Endurance Exercise Training Augments Diastolic Filling at Rest and During Exercise in Healthy Young and Older Men

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Background. Diastolic filling at rest is altered markedly with advancing age. Whether exercise training can improve diastolic filling at rest or during exercise in either healthy older or healthy young men has not been determined. The purpose of this study was to determine if 6 months of aerobic exercise training improves diastolic filling.

Methods and Results. Radionuclide diastolic filling parameters were measured at rest and during exercise in 14 older (age, 60 to 82 years) and 17 young (age, 24 to 32 years) rigorously screened healthy males before exercise training and in 13 older and 11 young men after 6 months of endurance exercise training. Diastolic filling rates were expressed in two ways, as absolute milliliters of blood (mL·s⁻¹·m⁻²) and normalized to the end-diastolic volume. At baseline, the peak early filling rates were lower in the older group compared with the young group as expressed in absolute milliliters of blood (older, 85±7 mL·s⁻¹·m⁻²; young, 173±10 mL·s⁻¹·m⁻²; P=.0001) and in end-diastolic volume per second (1.66±0.11 versus 2.55±0.08, P=.0001), whereas the peak atrial filling rates were greater in absolute milliliters of blood (85±5 versus 56±7 mL·s⁻¹·m⁻², P=.003) and in end-diastolic volume per second (1.70±0.12 versus 0.80±0.06, P=.0001). During exercise, at any given heart rate, the older group had a lower peak filling rate than the young group. Also, at peak exercise, the single peak filling rate was decreased in the older group in mL·s⁻¹·m⁻² (384±19 versus 565±36 mL·s⁻¹·m⁻², P=.0002) and in end-diastolic volume per second (6.01±0.25 versus 7.91±0.28 end-diastolic volume per second, P=.0001). Six months of intensive aerobic exercise training had similar effects in the old and young groups overall. Maximal oxygen consumption increased 19% (ANOVA training effect, P=.0001) and echocardiographic left ventricular mass increased 8% (ANOVA training effect, P=.002). Training increased the resting peak early filling rate in absolute milliliters of blood by +14% (ANOVA training effect, P=.02). During exercise, the peak early or single peak filling rate at any given heart rate was increased. At peak exercise, the single peak filling rate was increased by 14% in mL·s⁻¹·m⁻² (ANOVA training effect, P=.0004). The only age-related differential effect of training was on the peak atrial filling rate in end-diastolic volume per second, which decreased by 27% in the older group but was unchanged in the young (+5%) (ANOVA young versus older, P=.001). The independent predictors of a greater maximal oxygen consumption by multivariate analysis were a higher peak exercise heart rate, a greater resting peak early filling rate, the exercise trained state, and a younger age.

Conclusions. Healthy older men have reduced early diastolic filling at rest and during exercise compared with young men. Endurance exercise training enhances early diastolic filling at rest and during exercise in both the old and the young. Training reduces the elevated resting atrial filling rate in the old, whereas the young were unchanged. The training-induced augmentation of early diastolic filling at rest and during exercise may be an important adaptation to allow an increase in stroke volume at rest and an increase in stroke volume, cardiac output, and maximal oxygen consumption during exercise. (Circulation 1993;88:116-126)

Key Words • diastole • aging • exercise • radionuclide angiography

One of the hallmarks of cardiac aging is altered resting diastolic filling, characterized by a decreased peak early filling rate, an increased peak atrial filling rate, a decreased early-atrial ratio, and a prolonged time constant of relaxation. The age-associated differences in diastolic filling parameters are unrelated to left or right ventricular filling pressures, as these are unaltered with age in healthy subjects. The age-associated alterations in diastolic filling may con-
tribute to the 35% to 40% prevalence of subjects with congestive heart failure who have normal systolic function.\textsuperscript{10,11}

Although pathological hypertension, as occurs with hypertension, aortic stenosis and hypertrophic cardiomyopathy, impairs diastolic filling,\textsuperscript{12-15} physiological hypertrophy that occurs as the result of exercise training does not impair diastolic filling.\textsuperscript{8,16-22} Animal studies have shown an improvement in diastolic function with exercise training.\textsuperscript{23-28} Cross-sectional studies in humans have suggested that exercise training may improve diastolic filling.\textsuperscript{8,17,18,21,22,29} Whereas longitudinal training studies in the young have shown no change\textsuperscript{30} or an improvement in diastolic filling.\textsuperscript{31} However, there are no longitudinal studies in healthy elderly subjects, which would be of particular interest, because of the altered diastolic filling that occurs with aging.\textsuperscript{1,8,22}

The first purpose of this study was to determine the effects of aging on diastolic filling at rest and during exercise in healthy men. The second purpose was to determine whether 6 months of aerobic exercise training improves diastolic filling parameters in healthy elderly and young men. Our results document that endurance training enhances diastolic filling at rest and during exercise in healthy older and young men.

**Methods**

**Subjects**

The study population consisted of 14 older (mean age, 68 years; range, 60 to 82 years) and 17 young (mean age, 28 years; range, 24 to 32 years) healthy untrained male volunteers. Exclusion criteria included current smoking, hypertension, chronic use of any medication, any metabolic or cardiovascular disease, exercise-limiting arthritis or pulmonary disease, or regular exercise. All subjects were healthy with unremarkable medical histories, physical examinations, resting ECGs, complete blood counts, serum chemistry screens including cholesterol, and normal M-mode, two-dimensional and Doppler echocardiograms. Subjects underwent Bruce protocol maximal exercise testing, which included post-exercise and redistribution tomographic thallium imaging in the older subjects. No young subjects were excluded on the basis of their exercise test results; however, 22 older subjects were excluded because of an abnormal exercise test.

Seventeen young and 14 older men entered the study and were evaluated before exercise training. Eleven of the young and 13 of the older subjects completed 6 months of exercise training and were evaluated after exercise training. All studies were conducted at least 36 hours after the last episode of exercise training to avoid the acute effects of exercise. The study was approved by the Human Subjects Committee of the University of Washington, and all subjects gave informed written consent.

**Exercise Training**

The 6-month training program consisted of walking, jogging, and bicycling (10 minutes of stretching, 10 minutes of warmup, 45 minutes of exercise, and 10 minutes of cool down) four to five times per week in a closely supervised and monitored setting. Training began at 50% to 60% of heart rate reserve and increased to 80% to 85% by the fourth month. Maximal oxygen consumption was measured using a maximal Bruce protocol exercise treadmill test.

**Study Protocol**

On the morning of the study the subjects reported to the laboratory after a small breakfast and abstinence from caffeine. Red blood cells were labeled with $^{99m}$Tc using the modified in vivo method of Callahan et al.\textsuperscript{32} Radionuclide ventriculograms were acquired during supine rest (a 15-million count and a 2-minute resting acquisition), with the legs moderately elevated in the exercising position (2 minutes), and during the last 2 minutes of each exercise stage. Symptom-limited supine bicycle exercise was performed starting at a work rate of 200 kpm and increasing 200 kpm every 3 minutes until exhaustion. Radionuclide ventriculograms were acquired during the last 2 minutes of each exercise stage. The last completed stage was considered to be the symptom-limited peak work rate.

**Data Collection and Processing**

**Echocardiography.** Resting echocardiograms were performed with an Ultramark 8 (Advanced Technology Laboratories, Bothell, Wash) or Hewlett Packard 500 (Andover, Mass) ultrasound machines. The left ventricular mass index was measured by the method of Devereaux and Reichek.\textsuperscript{33}

**Radionuclide ventriculography.** Radionuclide left ventriculograms were performed using ECG-synchronized blood pool imaging at rest and during the final 2 minutes of each exercise stage. Resting images were acquired for 15 million counts, and exercise images were for 2 minutes (20 ms per frame) using a GE300 A/M camera (Milwaukee, Wis) with a high sensitivity parallel hole collimator, a software zoom of 1.5, a 64×64-pixel 16-bit word mode image, a 20% energy window, a beat rejection window of ±20% using dynamic arrhythmia filtration,\textsuperscript{34} and a forward/backward reconstruction of the time-activity curve\textsuperscript{35} as previously described.\textsuperscript{36} The first 30% of the time-activity curve is from the forward acquisition, whereas the last 10% of the time-activity curve is from the backward acquisition. The intermediate portion of the time-activity curve (30% to 90%) is ramped from both the forward and backward acquisitions. Radionuclide ventriculograms were processed as previously described in our laboratory.\textsuperscript{36} The images were temporally and spatially smoothed. Automated regions of interest were obtained for each 20-ms image throughout the cardiac cycle. These regions of interest were applied to the unfiltered (raw) data to obtain a time-activity curve. The time-activity curve was smoothed with a four-harmonic Fourier transform. The peak early filling rate and the peak atrial filling rate were derived from the first derivative of the time-activity curve along with the RR interval, diastolic filling period, time to peak early filling rate, and time to peak atrial filling rate measured from end systole. At heart rates of more than 95 beats per minute, the peak early filling rate and the peak atrial filling rate typically merge into a single peak.\textsuperscript{34} When this occurred, the single peak filling rate and the time to single peak filling rate were measured.

Numerous methods have been used to normalize diastolic filling parameters. We chose to express the radionuclide filling rates by two different methods. First, the peak early filling rate was normalized to the end-diastolic volume (end-diastolic volume per second). Be-
cause exercise training is known to increase the resting end-diastolic volume, changes in diastolic filling may be
masked by changes in the normalizing parameter (end-
diastolic volume). The second method we used expressed
the filling parameters as an absolute filling rate in mL·s⁻¹·m⁻², similar to previous studies using con-
trast ventriculography.⁷ The end-diastolic volume
was measured by a radionuclide count-based technique pre-
viously developed and validated against contrast ven-
triculography in our laboratory.⁶ We normalized for
differences in body surface area, as previous investiga-
tors have shown that the absolute peak early filling rate
is related to body surface area⁴¹:

\[
\text{PEFR(ML} \cdot \text{s}^{-1} \cdot \text{m}^{-2}) = \frac{\text{PEFR(EDV/s)} \cdot \text{EDV(mL)}}{\text{BSA(m}^2)},
\]

where PEFR is peak early filling rate, EDV is end-diastolic
volume, and BSA is body surface area. The peak
atrial filling rate and the single peak filling rate also
were calculated by the above two methods (end-diastolic
volume per second and mL·s⁻¹·m⁻²).

The test-retest reproducibility (±1 SEE) comparing
two supine resting acquisitions (15 million count and 2
minute) were for heart rate (±2.8 beats per minute),
ejection fraction (±3.4 EF units), end-diastolic volume
index (±7.4 mL/m²), end-systolic volume index (±3.9
mL/m²), stroke volume index (±4.6 mL/m²), cardiac index
(±0.27 L·min⁻¹·m⁻²), peak atrial filling rate (±0.34
end-diastolic volume per second and ±23 mL·s⁻¹·m⁻²),
peak early filling rate (±0.03 end-diastolic volume per
second and ±30 mL·s⁻¹·m⁻²), and peak ejection rate
(±0.32 end-diastolic volume per second and ±24
mL·s⁻¹·m⁻²). There were no significant differences by
paired \( t \) test between the two supine resting radionuclide
acquisitions for any measurement, and the mean differ-
ences were less than 1% for all variables.

Statistical analysis. All data are expressed as
mean±SEM. The results for the older subjects are pre-
sented first, and for the young, second. The young and
older groups before exercise training were compared by an
unpaired \( t \) test. The effects of exercise training were
compared by a two-way ANOVA for repeated measures,
which provides two \( P \) values. The first \( P \) value, training
effect, represents the effects of training on the entire
group, combining the young and the older subjects as a
single group, similar to a paired \( t \) test. The second \( P \) value,
training effect * young/older, represents the interaction of
training and age. This statistic indicates any differential
training effects in the young and old subjects. All percent
differences and changes are for the mean values. Univari-
ate linear regression was performed to determine predi-
ctors of maximal oxygen consumption using left ventricular
mass, peak atrial filling rate (rest), peak early filling rate
(rest), single peak filling rate (peak exercise), and the
following variables at rest and peak exercise: end-diastolic
volume index, end-systolic volume index, stroke volume
index, cardiac index, ejection fraction, systolic blood pres-
sure, diastolic blood pressure, mean arterial pressure,
heart rate, and peak ejection rate index. Univariate vari-
able with \( P \leq .10 \) were entered in a stepwise multivariate
linear regression to determine the independent predictors
of maximal oxygen consumption. Statistical significance
was established at the level of \( P \leq .05 \).

Results

The results are presented in four sections: as the
overall difference between the young and the older
groups before exercise training, as the effects of training
with both the young and older groups combined as a
single group, and as the differential effects of training in
the older and young groups. Last, the results of the univari-
ate and multivariate analyses are presented.

Comparison of Older and Young Groups Before
Exercise Training

General. Body surface areas were similar in the two
groups (Table 1). The supine resting blood pressures
were higher in the older subjects (all \( P \leq .01 \)). The
maximal oxygen consumption was 34% less (\( P < .0001 \))
and the peak work rate was 29% lower (\( P < .0001 \)) in the
older subjects. The left ventricular mass index was not
significantly different between groups (\( P = .09 \)).

Resting diastolic filling parameters. The older subjects
had evidence for age-associated alterations in diastolic
filling (Table 1 and Fig 1). The resting RR interval,
diastolic filling period, time to peak atrial filling, and
time to peak early filling were similar in the older and
young subjects. The peak early filling rate was decreased
in the older group compared with the young, as mea-
sured by both end-diastolic volume per second (−35%,
\( P < .0001 \)) and mL·s⁻¹·m⁻² (−51%, \( P < .0001 \)). The peak
atrial filling rate was increased in the older sub-
jects when expressed in end-diastolic volume per second
(+112%, \( P < .0001 \)) and in mL·s⁻¹·m⁻² (+52%,
\( P = .003 \)).

Diastolic filling parameters during exercise. During
peak exercise, the elderly had a lower peak heart rate,
which resulted in a longer diastolic filling period (Table 1).
The time to single peak filling at peak exercise was
similar in the two groups. The single peak filling rate
normalized to the end-diastolic volume was 24% less in
the older subjects (\( P \leq .0001 \)), and the absolute single
peak filling rate at peak exercise (mL·s⁻¹·m⁻²) was
32% less in the older subjects (\( P = .0002 \)) (Fig 1).

The peak filling rates during exercise are shown in Fig
2. At the 600 km per hour and the peak work rate, all subjects
had only a single peak filling rate, but at rest and lower
work rates (200 and 400 km), most subjects had
separate peak early filling rate and peak atrial filling
rate. In these cases, the peak early filling rate was used
for Fig 2. As shown in Fig 2, the peak filling rate
increased linearly with heart rate in both the older and
the young subjects. However, at any given heart rate
during exercise, the peak filling rate was lower in the
older group.

Effects of Exercise Training on the Entire Group

General. Exercise training increased the maximal oxy-
gen consumption by 19% (+7±1 mL·kg⁻¹·min⁻¹ [Table
2] training effect, \( P < .0001 \)), whereas the peak work rate
increased 26% (+242±29 kpm training effect, \( P < .0001 \)).
As would be expected with training, the resting heart rate
decreased 14% (\( P < .0001 \)), the end-diastolic volume
increased 13% (\( P = .001 \), and the resting cardiac index was
unchanged. Training increased the left ventricular mass
index by 8% (+7±2 g/m², \( P = .02 \)). There was a slight
decrease in body surface area.
Table 1. Radionuclide Diastolic Filling Parameters in Older and Young Men Before Exercise Training

<table>
<thead>
<tr>
<th></th>
<th>Young (n=14)</th>
<th>Older (n=17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>General comparisons</td>
<td></td>
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</tr>
<tr>
<td>Body surface area (m²)</td>
<td>2.08±0.05</td>
<td>1.97±0.03</td>
<td>.08</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>123±2</td>
<td>133±2</td>
<td>.003</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>75±2</td>
<td>83±2</td>
<td>.006</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>91±1</td>
<td>99±2</td>
<td>.0006</td>
</tr>
<tr>
<td>Maximum VO₂ (mL·kg⁻¹·min⁻¹)</td>
<td>43.5±1.2</td>
<td>28.8±1.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>85±5</td>
<td>98±5</td>
<td>.09</td>
</tr>
<tr>
<td>Peak work rate (kpm)</td>
<td>1106±49</td>
<td>771±35</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Resting diastolic filling parameters

Heart rate (bpm) | 59±1 | 63±3 | NS
RR interval (ms) | 1007±27 | 966±41 | NS
DFP (ms) | 664±23 | 629±30 | NS
TPEF (ms) | 159±6 | 179±18 | NS
TPAF (ms) | 587±24 | 551±26 | NS
PEFR (EDV/s) | 2.55±0.08 | 1.66±0.11 | <.0001
PAFR (EDV/s) | 0.80±0.06 | 1.70±0.12 | <.0001
PEFR (mL·s⁻¹·m⁻²) | 173±10 | 85±7 | <.0001
PAFR (mL·s⁻¹·m⁻²) | 56±7 | 85±5 | .003

Peak exercise diastolic filling parameters

Heart rate (bpm) | 169±3 | 134±4 | <.0001
RR interval (ms) | 333±6 | 430±11 | <.0001
DFP (ms) | 147±5 | 177±8 | .003
TSPF (ms) | 107±5 | 117±7 | NS
SPFR (EDV/s) | 7.91±0.28 | 6.01±0.25 | <.0001
SPFR (mL·s⁻¹·m⁻²) | 565±36 | 384±19 | .0002

LVMI, left ventricular mass index; DFP, diastolic filling period; TPEF, time to peak early filling; TPAF, time to peak atrial filling; PEFR, peak early filling rate; PAFR, peak atrial filling rate; TSPF, time to single peak filling; SPFR, single peak filling rate; EDV, end-diastolic volume.

Resting diastolic filling parameters. The bradycardic effect of exercise training resulted in a marked increase in the diastolic filling period, time to peak atrial filling, and RR interval (all P<.0001), whereas the time to peak early filling was unchanged (Table 3 and Fig 3). The peak early filling rate normalized to the end-diastolic volume and diastolic filling increased 16% (P=.002). Exercise training resulted in a 14% increase in the absolute resting peak early filling rate in mL·s⁻¹·m⁻² (+18±7 mL·s⁻¹·m⁻², P=.02), whereas the absolute peak atrial filling rate (mL·s⁻¹·m⁻²) was unchanged.

Diastolic filling parameters during exercise. The peak heart rate, diastolic filling period, time to single peak filling rate, and the single peak filling rate normalized to

![Bar graphs](https://example.com/bar_graphs.png)

Fig 1. Bar graphs of resting peak atrial filling rate (PAFR), resting peak early filling rate (PEFR) and the peak exercise single peak filling rate (SPFR) of older and young groups compared before exercise training by two different methods: normalized to the end-diastolic volume (EDV per second) (left) and as an absolute peak filling rate (mL·s⁻¹·m⁻²) (right).
the end-diastolic volume were unchanged with training (Table 4 and Figs 3 and 4). However, training resulted in a 14% increase in the absolute single peak filling rate in mL·s⁻¹·m⁻² (+66±20 mL·s⁻¹·m⁻², P=.004). Exercise training increased the peak early or single peak filling rate at rest and during exercise at all matched heart rates (Fig 4).

**Differential Effects of Exercise Training on the Older and Young Subjects**

**General.** The older subjects had a slight decrease in body surface area due to a small decrease in weight, whereas the young were unchanged with exercise training (Table 2, training * young/older, P=.01). Exercise training induced similar increases in both groups for the maximal oxygen consumption (older, +6.2±1.3 mL·kg⁻¹·min⁻¹ [+21%]; young, +7.5±1.2 mL·kg⁻¹·min⁻¹ [+17%]). There was a lesser increase in the peak work rate in the older group if expressed as an absolute work rate increase (older, +184±27 kpm; young, +309±49 kpm; training * young/older, P=.03) but not if expressed as a percent increase from the preexercise work rate (older, +24%; young, +28%; P=.35). The training-induced bradycardia and the increase in the left ventricular mass index were similar in both groups.

**Resting diastolic filling parameters.** The bradycardic effect of exercise training on diastolic time intervals was similar in both groups (Table 3). Exercise training had differential training effects on the peak atrial filling rate in the two groups. The peak atrial filling rate (end-diastolic volume per second) decreased 27% (−0.47±0.10 end-diastolic volume per second) in the older subjects after training but was unchanged (+5%) in the young (training * young/older, P=.001). By post hoc paired t test, the 27% decrease in the older subjects was highly significant (P=.0006), whereas the 5% increase in the young was not significant (P=NS). A similar trend was
TABLE 2. General Comparison of Older (n=13) and Young (n=11) Men Before and After Exercise Training

<table>
<thead>
<tr>
<th></th>
<th>Preexercise training</th>
<th>Postexercise training</th>
<th>Training effect</th>
<th>Training effect young/older</th>
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</thead>
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<tr>
<td><strong>Body surface area (m²)</strong></td>
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<tr>
<td>Young</td>
<td>2.04±0.07</td>
<td>2.04±0.07</td>
<td>.006</td>
<td>.01</td>
</tr>
<tr>
<td>Older</td>
<td>1.95±0.03</td>
<td>1.92±0.03</td>
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<tr>
<td><strong>Maximum VO₂ (mL·kg⁻¹·min⁻¹)</strong></td>
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<td></td>
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<tr>
<td>Young</td>
<td>44.5±1.5</td>
<td>52.1±1.9</td>
<td>&lt;.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Older</td>
<td>28.9±1.3</td>
<td>35.1±1.0</td>
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<td></td>
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<tr>
<td><strong>LVMI (g/m²)</strong></td>
<td></td>
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</tr>
<tr>
<td>Young</td>
<td>81.9±5.5</td>
<td>90.0±5.9</td>
<td>.002</td>
<td>NS</td>
</tr>
<tr>
<td>Older</td>
<td>98.1±5.9</td>
<td>103.0±7.5</td>
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<tr>
<td><strong>Peak work rate (kpm)</strong></td>
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<tr>
<td>Young</td>
<td>1109±73</td>
<td>1418±87</td>
<td>&lt;.0001</td>
<td>.03</td>
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<tr>
<td>Older</td>
<td>784±36</td>
<td>969±50</td>
<td></td>
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</tr>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>59±1</td>
<td>52±2</td>
<td>&lt;.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Older</td>
<td>63±3</td>
<td>53±2</td>
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</tbody>
</table>

LVMI, left ventricular mass index.

noted when the peak atrial filling rate is expressed in mL·s⁻¹·m⁻² with an 8% decrease (−7±5 mL/m²) in the older subjects and a 9% increase (6±7 mL/m²) in the young; however, this difference did not reach statistical significance (training * young/older, P=.13). This decrease in the peak atrial filling rate in the older

TABLE 3. Resting Radionuclide Diastolic Filling Parameters in Older (n=13) and Young (n=11) Men Before and After Exercise Training

<table>
<thead>
<tr>
<th></th>
<th>Preexercise training</th>
<th>Postexercise training</th>
<th>Training effect</th>
<th>Training effect young/older</th>
</tr>
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<tbody>
<tr>
<td><strong>RR interval (ms)</strong></td>
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<td></td>
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<tr>
<td>Young</td>
<td>985±23</td>
<td>1129±36</td>
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<tr>
<td>Older</td>
<td>957±43</td>
<td>1143±48</td>
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<tr>
<td><strong>DFP (ms)</strong></td>
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<tr>
<td>Young</td>
<td>642±21</td>
<td>771±35</td>
<td>&lt;.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Older</td>
<td>623±31</td>
<td>768±45</td>
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<tr>
<td><strong>TPEF (ms)</strong></td>
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<tr>
<td>Young</td>
<td>151±6</td>
<td>149±6</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Older</td>
<td>182±20</td>
<td>198±14</td>
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<tr>
<td><strong>TPAF (ms)</strong></td>
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<tr>
<td>Young</td>
<td>569±23</td>
<td>687±34</td>
<td>&lt;.0001</td>
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<tr>
<td>Older</td>
<td>546±28</td>
<td>668±42</td>
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<tr>
<td><strong>PEFR (EDV/s)</strong></td>
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</tr>
<tr>
<td>Young</td>
<td>2.53±0.11</td>
<td>2.60±0.11</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Older</td>
<td>1.68±0.12</td>
<td>1.68±0.07</td>
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<tr>
<td><strong>PAFR (EDV/s)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>0.85±0.07</td>
<td>0.89±0.08</td>
<td>.002</td>
<td>.001</td>
</tr>
<tr>
<td>Older</td>
<td>1.71±0.07</td>
<td>1.25±0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PEFR (mL·s⁻¹·m⁻²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>184±13</td>
<td>199±18</td>
<td>.02</td>
<td>NS</td>
</tr>
<tr>
<td>Older</td>
<td>86±8</td>
<td>106±8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PAFR (mL·s⁻¹·m⁻²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>65±10</td>
<td>71±10</td>
<td>NS</td>
<td>.13</td>
</tr>
<tr>
<td>Older</td>
<td>85±6</td>
<td>78±6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DFP, diastolic filling period; TPEF, time to peak early filling; TPAF, time to peak atrial filling; PEFR, peak early filling rate; EDV, end-diastolic volume. Values are mean±SEM.
Subjects is unlikely to be explained by differences in the heart rate, as the decrease in the heart rate was similar in both groups.

Both groups had a similar increase in the peak early filling rate measured in mL·s⁻¹·m⁻² (older, +20 ± 6 mL·s⁻¹·m⁻² +23%; young, +15 ± 14 mL·s⁻¹·m⁻² +8%); training effect, P = .02; training * young/older, P = NS), whereas the peak early filling rate expressed in end-diastolic volume per second was unchanged (older, +0%; young, +3%; training * young/older, P = NS).

**Diastolic Filling Parameters during Exercise.** The peak heart rate, diastolic filling rate, and single peak filling rate normalized to the end-diastolic volume were unchanged with training in either group (Table 4). However, the peak exercise single peak filling rate increased similarly in both groups measured in mL·s⁻¹·m⁻² (older, +79 ± 27 mL·s⁻¹·m⁻² +21%; young, +50 ± 32 mL·s⁻¹·m⁻² +9%); training, P = .0004; training * young/older, P = NS).

Thus, the major age-associated differential training effect was a selective decrease in the older subjects in the pretraining elevated resting peak atrial filling rate (measured in end-diastolic volume per second).

**Correlates of Maximum Oxygen Consumption.**

Univariate analysis was performed using all pretraining (n = 31 including the seven subjects who did not complete training) and posttraining (n = 24) subjects (Table 5 and Fig 5). The strongest univariate predictors for a greater maximum oxygen consumption were a higher peak heart rate (r = .79), a younger age (r = .78), a higher peak cardiac index (r = .76), a higher resting peak early filling rate, peak exercise single peak filling rate, and peak ejection rate whether measured in mL·s⁻¹·m⁻² (r = .74, r = .65, r = -.69) or in end-diastolic volume per second (r = .68, r = .62, r = -.59). The resting peak atrial filling rate was not significantly correlated with maximum oxygen consumption whether measured in mL·s⁻¹·m⁻² (r = .14, P = NS) or in end-diastolic volume per second (r = .27, P = NS).

Multivariate analysis was performed using all univariate variables with P ≤ 0.1. The multivariate independent predictors (P < 0.05) of a greater maximal oxygen consumption were a higher peak heart rate, a higher resting peak early filling rate (mL·s⁻¹·m⁻²), exercise training, and a younger age (Table 6).

**Discussion.**

There are three major findings of this study. First, aging in healthy men is associated with marked alterations of diastolic filling parameters both at rest and during exercise. Second, exercise training augments early diastolic filling at rest and during exercise in both older and young men. This augmentation of diastolic filling during exercise may contribute to the increased maximal stroke volume, cardiac output, and maximal oxygen consumption after exercise training. Third, diastolic filling parameters (resting peak early filling rate or peak exercise single peak filling rate) correlate with the maximal oxygen consumption in univariate and multivariate analyses, suggesting that diastolic performance may determine, in part, maximal exercise capacity.

**Aging.**

Numerous studies have shown marked age-associated alterations of diastolic filling parameters. The present study confirms those previous studies and extends them in that we measured diastolic filling both at rest and during exercise. The marked age-associated abnormalities of resting diastolic filling parameters persisted throughout exercise. At any given heart rate, the peak early filling rate and the single peak filling rate were reduced in the older group (Fig 3). Thus, healthy elderly men have markedly impaired diastolic filling at rest, which persists during exercise.
TABLE 5. Univariate Analysis of Maximal Oxygen Consumption Combining Preexercise (n=31) and Postexercise (n=24) Training Data at Rest and at Peak Exercise

<table>
<thead>
<tr>
<th>Maximal oxygen consumption (mL·kg⁻¹·min⁻¹)</th>
<th>Correlation coefficient</th>
<th>P at entry into model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak exercise heart rate (bpm)</td>
<td>+.79*</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-.78*</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Peak exercise cardiac index (L·s⁻¹·m⁻²)</td>
<td>+.76*</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Resting PEFR (mL·s⁻¹·m⁻²)</td>
<td>+.74*</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Peak exercise PER (mL·s⁻¹·m⁻²)</td>
<td>-.69*</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Resting PEFR (EDV/s)</td>
<td>+.68*</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Peak exercise SFPR (mL·s⁻¹·m⁻²)</td>
<td>+.65*</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Peak exercise SFPR (EDV/s)</td>
<td>+.62*</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Peak exercise PER (EDV/s)</td>
<td>-.59*</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Resting stroke volume index (mL/m²)</td>
<td>+.54*</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Resting PER (mL·s⁻¹·m⁻²)</td>
<td>-.52*</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Peak exercise stroke volume index (mL/m²)</td>
<td>+.50*</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Peak exercise ejection fraction (EF units)</td>
<td>+.50*</td>
<td>&lt;.0001</td>
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<tr>
<td>Resting end-diastolic volume index (mL/m²)</td>
<td>+.50*</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Resting diastolic blood pressure (mm Hg)</td>
<td>-.50†</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Resting cardiac index (L·s⁻¹·m⁻²)</td>
<td>+.42†</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Peak exercise systolic blood pressure (mm Hg)</td>
<td>-.41†</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Resting end-systolic volume index (mL/m²)</td>
<td>+.38†</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Resting systolic blood pressure (mm Hg)</td>
<td>-.34†</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Resting heart rate (bpm)</td>
<td>-.33†</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Exercise training (pretraining, 0; posttraining, 1)</td>
<td>+.32‡</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Resting PAFR (EDV/s)</td>
<td>+.27</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Peak exercise end-diastolic volume index (mL/m²)</td>
<td>+.24</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Peak exercise end-systolic volume index (mL/m²)</td>
<td>-.20</td>
<td>&lt;.0001</td>
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<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>-.19</td>
<td>&lt;.0001</td>
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<tr>
<td>Peak exercise diastolic blood pressure (mm Hg)</td>
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<tr>
<td>Resting ejection fraction (EF units)</td>
<td>+.15</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Resting PAFR (mL·s⁻¹·m⁻²)</td>
<td>+.14</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Resting PER (EDV/s)</td>
<td>+.03</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

PEFR, peak early filling rate; PAFR, peak atrial filling rate; SFPR, single peak filling rate; PER, peak ejection rate; EDV, end-diastolic volume.

*P≤.0001, †P≤.01, ‡P≤.05.

Postulated mechanisms for the age-associated alterations in diastolic filling include an increase in myocardial stiffness that is present in rats but may not be present in humans, an age-related increase in left ventricular mass, and an age-related increase in the time constant of relaxation. However, in humans, myocardial stiffness does not correlate with the peak early filling rate. In animals, there is an age-associated prolongation of the contraction duration, due mainly to a delayed relaxation of the aged myocardium. The mechanism of the prolonged contraction duration probably is due to an age-associated decrease in calcium uptake by the sarcoplasmic reticulum. Decreased mitochondrial fatty acid oxidation and cytochrome c oxidase also may play a role in the delayed relaxation.

Asynchronous myocardial contraction in the elderly also may contribute to the age-associated decrease in diastolic filling.

Diastolic Filling During Exercise

Diastolic filling during exercise has not been studied extensively in humans. Previous investigators have shown that the peak filling rate during exercise is related linearly to the heart rate in young subjects and that the elderly have a reduced peak filling rate at rest and during peak exercise. In our study, the peak filling rate was decreased in the older group at rest and at all work rates. The reduction in the peak filling rate in the older group at peak exercise is especially marked, probably due to the age-associated decrease in the maximal heart rate.

The increased diastolic filling during acute exercise presumably is secondary to an increased pressure gradient between the left ventricle and left atrium during early diastole. At submaximal exercise in dogs, the augmented diastolic filling is due to a marked downward shift of the early portion of the left ventricular pressure-volume curve (~3 to ~6 mm Hg), whereas the mean left atrial pressure is unchanged. The negative minimum left ventricular pressure (~1 to ~3 mm Hg) that occurs during submaximal exercise results in an increase in the transmural pressure gradient, creating a "diastolic suction" that augments early diastolic filling. This downward shift of the early portion of the left ventricular pressure-volume loop, "diastolic suction," that occurs during exercise presumably is due to enhanced sympathetic activation as similar results are seen with isoproterenol in humans or dobutamine in dogs, and ß-blockers will prevent the "diastolic suction" in dogs and eliminate age-related differences in diastolic filling during exercise in healthy young and older men. Although there is no increase in the left atrial pressure at submaximal exercise in dogs, at peak exercise in humans there is a small (+4 mm Hg) increase in the mean pulmonary capillary wedge pressure, which also would increase the transmural pressure gradient and tend to increase early diastolic filling. Thus, there are two potential mechanisms to augment diastolic filling during exercise: an increase in the "diastolic suction" of the left ventricle and an increase in the left atrial pressure. The relative contributions of these two mechanisms to increased ventricular filling during exercise in older and young subjects before and after exercise training are uncertain. The increased diastolic filling during exercise in dogs also is associated with a 25% to 40% decrease in the time constant of relaxation.

TABLE 6. Multivariate Analysis of Maximal Oxygen Consumption Combining Preexercise (n=31) and Postexercise (n=24) Training Data

<table>
<thead>
<tr>
<th>Maximal oxygen consumption (mL·kg⁻¹·min⁻¹)</th>
<th>P at entry into model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak heart rate (bpm)</td>
<td>0.135±0.055</td>
</tr>
<tr>
<td>Resting PEFR (mL·s⁻¹·m⁻²)</td>
<td>0.040±0.145</td>
</tr>
<tr>
<td>Training (preexercise, 0; postexercise, 1)</td>
<td>5.84±1.29</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.174±0.067</td>
</tr>
</tbody>
</table>

PEFR, peak early filling rate; Correlation coefficient, .90, intercept, 18.9; and SEE, ±4.5 mL·kg⁻¹·min⁻¹.
Exercise Training

Exercise training produced major effects on early diastolic filling with a 14% increase in the resting peak early filling rate and a 14% increase in the peak exercise single peak filling rate when expressed in mL·s⁻¹·m⁻².

Previous studies have shown that the physiological hypertrophy that occurs in young athletes is not associated with impaired diastolic filling. ¹⁷-²¹ Cross-sectional studies in humans have suggested that exercise training may improve diastolic filling in young subjects. ¹⁷,¹₈,²¹,²⁰ Longitudinal training studies in the young have shown either no change in diastolic filling measured by M-mode echocardiography or a 9% increase in the average early filling rate at rest. ³⁰ There are very little data on the effects of exercise training on diastolic filling in elderly subjects. Cross-sectional studies using Dopppler echocardiography have found that elderly athletes had a lower peak atrial filling velocity than a sedentary elderly group,⁶,²² similar to the 27% decrease in the peak atrial filling rate in the older group in our study after exercise training. There are no previous longitudinal studies in older subjects of the effects of exercise training at rest or during exercise.

Our longitudinal data in both young and older subjects, in which training increased left ventricular mass significantly, further confirm that physiological hypertrophy does not impair diastolic filling but rather is associated with an improvement of absolute early diastolic filling rates at rest and at all heart rates during exercise in both the young and the elderly. In addition, exercise training in the elderly resulted in a decreased atrial contribution to ventricular filling. The increase in diastolic filling at peak exercise may be one mechanism to provide a greater stroke volume and thereby a greater cardiac output and maximal oxygen consumption at peak exercise after exercise training.⁵³

Left ventricular diastolic filling is closely correlated with systolic function as measured by the ejection

Fig 4. - Plot of heart rate versus the peak filling rate at rest, 200 kpm, 400 kpm, 600 kpm, and peak exercise before and after exercise training combining the young and the older groups. At all matched heart rates, the peak filling rate is higher after exercise training.

Fig 5. - Scatterplot of maximal oxygen consumption before exercise training strongly correlated with the resting peak early filling rate and the peak exercise single peak filling rate.
fraction. Older subjects have normal ejection fractions at rest but a blunted increase during exercise and during β-adrenergic stimulation with isoproterenol compared with young subjects. Ehsani et al have shown that exercise training in older men can enhance left ventricular systolic function during exercise. Exercise training in young subjects may improve the echocardiographic fractional shortening response to isoproterenol. However, we found no change after exercise training in the age-related blunting of the chronotropic or inotropic response to isoproterenol. Thus, a training-induced augmentation in the left ventricular systolic response to β-adrenergic agonists probably is not necessary for the training-induced augmentation of diastolic filling parameters.

The mechanism of the improved ventricular filling after exercise training at rest and peak exercise in both the older and young subjects is uncertain. Studies in rats have shown that exercise training decreases the contraction duration due to a shortened relaxation time, improves the rate of decline of the left ventricular pressure (maximum −dP/dt, decreases the time constant of relaxation, increases calcium uptake by the sarcoplasmic reticulum, increases fatty acid oxidation, and increases cytochrome c oxidase levels. Thus, exercise training in rats results in improvements in most of the abnormalities that are thought to cause the age-associated alterations in diastolic function. The mechanisms by which exercise training results in these changes is uncertain.

Study Limitations

We did not use invasive methods to measure diastolic function as these were deemed inappropriate in a healthy asymptomatic population. Magorien et al have shown that the radionuclide peak early filling rate was strongly correlated with the active phase of diastolic relaxation (maximum −dP/dt, r = −.85) and with an increased left ventricular end-diastolic pressure (r = −.62) but was not correlated with the passive phase of diastolic filling (chamber stiffness, Kd, r = −.08). The increased diastolic filling during exercise is associated with a decrease in the time constant of relaxation, r = −.95. Thus, we cannot state with certainty that the changes in diastolic filling that occur with exercise training actually reflect an improvement in diastolic function or merely reflect differences in the loading conditions of the left ventricle. However, previous investigators have found exercise training induced no change in preload, as measured by right atrial and pulmonary capillary wedge pressure, at rest or during exercise, and we found no difference in afterload, estimated by mean arterial pressure, at rest or peak exercise (data not shown). We studied only men and thus our results may not be generalizable to healthy women, who predominate in the elderly population. We studied a relatively broad range of older subjects, which may mask age changes that can occur within an elderly group.

Diastolic filling parameters are very sensitive to the method used for normalization. The peak early filling rate in mL·s⁻¹·m⁻² probably is the best method to use when comparing the same individual during an intervention where the end-diastolic volume, heart rate, or ejection fraction may change (i.e., exercise, drugs, posture). The peak early filling rate, normalized to the end-diastolic volume, has significant limitations as a measure of diastolic filling as it is dependent on the heart rate, age, and ejection fraction. Thus, studies of diastolic filling probably should express the results by more than one method.

Conclusions

Healthy older men have markedly decreased early diastolic filling at rest and during exercise at all matched heart rates. Endurance exercise training enhances early diastolic filling at rest and during exercise in both the old and the young at all heart rates and also reduces the elevated resting peak atrial filling rate of the elderly. Both rest and exercise measurements of diastolic filling are relatively highly correlated with the maximal oxygen consumption, by both univariate and multivariate analyses, suggesting the potential importance of early diastolic filling in determining maximal oxygen consumption. The training-induced augmentation of early diastolic filling at rest and during exercise may be an important adaptation to allow an increase in stroke volume at rest and an increase in stroke volume, cardiac output, and maximal oxygen consumption during exercise.

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Endurance exercise training augments diastolic filling at rest and during exercise in healthy young and older men.
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