

# The Effects of Aging and Physical Activity on Doppler Measures of Diastolic Function

Anand Prasad, MD<sup>a</sup>, Zoran B. Popovic, MD<sup>b</sup>, Armin Arbab-Zadeh, MD<sup>c</sup>, Qi Fu, MD, PhD<sup>a</sup>, Dean Palmer, MS<sup>a</sup>, Erika Dijk, BS<sup>d</sup>, Neil L. Greenberg, PhD<sup>b</sup>, Mario J. Garcia, MD<sup>b</sup>, James D. Thomas, MD<sup>b</sup>, and Benjamin D. Levine, MD<sup>a,\*</sup>

Healthy aging results in changes in Doppler measures of diastolic function. It is unclear whether these alterations are a specific manifestation of the aging process or reflect a cardiac adaptation to a more sedentary lifestyle. It was hypothesized that healthy, but sedentary, aging would result in slowing of diastolic filling and myocardial relaxation, whereas lifelong endurance training would prevent such changes. Doppler data were measured in young subjects and sedentary and fit seniors across a broad range of loading conditions. Thirteen sedentary healthy (70 ± 4 years) and 12 fit Masters athlete (68 ± 3 years) seniors were recruited. Twelve young healthy (32 ± 9 years) subjects were used for comparison. Pulmonary capillary wedge pressure and Doppler variables were measured at the 6 loading conditions of baseline (twice), -15 and -30 mm Hg lower body negative pressure, and 2 levels of saline solution infusion. Doppler variables consisted of early and late mitral inflow velocity (E/A) ratio, isovolumetric relaxation time (IVRT), tissue Doppler velocities (TDI E<sub>mean</sub>), and propagation velocity of mitral inflow. Aging resulted in a decrease in E/A ratio (p < 0.001), TDI E<sub>mean</sub> (p < 0.001), and propagation velocity of mitral inflow (p < 0.001) and an increase in IVRT (p = 0.001). Lifelong endurance training did not completely prevent the changes in E/A ratio (p = 0.212), IVRT (p = 0.546), or propagation velocity of mitral inflow (p = 1.00). Fit seniors were able to achieve E/A ratios of 1.0 during baseline and saline solution infusion. TDI E<sub>mean</sub> was higher in fit versus sedentary seniors at baseline (p = 0.012) and during maximal lower body negative pressure (p = 0.036), but not during saline solution infusion (p = 0.493). In conclusion, age-associated abnormalities in Doppler measures of myocardial filling and relaxation are only partially minimized by lifelong endurance training and therefore may be more specific to the aging process than secondary to years of deconditioning. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99:1629–1636)

Normal aging, even in the absence of co-morbidities, results in marked changes in Doppler measures of ventricular filling and relaxation, including reversal of the early and late mitral inflow velocities (decreased E/A ratio) and prolongation of isovolumetric relaxation time (IVRT).<sup>1</sup> These variables, although reproducible, have several limitations in their ability to accurately reflect diastolic function, including significant preload dependence and lack of specificity for dynamic relaxation processes.<sup>2</sup> In addition, it is unclear whether alterations in these Doppler variables with senescence are a specific manifestation of the aging process or

reflect a secondary cardiac adaptation to a more sedentary lifestyle.<sup>3</sup>

Recently, our laboratory showed that static left ventricular stiffness markedly increased during healthy sedentary aging, whereas lifelong endurance training preserved static left ventricular compliance.<sup>4</sup> These data showed that ≥1 component of diastole, namely static chamber compliance, was significantly influenced by fitness. We therefore hypothesized that normal healthy, but sedentary, aging would result in slowing of Doppler measures of diastolic filling and dynamic myocardial relaxation, whereas lifelong endurance training would prevent such changes. To test this hypothesis, traditional Doppler mitral inflow variables, as well as modern echocardiographic techniques such as tissue Doppler imaging (TDI) and color M-mode-derived data, were measured cross-sectionally in young subjects and sedentary and fit seniors across a broad range of loading conditions. This approach allowed for direct comparison of effects of static ventricular chamber compliance and relaxation and their integrative effect on diastolic function.

## Methods

**Subjects:** Thirteen sedentary healthy (70 ± 4 years; 7 men, 6 women) and 12 fit (68 ± 3 years; 6 men, 6 women)

<sup>a</sup>Institute for Exercise and Environmental Medicine, Presbyterian Hospital and University of Texas Southwestern Medical Center, Dallas, Texas; <sup>b</sup>Cleveland Clinic Foundation, Cleveland, Ohio; <sup>c</sup>Johns Hopkins University, Baltimore, Maryland; and <sup>d</sup>Department of Integrative Physiology, University Medical Center, Nijmegen, The Netherlands. Manuscript received December 19, 2006; revised manuscript received and accepted January 23, 2007.

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\*Corresponding author: Tel.: 214-345-4619; fax: 214-345-4618.

E-mail address: benjaminlevine@texashealth.org (B.D. Levine).

Table 1  
Baseline hemodynamic measurements

Variable	Young (n=12)	Sedentary Seniors (n=13)	Fit Seniors (n=12)
Age (yrs)	32.3 ± 9.0* <sup>†</sup>	69.8 ± 3.0	67.8 ± 3.0
Body surface area (m <sup>2</sup> )	1.90 ± 0.27	1.85 ± 0.17	1.74 ± 0.24
Maximal oxygen uptake (mL · min <sup>-1</sup> · m <sup>-2</sup> )	40.6 ± 10.1*	21.6 ± 2.8	38.3 ± 5.9*
Stroke volume index at rest (ml/m <sup>2</sup> )	34.2 ± 6.9	39.2 ± 6.9	57.1 ± 15.7* <sup>‡</sup>
Left ventricular end-diastolic volume index at rest (ml/m <sup>2</sup> )	53 ± 6	56 ± 10	80 ± 11* <sup>‡</sup>
Left ventricular systolic volume index at rest (ml/m <sup>2</sup> )	19 ± 5	17 ± 4	23 ± 6* <sup>‡</sup>
Ejection fraction (%)	64.0 ± 0.1	70 ± .03	72 ± 0.1 <sup>‡</sup>
Left ventricular mass index (g/m <sup>2</sup> )	76.0 ± 11*	69.2 ± 11	78 ± 18*
Mass-to-volume ratio (g/ml)	1.44 ± 0.24	1.27 ± 0.31	1.18 ± 0.42 <sup>‡</sup>
Left ventricular wall thickness (mm)	1.25 ± 0.19	1.17 ± 0.10	1.22 ± 0.18

Data presented as mean ± SD.

Left ventricular end-diastolic volume, end-systolic volume, and stroke volume were determined using magnetic resonance imaging as previously described.<sup>4</sup>

\* Statistically significant difference from sedentary seniors.

<sup>†</sup> Statistically significant difference from fit seniors.

<sup>‡</sup> Statistically significant difference from young controls.

seniors were recruited for this study. Twelve young healthy sedentary (32 ± 9 years; 9 men, 3 women) subjects were also studied and used for comparison. Senior subjects are the same patients who had their hemodynamic parameters and static left ventricular compliance reported previously, whereas young controls were drawn from published and unpublished studies in our laboratory.<sup>4</sup> Hemodynamic data are listed in Table 1. All subjects were meticulously screened for systemic hypertension using 24-hour ambulatory blood pressure monitoring and cardiac disease, including structural heart and hemodynamically significant obstructive coronary disease, using a history, physical examination, and resting and after-exercise transthoracic echocardiograms.

Exclusion criteria for this study included valvular heart disease, atrial flutter/fibrillation, systemic hypertension (mean daytime blood pressure >140/90 mm Hg), electrocardiogram changes suggestive of ischemic disease, left branch bundle block, greater than first-degree atrioventricular block, baseline or exercise-induced wall motion abnormalities, untreated thyroid disorders, renal insufficiency, chronic lung disease, regular cigarette smoking within the past 10 years, body mass index ≥30 kg/m<sup>2</sup>, cardiovascular medication, or warfarin use.

All participants in the fit group had performed and were still actively competing in multiple endurance competitions, including marathons, triathlons, and/or middle-distance events for decades (23 ± 8 years) and several competed at a national and even international level. Mean maximal oxygen uptakes of men and women Masters athletes were in the top 10% of their age group (40.3 ± 7 and 35.3 ± 4 ml/kg/min, respectively). In contrast, sedentary participants were excluded if they performed aerobic exercise for >30 minutes 3 times a week. 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.

**Experimental protocol:** Subjects were studied in the resting, supine, or left lateral position. A 6Fr balloon-tipped

fluid-filled catheter (Edwards Lifesciences, Irvine, California) was placed using fluoroscopic guidance through an 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, as well as by the presence of an appropriate pulmonary capillary wedge pressure (PCWP) waveform.

Cardiac filling was first decreased using lower body negative pressure (LBNP) as previously described.<sup>5</sup> Two levels of LBNP used were -15 and -30 mm Hg. Measurements of mean PCWP, immediately followed by Doppler echocardiographic measurements (discussed next), were made after 5 minutes at each level of LBNP. After release of the negative pressure and confirmed return to hemodynamic baseline, cardiac filling was increased through a rapid infusion of warm (37°C) isotonic saline solution at 100 ml/min. Measurements were repeated after the infusion of 15 and 30 ml/kg.

**Echocardiography:** For all subjects, at each level of cardiac loading/unloading, a transthoracic echocardiogram was obtained using an ATL (Advanced Technology Laboratories, Bothell, Washington) HDI 5000CV (software version 10.1) echocardiograph. Apical 4-chamber views were used to make each measurement. Volumes were determined using a modified Simpson's method that was used in our previous studies.<sup>4</sup> Every effort was made to ensure that the images were not foreshortened and there was optimal endocardial definition. All images were stored on 3.5-inch magnetic optical disc and evaluated blindly offline by an experienced sonographer.

**DOPPLER MEASUREMENTS:** To evaluate mechanical processes influencing early and late diastolic filling, both traditional (E, A, and IVRT) and newer (TDI and propagation velocity of early mitral inflow) Doppler variables were measured. Figure 1 shows a guide of the relation between pressure gradients and Doppler measurements. Individual measures, although not specific for catheter-derived pressures, provide a general overview of processes occurring

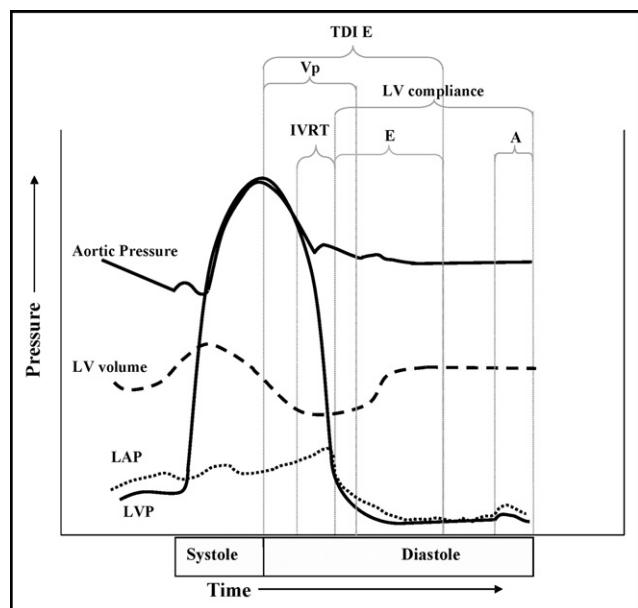


Figure 1. Composite evaluation of diastolic function using Doppler echocardiography. LAP = left atrial pressure; LV compliance = left ventricular end-diastolic pressure–volume relation; LVP = left ventricular pressure; Vp = early propagation velocity of mitral inflow.

during specific phases of the Wiggers cycle.<sup>6</sup> All of the following measurements were made during quiet held expiration with 4 to 6 consecutive cardiac cycles averaged for each level of cardiac filling.

**PULSED WAVE DOPPLER:** Pulse-waved Doppler, using a sample volume of 2.0 mm placed at the tips of the mitral valve leaflets, was used to determine peak velocities of mitral inflow (E and A velocities). Using a 5-chamber apical view, the interval between aortic outflow during systole and opening of the mitral valve (IVRT) was also determined after the sample volume was increased to 4.0 mm.

**TISSUE DOPPLER IMAGING:** In the apical 4-chamber view, the septal wall was first highlighted in the tissue Doppler mode. Using pulse-wave Doppler, a sample volume of 4.0 mm was placed at the septal side of the mitral annulus. The resulting early diastolic waveform velocity was recorded and the process was repeated for the lateral wall. Values were averaged to obtain TDI  $E_{\text{mean}}$ .<sup>7</sup>

**COLOR M-MODE/PROPAGATION VELOCITY OF EARLY MITRAL INFLOW:** A color M-mode image of left ventricular inflow was obtained with the sampling area positioned to extend from midatrium to the apex, directly through the mitral valve orifice. The scale was reduced sufficiently to result in clear aliasing within the early portion of the mitral inflow. The resulting mitral inflow spatiotemporal velocity profile pattern was used to derive the early propagation velocity of mitral inflow. This technique was described previously.<sup>8</sup>

**Statistical analysis:** Data are presented as mean  $\pm$  SEM. Groups were compared using 2-way repeated-measures analysis of variance with analysis of interactions (group  $\times$  filling condition). Analysis of slope relationships and comparison of data during specific levels of cardiac

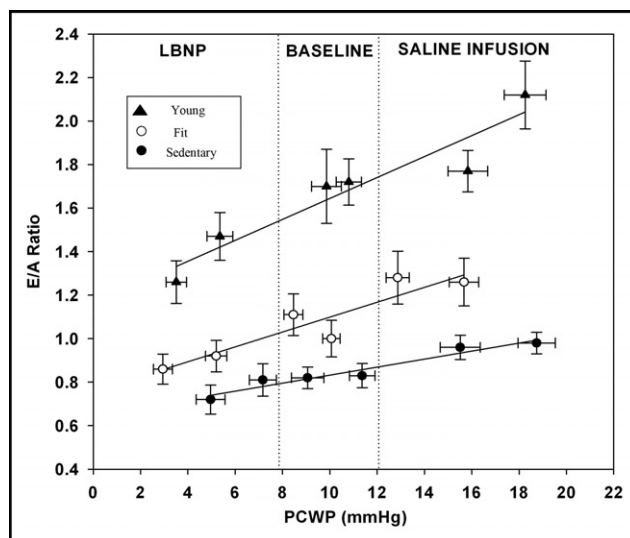


Figure 2. Early (E) to late (A) transmitral Doppler velocity ratios across loading conditions. Two-way repeated-measures analysis of variance: young versus seniors ( $p < 0.001$ ), fit seniors versus sedentary seniors ( $p = 0.212$ ). In contrast to sedentary seniors, fit subjects had E/A ratios  $> 1.0$  at baseline (mean E/A ratio  $1.06 \pm 0.31$  in the fit group vs  $0.822 \pm 0.18$  in the sedentary group,  $p = 0.002$ ) and during saline solution infusion (mean E/A ratio  $1.3 \pm 0.39$  in the fit group vs  $0.97 \pm 0.19$  in the sedentary group,  $p = 0.005$ ).

filling were performed using 1-way analysis of variance. A  $p$  value  $< 0.05$  was considered statistically significant.

## Results

**E/A ratio:** Healthy, but sedentary, aging resulted in a decrease in E/A ratio at baseline, as well as during cardiac unloading and loading (young vs seniors,  $p < 0.001$ ; Figure 2). Sedentary seniors were unable to generate an E/A ratio  $\geq 1.0$ , even during maximal cardiac filling, whereas young subjects had an E/A ratio  $> 1.0$  even at maximal cardiac unloading. As previously documented in the literature, E/A ratio was preload dependent.<sup>2</sup> In all 3 groups of subjects, E/A ratios increased as filling pressures increased. This relation was most noticeable in young subjects, who had a marked increase in E/A ratio with cardiac filling (young vs seniors,  $p < 0.001$ ).

Across loading conditions, fit seniors had markedly lower E/A ratios than the young ( $p < 0.001$ ). Overall, fit seniors had E/A ratios similar to sedentary seniors (2-way repeated-measures analysis of variance,  $p = 0.212$ ). However, in contrast to sedentary seniors, fit seniors had E/A ratios  $> 1.0$  at baseline (mean E/A ratio  $1.06 \pm 0.31$  in the fit group vs  $0.822 \pm 0.18$  in the sedentary group,  $p = 0.002$ ) and during saline solution infusion (mean E/A ratio  $1.3 \pm 0.39$  in the fit group vs  $0.97 \pm 0.19$  in the sedentary group,  $p = 0.005$ ).

**Isovolumetric relaxation time:** Like E/A ratio, IVRT was also preload dependent. IVRT at baseline was significantly longer in sedentary seniors compared with young subjects, and this relation was further magnified during cardiac unloading ( $p = 0.001$ ; Figure 3). During increased cardiac filling, sedentary seniors were able to shorten the IVRT (from  $144.91 \pm 5.44$  ms at baseline to  $114.38 \pm 4.45$

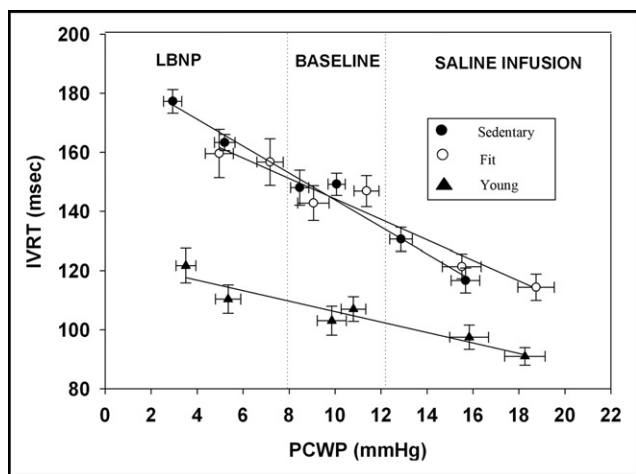


Figure 3. IVRT: 2-way repeated-measures analysis of variance for young versus seniors ( $p < 0.001$ ) and fit seniors versus sedentary seniors ( $p > 0.50$ ).

at maximal saline solution infusion). However, by comparison, young subjects still had significantly shorter IVRTs at higher filling pressures ( $90.98 \pm 2.93$  ms,  $p = 0.001$ ).

IVRT was longer in fit seniors than young subjects across all filling conditions ( $p < 0.001$ ). There was no significant effect of training noted at any filling pressure ( $p = 0.546$ ). Like sedentary seniors, fit subjects were also able to shorten the IVRT during cardiac loading. However, even during maximal saline solution infusion, the fit were still unable to normalize the relaxation time in comparison to the young ( $p < 0.001$ ).

**TDI  $E_{\text{mean}}$  of septal and lateral ventricular walls:** Contrary to previously published data,<sup>9</sup> TDI velocities in the present study were very preload dependent, increasing in all groups in response to volume loading and decreasing in response to cardiac unloading (Figure 4). Healthy sedentary aging resulted in a significant slowing of TDI  $E_{\text{mean}}$  myocardial motion velocities across all filling conditions ( $p < 0.001$ ).

At baseline, fit senior subjects had TDI  $E_{\text{mean}}$  myocardial motion velocities that were significantly slower than those of young subjects ( $p < 0.001$ ) and halfway between the young and older sedentary seniors. However, at maximal cardiac unloading, fit subjects and young subjects had similar TDI  $E_{\text{mean}}$  velocities ( $p = 0.334$ ). Fit subjects during baseline and maximal cardiac unloading had TDI  $E_{\text{mean}}$  velocities that were significantly faster than those of their sedentary counterparts ( $p = 0.012$  and  $p = 0.036$ , respectively). This relation was not maintained during saline solution infusion ( $p = 0.493$ ).

**Propagation velocity of early mitral inflow:** Aging resulted in a decrease in propagation velocity of early mitral inflow at all filling pressures measured ( $p < 0.001$ , Figure 5). Despite the described fitness effects on TDI velocities, there was no alteration in propagation velocity of early mitral inflow with lifelong endurance training ( $p = 1.00$ ).

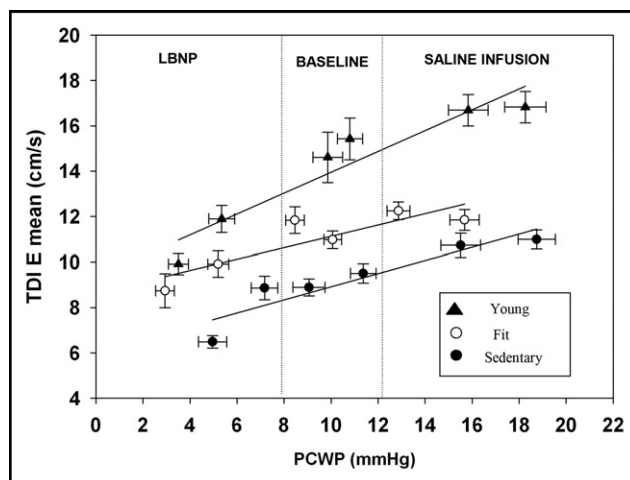


Figure 4. TDI  $E_{\text{mean}}$  velocities across filling pressures. Healthy sedentary aging resulted in slowing of TDI  $E_{\text{mean}}$  velocities ( $p < 0.001$ ). Fit senior subjects had faster TDI  $E_{\text{mean}}$  velocities at baseline and during cardiac unloading ( $p = 0.012$  and  $p = 0.036$ ) than sedentary seniors, but not during saline solution infusion ( $p = 0.493$ ).

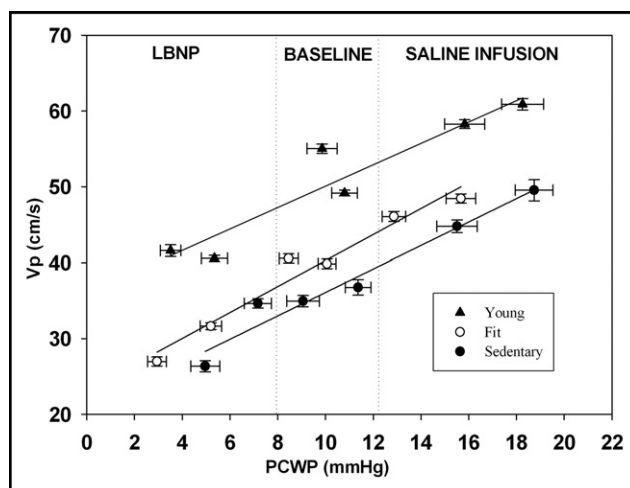


Figure 5. Early propagation velocity of mitral inflow ( $V_p$ ) across loading conditions. Aging resulted in a decrease in  $V_p$  ( $p < 0.001$ ). Endurance training had no significant impact on  $V_p$  ( $p = 1.00$ ).

## Discussion

There are 2 primary findings of the present study. First, measures of transmitral left ventricular filling (E/A ratio), global relaxation (IVRT), dynamic longitudinal wall relaxation (TDI velocities), and diastolic suction (propagation velocity of early mitral inflow) were profoundly altered by aging, and these differences were present across a wide range of physiological filling pressures. Specifically, despite the preload dependence of all Doppler measurements, volume loading did not normalize Doppler measures of ventricular filling in aged individuals and did not impair filling parameters in young subjects to the same degree as present in seniors at rest. Furthermore, in distinct contrast to previously published static chamber compliance data for these subjects, lifelong endurance training had only a modest effect on preserving myocardial relaxation. Although age-related changes in certain measures of myocardial relax-

ation and diastolic filling (IVRT and propagation velocity of early mitral inflow) appeared to be specific to cardiac senescence, TDI and E/A velocities appeared to be at least somewhat sensitive to training.

**Comprehensive Doppler assessment of diastolic function:** Previously, Fleg et al<sup>10</sup> showed a lack of lifelong training effect on peak E/A ratios at rest in male athletes aged 52 to 76 years compared with sedentary and young controls. However, such attempts to delineate the effects of aging versus physical activity on Doppler measures of “diastolic function” were limited by issues related to subject selection (wide age range and male predominance), lack of invasive hemodynamic correlation, and use of only transmitral filling velocities.<sup>3,10</sup>

The findings of the present study are unique in that they assess multiple aspects of diastole with concomitant measurement of PCWP. Each Doppler variable gives a window into the different phases of diastole (Figure 1). Each Doppler variable reflects multiple interrelated mechanical processes. Individually, they are neither perfect nor absolute measures of diastole, but taken together, they allow better understanding of overall global diastolic performance. To reach such a comprehensive characterization of left ventricular lusitropy, the information gained from each Doppler variable must be examined individually in the context of pressure gradients and static left ventricular compliance.

In the following discussion, each Doppler measurement and its associated phase of diastole is examined sequentially in time beginning with IVRT, then TDI E and propagation velocity of early mitral inflow, and finally the global composite measurement E/A ratio. The role of afterload and its impact on diastolic suction that links systole with diastole during the subsequent cardiac cycle is discussed last.

**IVRT:** IVRT reflects a relatively specific measure of prefilling ventricular relaxation determined by the relation between left atrial pressure and left ventricular early diastolic pressure (Figure 1). In both human and animal studies, direct catheter-derived measurements of Tau correlated closely with Doppler determinations of IVRT.<sup>11</sup> In the present study, healthy sedentary aging resulted in prolongation of IVRT across a broad spectrum of physiologic filling pressures, and lifelong training did not alter this finding. Whereas IVRT was clearly influenced by preload, the higher IVRTs in seniors relative to young controls were not caused by differences in left atrial pressure. Baseline PCWP was not different among the 3 subject groups despite marked differences in static compliance. Moreover, even at the highest filling pressures, IVRT of older subjects was considerably longer than that of young subjects at baseline. These data taken together suggest that normal aging leads to a decrease in rate of left ventricular relaxation occurring before opening of the mitral valve. This loss of relaxation is specific to the aging process and not a function of physical fitness. Furthermore, fit and sedentary seniors had IVRTs that were nearly identical despite marked differences in static left ventricular chamber compliance. Mechanical processes occurring during IVRT take place during the earliest portion of diastole before the influx of blood into the ventricle and thus appear to be independent of static myocardial stiffness.

**TDI E-wave velocity:** Tissue Doppler E wave velocities reflect annular myocardial motion in the longitudinal plane. The onset of TDI E velocity under supine resting conditions precedes the onset of the conventional Doppler E-wave velocity.<sup>12</sup> TDI E velocities therefore reflect myocardial relaxation and recoil after aortic valve closure just before and then during early mitral inflow (Figure 1). Again, like the previously discussed Doppler variables, TDI E in all 3 groups of healthy subjects was preload dependent. There was a clear age-related decrease in TDI E velocities across loading conditions. In contrast to other Doppler measures, TDI velocities appeared to be more responsive to physical fitness, and these improvements may be caused by multiple factors. It is possible that TDI variables are influenced by factors other than intrinsic relaxation. For example, the influence of static ventricular compliance on TDI velocities is unclear. Fit senior subjects had much more compliant hearts than sedentary subjects, and this may have contributed to faster lateral wall velocities in this group. However, young and fit subjects were nearly identical in terms of static compliance and yet clearly had different TDI velocities at higher filling pressures, suggesting that chamber compliance is not the exclusive regulator of wall velocities during cardiac loading.

Alternatively, the improvement in mean TDI velocities may partially be influenced by a slower heart rate in fit senior subjects compared with sedentary senior subjects (Table 2). In animal models, early TDI velocities at the mitral annulus correlated inversely with heart rates.<sup>13</sup> However, such a phenomenon would be expected to increase TDI velocities of fit subjects during both cardiac unloading and loading. The underlying mechanism responsible for the training-induced changes in TDI velocities remains unclear.

**Vp:** Propagation velocity of early mitral inflow represents the propagation velocity of the earliest influx of blood entering the left ventricle just after mitral valve opening (Figure 1). Like IVRT, propagation velocity of early mitral inflow is also strongly influenced by intrinsic left ventricular relaxation. In addition, propagation velocity of early mitral inflow is impacted on by passive filling and small intraventricular pressure gradients within the ventricular cavity that actively draw blood from the base to the apex.<sup>14</sup> These intraventricular pressure gradients previously were shown to reflect the magnitude of myocardial suction during early diastole.<sup>15</sup> In the present study, propagation velocity of early mitral inflow increased in all 3 groups with saline solution infusion and decreased during LBNP, showing the preload dependence of propagation velocity of early mitral inflow in normal healthy subjects. For a given PCWP, sedentary aging resulted in decreased velocity of blood moving from the mitral annulus toward the left ventricular apex. This process was specific to aging and not altered by physical fitness. Again, much like IVRT, the age-related decrease in propagation velocity of early mitral inflow cannot be explained by changes in static chamber compliance.

**E/A ratio:** E/A ratio is a composite measure of both early and late transmitral filling. It is a relatively nonspecific measure influenced by early diastolic mechanics, ventricular stiffness, left atrial pressure, and atrial systole (Figure 1).

Table 2  
Effect of load on hemodynamic variables

Loading Condition	Young (n=12)	Sedentary Seniors (n=13)	Fit Seniors (n=12)
<b>LBNP -30</b>			
Heart rate (beats/min)	86 ± 14*	73 ± 12	62 ± 6*‡
Systolic blood pressure (mm Hg)	107 ± 14*	130 ± 15	112 ± 17*
Diastolic blood pressure (mm Hg)	68 ± 11*	76 ± 4	66 ± 11*
PCWP (mm Hg)	3.5 ± 1.5	5.0 ± 2.1	2.9 ± 1.4*
<b>LBNP -15</b>			
Heart rate (beats/min)	72 ± 13	68 ± 9	55 ± 4*‡
Systolic blood pressure (mm Hg)	109 ± 13*	136 ± 15	119 ± 17*
Diastolic blood pressure (mm Hg)	67 ± 9*	76 ± 7	69 ± 8*
PCWP (mm Hg)	5.4 ± 1.9*	7.2 ± 2.0	5.2 ± 1.6*
<b>LBNP baseline</b>			
Heart rate (beats/min)	65 ± 13	66 ± 9	53 ± 6*‡
Systolic blood pressure (mm Hg)	115 ± 12*	138 ± 14	124 ± 20*
Diastolic blood pressure (mm Hg)	68 ± 7*	78 ± 8	69 ± 9*
PCWP (mm Hg)	10.8 ± 1.9	11.4 ± 2.0	10.1 ± 1.3
<b>Normal saline solution baseline</b>			
Heart rate (beats/min)	68 ± 12	71 ± 9	58 ± 5*‡
Systolic blood pressure (mm Hg)	116 ± 11*	130 ± 12	118 ± 17†
Diastolic blood pressure (mm Hg)	67 ± 8	70 ± 5	64 ± 8
PCWP (mm Hg)	9.9 ± 2.2	9.1 ± 2.5	8.5 ± 1.4
<b>Normal saline solution infusion 1</b>			
Heart rate (beats/min)	79 ± 11	77 ± 7	62 ± 6*‡
Systolic blood pressure (mm Hg)	122 ± 16	132 ± 10	120 ± 17
Diastolic blood pressure (mm Hg)	65 ± 8	70 ± 4	63 ± 7
PCWP (mm Hg)	15.8 ± 2.9	15.5 ± 3.0	12.9 ± 1.7*‡
<b>Normal saline solution infusion 2</b>			
Heart rate (beats/min)	84 ± 14	82 ± 8	63 ± 6*‡
Systolic blood pressure (mm Hg)	123 ± 18	135 ± 13	124 ± 17
Diastolic blood pressure (mm Hg)	67 ± 10	73 ± 5	65 ± 8
PCWP (mm Hg)	18.3 ± 3.1	18.7 ± 2.8	15.7 ± 2.2*‡

Data presented as mean ± SD from lowest to highest cardiac filling pressure. Systolic and diastolic blood pressures were obtained using 24-hour ambulatory blood pressure monitoring. PCWP was obtained using right heart catheterization.

\* Statistically significant difference from sedentary seniors.

† Statistically significant difference from fit seniors.

‡ Statistically significant difference from young controls.

In the present study, sedentary aging resulted in a decrease in E/A ratio across loading conditions, suggesting greater dependence on late diastolic filling. Fit seniors in comparison to sedentary seniors appeared to have an improvement in E/A ratio (>1.0) at baseline and during saline solution infusion.

It is possible that preservation of static ventricular compliance may have allowed the relaxing ventricle to accommodate a larger volume of blood at a faster rate in early diastole during these conditions. In addition, baseline A-wave velocities were slower in the young and fit compared with sedentary subjects ( $44 \pm 11$ ,  $63 \pm 19$ , and  $72 \pm 18$  cm/s, respectively,  $p < 0.05$ ), potentially explainable by a smaller volume of atrial contraction into a chamber that is statically and operationally more compliant. Based on these data, E/A ratio appears to be influenced by both ventricular compliance and relaxation. In addition, E/A ratio is affected by changes in heart rate, specifically decreasing during periods of tachycardia.<sup>16</sup> The trained seniors had slower heart rates at rest than sedentary subjects, and this finding may have partially contributed to the higher baseline E/A ratios in the fit group. However, the modestly increased heart rate in the sedentary group was likely insufficient to

significantly hinder early diastolic filling because diastasis was maintained in these subjects with clear separation of the E and A waves during pulse wave Doppler interrogation of mitral inflow patterns.

**Influence of afterload on Doppler measures of diastolic function:** Left ventricular diastolic function, in addition to being preload dependent, is also afterload dependent.<sup>17</sup> Higher afterload decreases the ability of the ventricle to contract below the equilibrium volume during end-systole, thus preventing the development of diastolic suction during the next cardiac cycle. In the present study, the highly screened healthy, but sedentary, seniors had normal 24-hour ambulatory blood pressures, although as previously detailed, arterial elastance increased in sedentary seniors compared with fit seniors.<sup>4</sup> However, this increased arterial elastance did not result in a higher end-systolic volume index at rest in sedentary seniors (Table 1). This finding argues that at least at these levels of afterload, the healthy aged heart has sufficient contractile reserve to overcome modest increases in arterial elastance. This maintenance of ventricular contractile function in the face of increased afterload was shown in these subjects from their preserva-

tion or even augmented preload recruitable stroke work, as previously reported.<sup>4</sup>

The difference between baseline end-systolic volumes and equilibrium volumes derived from previously published compliance curves were also similar between the 2 groups of seniors ( $-17.9 \pm 19$  ml in sedentary subjects,  $-18.6 \pm 30$  in fit subjects,  $p = 0.95$ ), suggesting equivalent degrees of utilization of diastolic suction and consistent with their equivalent propagation velocity of early mitral inflow data.<sup>18</sup> Thus, despite dramatic differences in both arterial elastance and static chamber compliance, both senior cohorts had similar contractile function and Doppler parameters of ventricular relaxation. These data suggest that myocyte senescence rather than long-term adaptation of the heart to increased arterial elastance is the major pathophysiological process responsible for altered myocardial relaxation with aging.

**Physiologic differences between ventricular compliance and relaxation:** The impact of endurance training on static ventricular compliance and dynamic relaxation is strikingly disparate. Compliance appears to be a property that can be more readily influenced by changes in physical activity. The alteration in pressure–volume relation of the ventricle appears to be fluid in response to conditioning/deconditioning.<sup>19</sup> In contrast, relaxation appears more resistant to changes in physical activity in humans.

The training response discrepancy of these 2 diastolic components may reflect their fundamental physiological and mechanistic differences. Ventricular compliance is determined largely by the relation between relatively compliant cardiac muscle and comparatively less compliant connective tissue/extracellular matrix, which is regulated by a sizable collection of signaling pathways, including cytokines, angiotensin, and natriuretic peptides.<sup>20,21</sup> In this regard, aging has prominent effects on the balance between myocyte volume and extracellular matrix. For example, the aged heart has substantially fewer myocytes than young hearts, accompanied by significant increases in volume fraction of collagen.<sup>22</sup> In rats, this decreased number of myocytes is associated with increases in the size of each individual myocyte, which may be adaptive.<sup>22,23</sup> Increased myocardial fibrosis also was noted in senescent animal hearts and otherwise healthy, but aged, human hearts. These areas of interstitial fibrosis, predominantly in the subendocardium of the left ventricle, increase with age and may be related to the loss of myocyte volume as “replacement fibrosis.”<sup>22,24</sup> Connective tissue content and collagen cross-linking also decreased with endurance training.<sup>25,26</sup> Furthermore, exercise appears to have an antiapoptotic effect on myocytes that likely enhances chamber distensibility because myocytes are less stiff than collagen.<sup>26,27</sup> Thus, it is possible that lifelong endurance training may maintain myocyte volume and cell size and limit the development of fibrosis, thus preserving cardiac compliance.

In contrast, myocardial relaxation is predominantly influenced by myocyte calcium handling, but appears to be species specific. For example, endurance training enhances calcium uptake and improves myocyte excitation–contraction coupling in rats, but not in canines.<sup>28,29</sup> We speculate that key myocyte calcium regulators such as sarcoplasmic

or endoplasmic reticulum calcium (SERCA2) ATPase and phospholamban in human myocytes may be similarly resistant to exercise training. Aging of these systems may be the underlying cause of impaired myocardial relaxation with senescence.

**Clinical implications:** Findings of the present study have important clinical implications for the aging population. For example, the elderly appear to be particularly predisposed to the development of congestive heart failure because this diagnosis is the leading cause of hospitalizations in those >65 years of age.<sup>30</sup> In seniors, the underlying substrate for heart failure, particularly with preserved ejection fraction, may in part be the age-associated changes in both compliance and relaxation that we described. Although these mechanical changes may not be enough to explain the cause of congestive heart failure with preserved systolic function by themselves, superimposed conditions such as diabetes, coronary disease, or hypertension may tip the scale toward increased filling pressures and pulmonary congestion. Moreover, the development of a rapid irregular pattern of electrical activity, such as atrial fibrillation, may have particularly severe consequences for hearts that are relatively stiff and relax slowly. Regular lifelong physical activity may be expected to preserve cardiac compliance (in the absence of co-morbid conditions) and thereby decrease left ventricular end-diastolic pressure when relaxation is complete. However, given the data presented here, it should not be expected to completely normalize myocardial relaxation.

**Conclusions:** We show that in contrast to chamber compliance, age-associated changes in Doppler measures of ventricular relaxation were only minimally influenced by lifelong endurance training. These findings are present across a broad range of physiological filling pressures. These data show that changes in ventricular compliance with senescence are strongly influenced by physical activity, whereas changes in ventricular relaxation are more likely specific to cardiac senescence and may result from alterations in cardiac regulatory proteins that occur with aging.

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