Interestingly, the current results suggest that vigorous lifelong exercise training minimizes the impairment of the output variability in dynamic Starling mechanism with ageing. The reduced PAD variability (input signal) reflects better LV compliance and pressure variability from the influence of the respiratory bellows; in contrast, increased SV variability (output signal) reflects improved ejection and arterial compliance. The dynamic Starling mechanism links these 2 facts. Indeed, as supportive findings, we observed that LV stiffness and transmural stiffness index were greater, and Ea and cf-PWV were lower in committed and competitive exercisers than in sedentary subjects in the time domain (Table 3).[7] These data using completely different techniques are highly concordant with our previously reported data showing the some dose–response relationship with LV ventricular and myocardial stiffness,[7,11] and support the conclusion that 4 to 5 days per week of exercise over a lifetime is optimal for cardiovascular structure and function.

A descriptive summary of these findings are highlighted in the Figure 4, which illustrates that the slope of end-diastolic pressure–volume relationship and Ea is less steep in lifelong vigorous exercisers than those in sedentary seniors. In addition, the end-diastolic pressure–volume relationship in lifelong vigorous exercisers is shifted to the right.[26] The LVEDV and LVESV are greater in lifelong vigorous exercisers than those in sedentary seniors. Ultimately, SV in the lifelong vigorous exercisers is greater than that in the sedentary seniors. Assuming that the potential energy of both groups does not change, the external work (stroke work) is greater in lifelong vigorous exercisers and the ventricular-arterial coupling point is shifted rightward. This finding demonstrates that the rightward shift in the ventricular-arterial coupling point with greater LV compliance may lead to

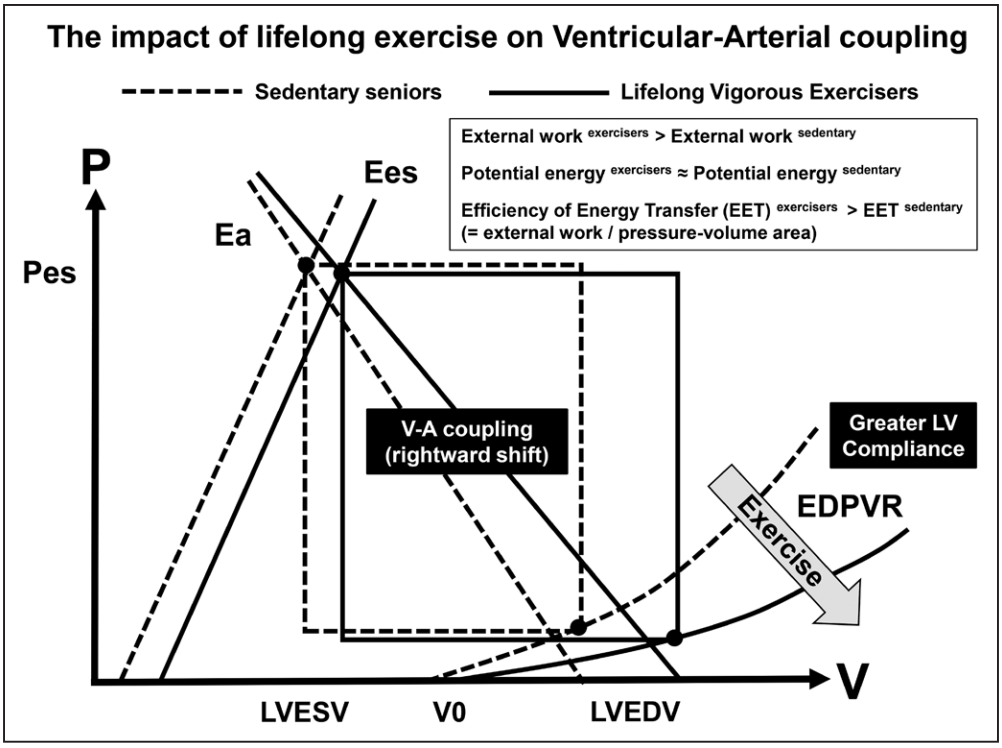

Figure 4. The impact of lifelong exercise on ventricular-arterial coupling between sedentary seniors and vigorous exercisers.
Ventricular-arterial coupling, as assessed by the dynamic Starling mechanism, is improved with the increasing dose of lifelong endurance training. The slope of end-diastolic pressure and volume relationship (EDPVR) and effective arterial elastance (Ea) is less steep in lifelong vigorous exercisers than those in sedentary seniors. In addition, the EDPVR in lifelong vigorous exercisers is shifted to right-sided. The left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) are greater in lifelong vigorous exercisers than those in sedentary seniors. The rightward ventricular-arterial coupling shift may lead to favorable efficiency of energy transfer (= external work / pressure-volume area) and cardiac energetics. Gray arrow indicates effect of lifelong exercise training; dot-line, cardiac property and pressure-volume loop of sedentary seniors; solid-line, lifelong vigorous exercisers. Ees indicates LV elastance at end-systolic time; P, LV pressure; Pes, Pressure at end-systole; V, LV volume; V0, LV unstressed or equibilrium volume (the LV assumption volume of EDPVR at which *P*=0 mm Hg).

favorable efficiency of energy transfer (= external work / pressure-volume area) and cardiac energetics in the life long vigorous exercisers.

Potential Underlying Mechanisms

There are 3 essential cardiac properties that can influence the dynamic Starling mechanism and ultimately contribute to the efficient generation of SV: (1) diastolic compliance, (2) systolic contractile function, and (3) arterial stiffness.[27,28] LV diastolic stiffness increases with greater concentrations of collagen type 1 in the extracellular matrix and cardiomyocytes.[29,30] With aging, degradation of collagen type 1 is decreased because of the downregulation of matrix metalloproteinases and upregulation of tissue inhibitor of matrix metalloproteinases.[31] Additionally, titin, the giant elastic cytoskeletal protein, can elevate the stiffness of cardiomyocytes.[32] Titin has 2 major isoforms: N2B and N2BA. The ratio of these isoforms and their phosphorylation state determine LV passive stiffness.[33–35] Concurrently, aortic stiffening, an important determinant of LV afterload, is increased by the increasing ratio of collagen and elastin in the vessel wall.[36] Our study confirms the observations that lifelong exercise training can prevent the adverse cardiovascular remodeling and preserves LV function as shown by the increased transfer function gain of PAD–SV index.[8,9]

Implications for Preserving Youthful Dynamic Starling Mechanism

We have previously demonstrated that maintaining a physically active lifestyle prevents LV and vascular stiffening.[7,11] However, little is known about the cumulative effects of different doses of exercise and how this will impact cardiovascular function. The dynamic Starling mechanism is impaired in sedentary aging and heart failure with preserved ejection fraction (HFpEF) patients,[6,10] meaning inefficient ventricular-arterial coupling, which contributes to reduce forward output and pulmonary congestion. The present study further extends these data and provides new knowledge by revealing that lifelong endurance training can preserve the dynamic Starling mechanism, which may be attributed to the improvement of both LV and arterial compliance. Our findings may be applicable for the prevention of age-related cardiovascular disorders such as HFpEF. LV compliance and distensibility are reduced in HFpEF patients, and unfortunately there are no pharmacological agents that can improve symptoms or the prognosis of HFpEF.[37,38]

Study Strengths and Limitations

This study enrolled older adults largely from the CCLS who had been longitudinally tracked by a detailed history of exercise training and cardiovascular disease risk factors for >25 years.[15] The CCLS cohort is well characterized and has a high level of internal validity. In addition, transfer function analysis in this study is a novel approach to assess the efficiency between input and output time-varying hemodynamic system, such as the Starling mechanism.[23,39]

This study has several limitations. First, SV was measured indirectly using the Model Flow method, which has been validated,[10,12,39] and the noninvasive nature of this measurement allows the bedside monitoring of beat-by-beat SV changes. Second, the absolute value of PAD is not equivalent to PAWP or LVEDP. However, PAD is considered to be a suitable surrogate as shown by a strong positive linear relationship between PAWP and PAD, and it tracks changes in LV filling pressure quite well.[12] Third, this is a cross-sectional study and, as such, inferences about cause and effect must be made with caution. Baseline characteristics before exercise exposure are not known and may not have been balanced between the different strata, and this study does not account for exercise intensity on the cardiovascular benefits of regular exercise. High intensity exercise has been shown to confer cardiovascular benefits above and beyond moderate intensity exercise.[40,41] However, a lifelong exercise training study is difficult to conduct, and our study participants were well-characterized based on longitudinal observations.

Conclusions

Ventricular-arterial coupling, as assessed by the dynamic Starling mechanism, is improved with increasing dose of lifelong endurance training. Based on our findings, the optimal dose of lifelong endurance exercise for improving cardiovascular structure and function in late life appears to be ≥ 4 to 5 exercise sessions per week or more. The successful participation in lifelong exercise may maintain an efficient dynamic Starling mechanism, LV compliance, and arterial compliance in older adults and prevent the pathogenesis of age-related cardiovascular conditions such as HFpEF.

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Disclosures

None.

REFERENCES

1. Laslett LJ, Alagona P Jr, Clark BA III, Drozda JP Jr, Saldivar F, Wilson SR, Poe C, Hart M. The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of Cardiology. *J Am Coll Cardiol*. 2012;60(25 Suppl):S1–49. doi: 10.1016/j.jacc.2012.11.002
2. Driver JA, Djoussé L, Logroscino G, Gaziano JM, Kurth T. Incidence of cardiovascular disease and cancer in advanced age: prospective cohort study. *BMJ*. 2008;337:a2467. doi: 10.1136/bmj.a2467
3. Fujimoto N, Hastings JL, Bhella PS, Shibata S, Gandhi NK, Carrick-Ranson G, Palmer D, Levine BD. Effect of ageing on left ventricular compliance and distensibility in healthy sedentary humans. *J Physiol*. 2012;590:1871–1880. doi: 10.1113/jphysiol.2011.218271
4. 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. doi: 10.1161/01.CIR.0000048893.62841.F7
5. 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. doi: 10.1161/01.CIR.0000142863.71285.74
6. Shibata S, Levine BD. Effect of exercise training on biologic vascular age in healthy seniors. *Am J Physiol Heart Circ Physiol*. 2012;302:H1340–H1346. doi: 10.1152/ajpheart.00511.2011
7. Bhella PS, Hastings JL, Fujimoto N, Shibata S, Carrick-Ranson G, Palmer MD, Boyd KN, Adams-Huet B, Levine BD. Impact of lifelong exercise "dose" on left ventricular compliance and distensibility. *J Am Coll Cardiol*. 2014;64:1257–1266. doi: 10.1016/j.jacc.2014.03.062
8. Fujimoto N, Prasad A, Hastings JL, Bhella PS, Shibata S, Palmer D, Levine BD. Cardiovascular effects of 1 year of progressive endurance exercise training in patients with heart failure with preserved ejection fraction. *Am Heart J*. 2012;164:869–877. doi: 10.1016/j.ahj.2012.06.028
9. Fujimoto N, Prasad A, Hastings JL, Arbab-Zadeh A, Bhella PS, Shibata S, Palmer D, Levine BD. 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. doi: 10.1161/CIRCULATIONAHA.110.973784
10. Shibata S, Hastings JL, Prasad A, Fu Q, Okazaki K, Palmer MD, Zhang R, Levine BD. 'Dynamic' Starling mechanism: effects of ageing and physical fitness on ventricular-arterial coupling. *J Physiol*. 2008;586:1951–1962. doi: 10.1113/jphysiol.2007.143651

11. Shibata S, Fujimoto N, Hastings JL, Carrick-Ranson G, Bhella PS, Hearon CM Jr, Levine BD. The effect of lifelong exercise frequency on arterial stiffness. *J Physiol*. 2018;596:2783–2795. doi: 10.1113/JP275301
12. Shibata S, Hastings JL, Prasad A, Fu Q, Bhella PS, Pacini E, Krainski F, Palmer MD, Zhang R, Levine BD. Congestive heart failure with preserved ejection fraction is associated with severely impaired dynamic Starling mechanism. *J Appl Physiol (1985)*. 2011;110:964–971. doi: 10.1152/japplphysiol.00826.2010
13. EH. Starling. *The Linacre Lecture on the Law of the Heart*. London, UK: Longmans, Green and Co. 1918.
14. Carrick-Ranson G, Hastings JL, Bhella PS, Fujimoto N, Shibata S, Palmer MD, Boyd K, Livingston S, Dijk E, Levine BD. The effect of lifelong exercise dose on cardiovascular function during exercise. *J Appl Physiol (1985)*. 2014;116:736–745. doi: 10.1152/japplphysiol.00342.2013
15. Kohl HW, Blair SN, Paffenbarger RS Jr, Macera CA, Kronenfeld JJ. A mail survey of physical activity habits as related to measured physical fitness. *Am J Epidemiol*. 1988;127:1228–1239. doi: 10.1097/00008483-198810000-00012
16. Pereira MA, FitzerGerald SJ, Gregg EW, Joswiak ML, Ryan WJ, Suminski RR, Utter AC, Zmuda JM. A collection of Physical Activity Questionnaires for health-related research. *Med Sci Sports Exerc*. 1997;29(6 Suppl):S1–205.
17. Bhella PS, Prasad A, Heinicke K, Hastings JL, Arbab-Zadeh A, Adams-Huet B, Pacini EL, Shibata S, Palmer MD, Newcomer BR, Levine BD. Abnormal haemodynamic response to exercise in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2011;13:1296–1304. doi: 10.1093/eurjhf/hfr133
18. Levine BD, Lane LD, Buckey 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. doi: 10.1161/01.CIR.84.3.1016
19. Prasad A, Hastings JL, Shibata S, Popovic ZB, Arbab-Zadeh A, Bhella PS, Okazaki K, Fu Q, 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 with a preserved ejection fraction. *Circ Heart Fail*. 2010;3:617–626. doi: 10.1161/CIRCHEARTFAILURE.109.867044
20. Bhella PS, Pacini EL, Prasad A, Hastings JL, Adams-Huet B, Thomas JD, Grayburn PA, Levine BD. Echocardiographic indices do not reliably track changes in left-sided filling pressure in healthy subjects or patients with heart failure with preserved ejection fraction. *Circ Cardiovasc Imaging*. 2011;4:482–489. doi: 10.1161/CIRCIMAGING.110.960575
21. Fisher ML, De Felice CE, Parisi AF. Assessing left ventricular filling pressure with flow-directed (Swan-Ganz) catheters. Detection of sudden changes in patients with left ventricular dysfunction. *Chest*. 1975;68:542–547. doi: 10.1378/chest.68.4.542
22. van Lieshout JJ, Toska K, van Lieshout EJ, Eriksen M, Walløe L, Wesseling KH. Beat-to-beat noninvasive stroke volume from arterial pressure and Doppler ultrasound. *Eur J Appl Physiol*. 2003;90:131–137. doi: 10.1007/s00421-003-0901-8
23. Zhang R, Zuckerman JH, Giller CA, Levine BD. Transfer function analysis of dynamic cerebral autoregulation in humans. *Am J Physiol*. 1998;274(1 Pt 2):H233–H241. doi: 10.1152/ajpheart.1998.274.1.H233
24. Hieda M, Howden E, Shibata S, Tarumi T, Lawley J, Hearon CM Jr, Palmer D, Fu Q, Zhang R, Sarma S, Levine BD. Preload-corrected dynamic Starling mechanism in patients with heart failure with preserved ejection fraction. *J Appl Physiol*. 2018;124:76–82. doi: 10.1152/japplphysiol.00718.2017
25. Prasad A, Hastings JL, Shibata S, Popovic ZB, Arbab-Zadeh A, Bhella PS, Okazaki K, Fu Q, 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 with a preserved ejection fraction. *Circ Heart Fail*. 2010;3:617–626. doi: 10.1161/CIRCHEARTFAILURE.109.867044
26. Goto Y, Futaki S, Kawaguchi O, Hata K, Takasago T, Saeki A, Nishioka T, Suga H. Left ventricular contractility and energetic cost in disease models–an approach from the pressure-volume diagram. *Jpn Circ J*. 1992;56:716–721. doi: 10.1253/jcj.56.716
27. Kass DA. Ventricular arterial stiffening: integrating the pathophysiology. *Hypertension*. 2005;46:185–193. doi: 10.1161/01.HYP.0000168053.34306.d4
28. Kass DA, Maughan WL. From 'Emax' to pressure-volume relations: a broader view. *Circulation*. 1988;77:1203–1212. doi: 10.1161/01.CIR.77.6.1203
29. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J*. 2011;32:670–679. doi: 10.1093/eurheartj/ehq426
30. Weber KT, Brilla CG, Janicki JS. Myocardial fibrosis: functional significance and regulatory factors. *Cardiovasc Res*. 1993;27:341–348. doi: 10.1093/cvr/27.3.341
31. Ahmed SH, Clark LL, Pennington WR, Webb CS, Bonnema DD, Leonardi AH, McClure CD, Spinale FG, Zile MR. Matrix metalloproteinases/tissue inhibitors of metalloproteinases: relationship between changes in proteolytic determinants of matrix composition and structural, functional, and clinical manifestations of hypertensive heart disease. *Circulation*. 2006;113:2089–2096. doi: 10.1161/CIRCULATIONAHA.105.573865
32. LeWinter MM, Granzier H. Cardiac titin: a multifunctional giant. *Circulation*. 2010;121:2137–2145. doi: 10.1161/CIRCULATIONAHA.109.860171
33. Trombitás K, Wu Y, Labeit D, Labeit S, Granzier H. Cardiac titin isoforms are coexpressed in the half-sarcomere and extend independently. *Am J Physiol Heart Circ Physiol*. 2001;281:H1793–H1799. doi: 10.1152/ajpheart.2001.281.4.H1793
34. Borbély A, Falcao-Pires I, van Heerebeek L, Hamdani N, Edes I, Gavina C, Leite-Moreira AF, Bronzwaer JG, Papp Z, van der Velden J, Stienen GJ, Paulus WJ. Hypophosphorylation of the Stiff N2B titin isoform raises cardiomyocyte resting tension in failing human myocardium. *Circ Res*. 2009;104:780–786. doi: 10.1161/CIRCRESAHA.108.193326
35. Zile MR, Baicu CF, Ikonomidis JS, Stroud RE, Nietert PJ, Bradshaw AD, Slater R, Palmer BM, Van Buren P, Meyer M, Redfield MM, Bull DA, Granzier HL, LeWinter MM. Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin. *Circulation*. 2015;131:1247–1259. doi: 10.1161/CIRCULATIONAHA.114.013215
36. Lakatta EG. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part III: cellular and molecular clues to heart and arterial aging. *Circulation*. 2003;107:490–497. doi: 10.1161/01.CIR.0000048894.99865.02
37. Westermann D, Kasner M, Steendijk P, Spillmann F, Riad A, Weitmann K, Hoffmann W, Poller W, Pauschinger M, Schultheiss HP, Tschöpe C. Role of left ventricular stiffness in heart failure with normal ejection fraction. *Circulation*. 2008;117:2051–2060. doi: 10.1161/CIRCULATIONAHA.107.716886
38. Schwarzl M, Ojeda F, Zeller T, Seiffert M, Becher PM, Munzel T, Wild PS, Blettner M, Lackner KJ, Pfeiffer N, Beutel ME, Blankenberg S, Westermann D. Risk factors for heart failure are associated with alterations of the LV end-diastolic pressure-volume relationship in non-heart failure individuals: data from a large-scale, population-based cohort. *Eur Heart J*. 2016;37:1807–1814. doi: 10.1093/eurheartj/ehw120
39. Abdellatif M, Leite S, Alaa M, Oliveira-Pinto J, Tavares-Silva M, Fontoura D, Falcão-Pires I, Leite-Moreira AF, Lourenço AP. Spectral transfer function analysis of respiratory hemodynamic fluctuations predicts end-diastolic stiffness in preserved ejection fraction heart failure. *Am J Physiol Heart Circ Physiol*. 2016;310:H4–13. doi: 10.1152/ajpheart.00399.2015
40. Wisløff U, Ellingsen Ø, Kemi OJ. High-intensity interval training to maximize cardiac benefits of exercise training? *Exerc Sport Sci Rev*. 2009;37:139–146. doi: 10.1097/JES.0b013e3181aa65fc
41. Saint-Maurice PF, Troiano RP, Berrigan D, Kraus WE and Matthews CE. Volume of Light Versus Moderate-to-Vigorous Physical Activity: Similar Benefits for All-Cause Mortality? *J Am Heart Assoc*. 2018;7. doi: 10.1161/JAHA.118.008815