Left ventricular diastolic filling and systolic function of young and older trained and untrained men

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Baldi, James C., Kendra McFarlane, Helen C. Oxenham, Gillian A. Whalley, Helen J. Walsh, and Robert N. Doughty. Left ventricular diastolic filling and systolic function of young and older trained and untrained men. J Appl Physiol 95: 2570–2575, 2003. First published July 25, 2003; 10.1152/japplphysiol.00441.2003.—Aging is associated with impaired early diastolic filling: however, the effect of endurance training on resting diastolic function in older subjects is unclear. Heart rate and ventricular loading conditions affect mitral inflow velocity measured by Doppler echocardiography; therefore, tissue Doppler imaging of mitral annular velocity, which is relatively preload independent, was combined with mitral inflow velocity and maximal oxygen consumption (VO2max) in young (20–35 yr) and older (60–80 yr) trained and untrained men to determine whether endurance training is associated with an attenuation of age-associated changes in diastolic filling. As expected, VO2max was higher in trained men (P < 0.01) and lower in older men (P < 0.01). Peak early mitral inflow velocity (E) and early-to-late mitral inflow velocity ratios were lower in older vs. young men (P < 0.01); however, there was no training effect (P > 0.05). Peak early mitral annular velocity (E′) was higher and peak late mitral annular velocity (A′) was lower in young vs. older men (P < 0.01). A significant interaction effect was found for A′, E′/A′, and peak systolic mitral annular velocity (S′). Training was associated with lower A′ in young and higher A′ in older men. S′ was greater in trained vs. untrained older men (P < 0.05), but it was similar in trained and untrained young men. These findings suggest that early diastolic filling is not affected by training in older men, and the effect of training on A′ and S′ is different in young and older men.

diastolic function; aging; endurance training; maximal aerobic capacity (maximal oxygen consumption), tissue Doppler imaging

AGING IS ASSOCIATED WITH AN increase in left ventricular stiffness (7), which results in a prolongation of isovolumic relaxation time (9) and incomplete relaxation of the ventricle during early diastolic filling (25). Numerous investigations have shown that peak early diastolic mitral inflow velocity (E) is reduced in aged individuals (2, 10, 17, 18, 34). To maintain ventricular filling and stroke volume, peak late diastolic filling velocity (A) increases with age (2, 17), resulting in an age-associated decline in the early-to-late mitral inflow velocity ratio (E/A) ratio (17).

Aerobic fitness is associated with improved early diastolic function in young healthy subjects. Young trained athletes have increased E (20) and E/A (8, 11, 22, 26) compared with their nontrained counterparts. However, evidence to suggest that training has a similar effect in older athletes, or that training attenuates the normal age-associated decrease in E/A is inconclusive (8, 10, 28, 31). Endurance training has been shown to improve peak filling rate in older healthy men (19), and the E/A has been shown to be higher in highly trained older endurance athletes compared with age-matched healthy controls (8). However, Fleg et al. (10) showed that E and E/A were similar in well-trained athletes and nonathletes aged 52–76 yr, but lower than young untrained controls, suggesting that prolonged exercise training did not affect the age-associated impairment in E.

Discrepancies regarding the effects of exercise training on diastolic function in older subjects may be explained by limitations in the measurement of mitral inflow velocity using pulsed Doppler echocardiography or radionuclide imaging. E/A is inversely proportional to resting heart rate (13, 16) and is altered by acute increases in ventricular preload (5, 29). Thus previously reported increases in E/A in athletes may be partially explained by training-related reductions in resting heart rate (8, 31) and increases in ventricular preload resulting from increased plasma volume (6, 15). In addition, although mild impairment of diastolic function decreases E/A, more progressive impairment results in a higher E/A, termed “pseudonormal” filling, making interpretation of E/A alone difficult.

The echocardiographic assessment of diastolic function can be improved with tissue Doppler imaging (TDI), which can be used to measure the velocity of the mitral annulus during early (E′) and late (A′) diastole and during systole (S′). This method is affected less by changes in heart rate or preload (5, 29) than conventional mitral Doppler measures. Furthermore, the

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pseudonormalization that can be seen with mitral Doppler inflow velocities does not occur. Instead, E’ decreases progressively as diastolic filling progresses from normal to restrictive filling, resulting in a continuous reduction in E’-to-A’ ratio (E’/A’-') (29). Finally, the E-to-E’ ratio (E/E’) correlates with left ventricular filling pressure better than other echocardiographic measures of diastolic function, thus providing additional information regarding diastolic filling of the left ventricle (24). This investigation utilized TDI in combination with pulsed Doppler transmitral flow velocities in healthy young and older trained and untrained men to determine the effects of age and training on systolic and diastolic filling parameters.

METHODS

Subjects and preliminary testing. Subjects were recruited through advertisements in campus and community publications, local sport organizations, and published results of running competitions. After preliminary screening tests (see below), 20 older untrained men (60–80 yr), 19 older male athletes, 13 young untrained men (20–30 yr), and 13 young male athletes (yt) were enrolled into the study. Untrained subjects had not taken part in regular endurance training in the previous 2 yr. Several participated in recreational sports, but none participated in endurance sports such as running, cycling, or rowing. Trained individuals competed regionally, nationally, or internationally in endurance sports and had trained regularly for a minimum of 2 yr (older men 20.6 ± 9.3 yr, younger men 5.7 ± 2.8 yr). The study protocol was approved by the University of Auckland Human Subjects Review Committee, and all subjects provided informed, written consent.

During their first appointment, subjects filled out a medical history questionnaire and reviewed their medical history with a study investigator. Older subjects also received a physical examination. On the same visit, body composition was determined by a technician who was blinded to training history questionnaire and reviewed their medical history. After a 5- to 10-min warm-up at 50–60% of maximum heart rate, speed was increased in 1-min stages such that oxygen consumption (VO2) increased between 3 and 5 mL·kg⁻¹·min⁻¹ until the subject reached a “fast run.” Thereafter, grade was increased by 1–2% to achieve similar increases in VO2. With the use of this protocol, the total duration of all but one test (13 h and 30 min) was between 6 and 12 min. VO2 was measured every 15 s during exercise by using a Schiller CS-100 metabolic analyzer. The mean of the two highest consecutive VO2 values was defined as VO2 max. A test was accepted as a “true maximum” if any two of the following criteria were achieved: 1) a plateau in VO2, defined as the lack of increase in VO2 with an increase in work rate; 2) achievement of age-predicted maximal heart rate (220 – age); and 3) a respiratory exchange ratio of >1.10.

Echocardiography. Echocardiograms were obtained by using an Advanced Technology Laboratories HDI 5000 Ultra-sound machine (Bothell, WA). All images were obtained by trained cardiac sonographers according to a standard protocol and were recorded on videotape and acquired digitally for analysis (NovaMicrosonics, Eastman Kodak, Allendale, NJ). One investigator, blinded to group allocation, completed all measurements offline. Analyses used leading edge-to-leading edge method for M-mode measurements. For each parameter, three measurements were taken and an average value recorded.

M-mode recordings in the parasternal long-axis view were used to determine left atrial size, intraventricular septum (IVS) and left ventricular posterior wall (PW) thickness, left ventricular end-diastolic dimension (LVEDD), and left ventricular end-systolic dimensions (LVESD). Left ventricular mass (LVM) was calculated by using the American Society of Echocardiography formula and was indexed to body surface area (LVMI).

Mitral valve pulsed wave Doppler (PWD) recordings were obtained from the apical four-chamber view with a 5-mm PWD sample volume placed distal to the mitral annulus, between the mitral leaflets. The interrogation beam was aligned with mitral flow (14) and measured at the end of the expiratory phase of normal respiration. These images were used to determine E, A, E/A, and E-wave deceleration time (DT). Isovolumic relaxation time (IVRT), which was defined as the time interval between aortic valve closure and the onset of mitral inflow, was recorded with the sample volume in the left ventricular outflow tract. This was positioned to give a clear signal incorporating the aortic valve closing signal and the onset of mitral flow.

TDI. TDI of the mitral annulus was obtained from the apical four-chamber view by placing a 5-mm sample volume in the interventricular septum close to the mitral annulus. E’, A’, and E’/A’ were determined from these images. E’/A’ was also derived (21).

Statistical analysis. A 2 × 2 factorial analysis of variance was used to test for effects of age (young vs. older) and fitness level (trained vs. untrained). Where interaction effects were found, post hoc analysis was performed by using Bonferroni’s test. A P value of 0.05 was considered significant.

RESULTS

Physical characteristics. The physical characteristics of the subjects are shown in Table 1. The older men were shorter and lighter than their young counterparts. Body mass index was similar between age groups, but it was lower in trained vs. untrained subjects. Body fat and fat-free mass were affected by age and training status. Older men had higher body fat and lower fat-free mass than younger men, and trained men had lower body fat and higher fat-free mass than untrained men. Resting heart rate was lower in trained vs. untrained subjects, and systolic blood pressure was lower in young vs. older and trained vs. untrained men. Diastolic blood pressure was unaffected by age or training status.
V̇O₂ max was lower in older vs. young and untrained vs. trained men whether expressed as liters per minute or as milliliters per kilogram per minute. The age-differences in V̇O₂ max were similar between untrained and trained groups, and there was no interaction effect, suggesting aerobic training induces similar improvements in V̇O₂ max regardless of age. Similarly, maximum heart rate was lower in older vs. young and trained vs. untrained men. Training was also associated with lower maximal heart rate in both young and older subjects.

Echocardiography. Table 2 summarizes the echocardiographic characteristics of the subjects. Left atrial dimension was not affected by age or training. LVM and LVMI were greater in trained vs. untrained men; however, there was no age or interaction effect. There was no age or training effect on IVS or PW thickness; however, training was associated with a 20% increase in IVS thickness in older men and a 5% decrease in young men (P < 0.05). A similar trend was seen in PW thickness, which was 22% greater in older trained vs. untrained men but was similar in young trained and untrained men (P = 0.14). Training was associated with greater LVEDD and LVESD in both age groups, and these dimensions were lower in older men. Fractional shortening was greater in older men and was unaffected by training status.

### Table 2. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Older</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untrained</td>
<td>Trained</td>
<td>Untrained</td>
</tr>
<tr>
<td>Age, yr</td>
<td>24.8 ± 2.8</td>
<td>26.2 ± 3.7</td>
<td>65.7 ± 3.7</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.79 ± 0.08</td>
<td>1.93 ± 0.05</td>
<td>1.75 ± 0.04</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>83.4 ± 11.5</td>
<td>81.1 ± 8.6</td>
<td>77.5 ± 10.3</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.95 ± 0.57</td>
<td>2.03 ± 0.12</td>
<td>1.96 ± 0.15</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.2 ± 4.2</td>
<td>24.2 ± 3.1</td>
<td>25.1 ± 2.6</td>
</tr>
<tr>
<td>BF, %</td>
<td>22.9 ± 8.3</td>
<td>12.3 ± 5.5</td>
<td>26.6 ± 6.4</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>62.8 ± 8.8</td>
<td>70.6 ± 7.9</td>
<td>50.9 ± 4.6</td>
</tr>
<tr>
<td>Resting HR, beats/min</td>
<td>72.0 ± 4.2</td>
<td>56.5 ± 7.1</td>
<td>62.5 ± 8.5</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>125.9 ± 2.6</td>
<td>122.4 ± 2.8</td>
<td>139.5 ± 8.1</td>
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<tr>
<td>Diastolic BP, mmHg</td>
<td>76.8 ± 2.0</td>
<td>77.1 ± 2.3</td>
<td>78.3 ± 17.1</td>
</tr>
<tr>
<td>V̇O₂ max, ml·kg⁻¹·min⁻¹</td>
<td>46.5 ± 8.6</td>
<td>69.9 ± 9.48</td>
<td>31.5 ± 5.9</td>
</tr>
<tr>
<td>V̇O₂ max, l/min</td>
<td>3.8 ± 0.8</td>
<td>5.4 ± 1.1</td>
<td>2.5 ± 0.4</td>
</tr>
<tr>
<td>Maximum HR, beats/min</td>
<td>194.3 ± 5.2</td>
<td>183.7 ± 7.3</td>
<td>164.6 ± 15.2</td>
</tr>
</tbody>
</table>

Values are means ± SD. BSA, body surface area; BMI, body mass index; BF, body fat; FFM, fat-free mass; HR, heart rate; BP, blood pressure; V̇O₂ max, maximal oxygen consumption.

Table 2. Echocardiographic measurements

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Older</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untrained</td>
<td>Trained</td>
<td>Untrained</td>
</tr>
<tr>
<td>LA, mm</td>
<td>35.3 ± 3.8</td>
<td>38.7 ± 3.8</td>
<td>34.7 ± 8.6</td>
</tr>
<tr>
<td>IVS, mm</td>
<td>8.00 ± 0.44</td>
<td>7.60 ± 0.34</td>
<td>7.14 ± 0.39</td>
</tr>
<tr>
<td>PW, mm</td>
<td>8.29 ± 0.47</td>
<td>8.30 ± 0.45</td>
<td>7.30 ± 0.30</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>54.0 ± 4.8</td>
<td>58.2 ± 2.2</td>
<td>49.6 ± 4.2</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>37.7 ± 3.8</td>
<td>40.4 ± 2.7</td>
<td>31.6 ± 3.9</td>
</tr>
<tr>
<td>LVM, g</td>
<td>158.7 ± 54.0</td>
<td>183.3 ± 38.6</td>
<td>155.0 ± 6.4</td>
</tr>
<tr>
<td>LVMI</td>
<td>79.4 ± 9.7</td>
<td>90.2 ± 16.1</td>
<td>78.4 ± 24.3</td>
</tr>
<tr>
<td>FS, %</td>
<td>31.7 ± 4.9</td>
<td>30.4 ± 4.3</td>
<td>36.9 ± 5.7</td>
</tr>
<tr>
<td>E, cm/s</td>
<td>72.6 ± 8.9</td>
<td>72.6 ± 12.2</td>
<td>52.0 ± 10.9</td>
</tr>
<tr>
<td>A, cm/s</td>
<td>46.5 ± 7.4</td>
<td>40.4 ± 9.2</td>
<td>56.3 ± 11.2</td>
</tr>
<tr>
<td>E/A</td>
<td>1.59 ± 0.29</td>
<td>1.81 ± 0.35</td>
<td>1.92 ± 0.34</td>
</tr>
<tr>
<td>DT, ms</td>
<td>170.1 ± 33.6</td>
<td>160.8 ± 34.7</td>
<td>153.8 ± 26.0</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>58.5 ± 8.4</td>
<td>55.5 ± 8.9</td>
<td>88.9 ± 20.4</td>
</tr>
</tbody>
</table>

Values are means ± SD. LA, left atrium size; IVS, interventricular septum thickness; PW, posterior wall thickness; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVM, left ventricular mass; LVMI, left ventricular mass index; FS, fractional shortening; E, peak early mitral inflow velocity; A, peak late mitral inflow velocity; DT, E-wave deceleration time; IVRT, isovolumic relaxation time.
TDI. Comparing older men with younger men, E’ was lower (7.46 ± 1.46 vs. 11.78 ± 2.56 cm/s; P < 0.001), A’ was greater (11.38 ± 1.61 vs. 8.33 ± 1.81 cm/s; P < 0.001), and S’ was lower (7.68 ± 1.33 vs. 9.34 ± 1.59 cm/s; P < 0.05). There was no training or interaction effect on E’ (P > 0.05). Training was associated with different and opposite changes in A’ and S’ in the two age groups (interaction effect; P < 0.05). A’ was lower in young trained vs. untrained men (7.64 ± 1.55 vs. 8.98 ± 1.85 cm/s) but was greater in older trained vs. untrained men (11.91 ± 1.62 vs. 10.87 ± 1.48 cm/s). Similarly, S’ was greater in older trained vs. untrained men (8.31 ± 1.39 vs. 7.06 ± 0.94), whereas young trained and untrained men had similar S’ values (9.16 ± 1.50 vs. 9.61 ± 1.79 cm/s). Similarly, E’/A’ was higher in trained vs. untrained young men (1.57 ± 0.36 vs. 1.41 ± 0.56) but was not different between trained and untrained older men (0.65 ± 0.12 vs. 0.66 ± 0.13; P interaction < 0.05). These data are summarized in Fig. 1. E/E’ was lower in young men compared with older men (6.57 ± 1.58 vs. 7.36 ± 1.78; P < 0.05), but it was not affected by training status.

**DISCUSSION**

The data from this study have shown, as expected, that older men weigh less, have lower maximal heart rate, and lower \( V_{O2\text{max}} \) than younger men. In both groups, sustained endurance training was associated with lower body mass index, lower resting heart rate and blood pressure, higher fat-free mass, higher \( V_{O2\text{max}} \), and larger left ventricular dimensions and LVM. However, despite the utilization of contemporary echocardiographic methods, the study did not find conclusive evidence to show that endurance training was associated with an attenuated age-related decline in early diastolic filling. Instead, these results suggest that the effects of endurance training on resting diastolic and systolic function are different in young and older men.

Left ventricular early diastolic filling decreases progressively after the age of 20 yr (28). Reduced rates of Ca\(^{2+}\) uptake by the sarcoplasmic reticular Ca\(^{2+}\) pump [sarco(endo)plasmic reticulum Ca\(^{2+}\)-ATPase (SERCA2)] during early diastole (4, 12, 30) and increased left ventricular stiffness, which may result from altered deposition of myocardial collagen (23, 33), are likely mechanisms for the reduction in early diastolic filling that accompanies aging. In senescent rats, training increases sarcoplasmic reticular Ca\(^{2+}\) uptake (32), attenuates the age-associated changes in collagen deposition (33), and attenuates diastolic dysfunction (2). Whereas SERCA2a content is reduced in aged human myocardium (4), the effect of endurance training on SERCA2 content or rates of Ca\(^{2+}\) sequestration have not been examined in humans, and studies using noninvasive methods, such as Doppler echocardiography to measure a training effect on diastolic function in older men are equivocal (2, 8, 10). Our finding that E/A was similar between trained and untrained older men but lower than young men is consistent with some previous findings (10) and also is consistent with an age-related decline in E/A (8, 10, 31). However, others have shown that highly trained older men have higher E/A than untrained older men and that these values are comparable to untrained young men (8).

E/A is inversely proportional to heart rate (13), and thus changes in heart rate should be considered when interpreting diastolic filling properties. The difference in resting heart rates of the trained and untrained older men in the present study (56 vs. 63 beats/min) was less than that observed in the study by Douglas et al. (8), which reported marked changes in E/A with training in older men (trained 53 beats/min vs. untrained 74 beats/min). Thus their report of...
changes in mitral inflow velocity recordings may have reflected differences in resting heart rate rather than changes in myocardial relaxation. Training-induced alterations in preload should also be considered when interpreting Doppler measurements because preload impacts on the assessment of mitral filling. Hagberg et al. (15) recently showed that endurance-trained older men have higher total blood volume and end-diastolic volume indexes than older nontrained men. Acute volume expansion increases E and E/A measured by Doppler echocardiography (5, 29); thus changes in E/A may be affected by differences in the capacity and loading conditions of the left ventricle. This point is clearly illustrated in data from a 6-mo training study in healthy older men that showed that training increased peak diastolic filling velocity; however, this difference was not significant when filling velocity was indexed to left ventricular end-diastolic volume, which was also greater after training (19).

Our data, obtained with the use of TDI, a relatively preload independent measure of diastolic function (5, 29), indicate that the age-associated impairment of early diastolic filling is not affected by endurance training and show that exercise training is associated with different diastolic filling parameters in young and older men. E' was lower in older men, but it was similar between trained and untrained subjects in both age groups. However, A' was higher in older trained men and lower in young trained men relative to their age-matched healthy controls, suggesting that aerobic fitness is associated with increased late diastolic filling in older men. These findings may indicate that increased late left ventricular filling is a normal compensatory adaptation in aged men, which is augmented by endurance training.

Although it is impossible to identify the mechanism of reduced early diastolic filling from our data, indirect measures suggest that elevated LV filling pressure may have contributed to the impairment of early diastolic filling in older men. E/E', which is correlated with left ventricular filling pressure (24), was significantly higher in older vs. young subjects and was unaffected by training status. However, the levels of E/E' in this study were within the normal range (i.e., nonpathological) for all groups; thus the relevance of this finding is unclear. Furthermore, the correlation between E/E' and ventricular filling pressure has been established in patients referred for cardiac catheterization (24), which may not reflect the loading conditions of healthy individuals. These findings do, however, suggest that long-term endurance training does not alter the diastolic ventricular pressure changes associated with advancing age.

It is possible that the increase in S', and an associated increase in systolic intracellular Ca2+, acted to “delay” early diastolic relaxation in older trained men. Ca2+ channel blockade, which reduces systolic contractility by decreasing intracellular Ca2+, reduces IVRT and improves early diastolic filling in older men (27). Thus the increased S' in the trained older men might be expected to reduce early diastolic relaxation. However, both E and E' were similar between older trained and untrained men, suggesting that the duration of the Ca2+ transient was similar in these two groups. Furthermore, young men had similar S' compared with older trained men but had greater E and E'. SERCA2a activity is higher in younger individuals (4), which may result in more rapid early diastolic relaxation despite increases in intracellular Ca2+ during systole. The fact that older trained and untrained men had similar rates of early diastolic filling despite increased systolic velocity in the trained men may indicate that endurance training increases both systolic Ca2+ and the rate of Ca2+ uptake in older men, as has been shown in animals (32).

Our data are not sufficient to infer functional significance to the morphological differences between groups. Nonetheless, it is interesting that in older men, training was associated with greater IVS, which was similar to changes in S' and A'. However, in young men, training was associated with no change in IVS and S' and a decrease in A'. It is possible that the increased IVS and PW thickness (P = 0.14) in trained older men are associated with improvements in systolic function. Bouvier et al. (1) also reported increased ventricular wall thickness and improved systolic function in trained older men compared with untrained controls at rest and during exercise. However, longitudinal studies involving endurance training of older sedentary individuals have not reported significant increases in left ventricular wall thickness (8), LVMI (19), or systolic function (8), which may suggest that something other than training caused these changes.

In conclusion, the combination of Doppler and TDI indexes of systolic and diastolic function shows that prolonged training is not associated with an attenuation of the age-associated impairment in early diastolic function. In fact, our data show that S' and A' are greater in trained older men. These findings may indicate that the age-associated changes in resting diastolic function are augmented by endurance training, whereas impairments in systolic function are prevented. Furthermore, it suggests that endurance training is associated with different changes in diastolic function in young and older men.

DISCLOSURES

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