Gender differences in the decline in aerobic capacity and its physiological determinants during the later decades of life

Edward P. Weiss, Robert J. Spina, John O. Holloszy, and Ali A. Ehsani

1Section of Applied Physiology, Division of Geriatrics and Nutritional Sciences, and 2Cardiovascular Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri

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Weiss, Edward P., Robert J. Spina, John O. Holloszy, and Ali A. Ehsani. Gender differences in the decline in aerobic capacity and its physiological determinants during the later decades of life. J Appl Physiol 101: 938–944, 2006. First published February 23, 2006; doi:10.1152/japplphysiol.01398.2005.—We investigated the hemodynamic determinants of the age-associated decline in maximal oxygen uptake (V\textsubscript{O\textsubscript{2}}\text{max}) and the influence of gender on the decline in V\textsubscript{O\textsubscript{2}}\text{max} and its determinants in old and very old men and women. Sedentary, 60- to 92-yr-old women (n = 71) and men (n = 29), with no evidence of cardiovascular disease, underwent maximal treadmill exercise tests during which V\textsubscript{O\textsubscript{2}}\text{max} and maximal cardiac output (Q\textsubscript{max}) were determined. V\textsubscript{O\textsubscript{2}}\text{max} and age were inversely related in both women (−23 ± 2 ml·min\textsuperscript{-1}·yr\textsuperscript{-1}; P < 0.0001) and men (−57 ± 5 ml·min\textsuperscript{-1}·yr\textsuperscript{-1}; P < 0.0001). The absolute slope of the V\textsubscript{O\textsubscript{2}}\text{max} vs. age relationship was twofold steeper in men than in women (P < 0.0001). Q\textsubscript{max} was also inversely related to age in a gender-specific manner (women = −87 ± 25 ml·min\textsuperscript{-1}·yr\textsuperscript{-1}, P = 0.0009; men = −215 ± 50 ml·min\textsuperscript{-1}·yr\textsuperscript{-1}, P = 0.0002; P = 0.01 women vs. men). Age-related changes in maximal exercise arteriovenous oxygen content difference (a-V\textsubscript{D}O\textsubscript{2}) were marginally different (P = 0.08) between women (−0.12 ± 0.03 ml·dl\textsuperscript{-1}·yr\textsuperscript{-1}, P = 0.0003) and men (−0.22 ± 0.04 ml·dl\textsuperscript{-1}·yr\textsuperscript{-1}, P < 0.0001). Age-associated decreases in Q\textsubscript{max} and a-V\textsubscript{D}O\textsubscript{2} contributed equally to the declines in V\textsubscript{O\textsubscript{2}}\text{max} in both men and women. In the later stages of life, V\textsubscript{O\textsubscript{2}}\text{max}, Q\textsubscript{max}, and a-V\textsubscript{D}O\textsubscript{2} decrease with age more rapidly in older men than they do in older women. As a result, the gender differences dissipate in the later decades of life. Declines in Q\textsubscript{max} and a-V\textsubscript{D}O\textsubscript{2} contribute equally to the age-related decrease in V\textsubscript{O\textsubscript{2}}\text{max} in men and women.

METHODS

Subjects. Data for the present study were obtained from baseline tests performed on sedentary, nonsmoker subjects who were recruited for two exercise-training trials: one on 60- to 75-yr-old subjects (n = 56), and the other on 77- to 92-yr-old subjects (n = 44). For both studies, sedentary was defined as having not performed regular vigorous exercise of 20 min/day, 2 times/wk, over the 6 mo before screening. The physiological adaptations to training in both studies have been published (2, 4, 5, 15, 24). The Human Studies Committee at Washington University School of Medicine approved the studies, and subjects in both studies gave informed, written consent. None of the 60- to 75-yr-old participants had clinical evidence of heart disease, particularly coronary artery disease, as determined by clinical assessment and diagnostic exercise stress testing. Subjects were excluded if they had the following: 1) a history of coronary artery disease, 2) congestive heart failure, 3) aortic aneurysm, 4) insulin-dependent diabetes mellitus, 5) atrial fibrillation, 6) history of stroke, 7) self-reported history of hypertension, 8) if they were taking cardiac medications (i.e., beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers), or 9) if electrocardiographic evidence of myocardial ischemia (defined as >0.1 mV ST segment depression that is either horizontal or downsloping) occurred during the stress test. The second group, i.e., 77- to 92-yr-old subjects, consisted of subjects who had mild or moderate frailty (2, 4), as well as those who were not frail (5). All of the subjects had to be independent living and community dwelling, and the mildly to moderately frail participants all had some degree of difficulty performing activities of daily living, as has been described in detail previously (2). The rationale for including frail subjects is that frailty is an inherent characteristic of old age. The original enrollment criteria for the second group were different from those for the 60- to 75-yr-old subjects in that the presence of clinical evidence to study these issues in a large cohort of sedentary, older men and women. In an earlier study (19), our laboratory found that both determinants of V\textsubscript{O\textsubscript{2}}\text{max} (i.e., Q\textsubscript{max} and a-V\textsubscript{D}O\textsubscript{2}) were considerably lower in 60- to 70-yr-old men and women than in younger subjects. As an extension of these earlier findings, and because the number of people living to very old age is increasing rapidly, we focused on older, 60- to 92-yr-old men and women in the present study. We hypothesized that V\textsubscript{O\textsubscript{2}}\text{max} declines in older men and women as a result of age-related reductions in both Q\textsubscript{max} and a-V\textsubscript{D}O\textsubscript{2}. Furthermore, because there is a paucity of data comparing age-associated changes in maximal exercise capacity and cardiovascular function during maximal aerobic exercise in older men and women, we hypothesized that the age-related decline in V\textsubscript{O\textsubscript{2}}\text{max} is greater in men than in women, and that reductions in Q\textsubscript{max} and a-V\textsubscript{D}O\textsubscript{2} contribute to these declines in both men and women.
of cardiovascular disease and the use of cardiac medications were not exclusion criteria for the very old subjects. Therefore, to minimize the possibility of these confounding limitations for the present study, we applied the more rigorous exclusion criteria used previously for the 60- to 75-yr-old subjects and excluded the 77- to 92-yr-old subjects with clinical coronary artery disease and those who were taking cardiac medications. Because a higher proportion of the mild and moderately frail than the nonfrail subjects did not meet these criteria, and because severely frail individuals were screened out, the proportion of frail subjects in the 77- to 92-yr age range in this study may be lower than that in the general population. Among the 77- to 92-yr-old subjects, only 44 (32%) met the rigorous criteria listed above and were included in the present study. Therefore, data presented in this report are from 100 sedentary, asymptomatic, nonsmoker subjects.

Graded exercise test and VO2 max. VO2 max was determined by indirect calorimetry during a graded treadmill exercise test and as described previously (4, 15). Metabolic data were measured with a computer-interfaced system, including a dry gas meter (CD-4, Parkinson-Cowan), oxygen analyzer (S3-A, Applied Electrochemistry), CO2 analyzer (LB-2, Beckman), and 5 liter mixing chamber. Oxygen uptake (VO2) were determined noninvasively using closed-circuit acetylene rebreathing and the subject was monitored throughout the test. The incremental test started at a speed determined, during a warm-up period, to elicit ~70% of age-predicted maximum heart rate (HR max) and remained constant throughout the test while grade was increased by 1–2% every 1–2 min. The test continued until the subjects could no longer exercise due to exhaustion or until other conditions, such as ECG changes or development of symptoms, made it unsafe to continue. None of the subjects whose test was stopped because of cardiac symptoms or significant ECG changes was included in the present analyses. Peak respiratory exchange ratio (RER) was higher (P < 0.0001) in men (1.9 ± 0.01) than in women (1.3 ± 0.01). However, RER was not related to age in men (slope = 0.0011 ± 0.0018 RER units/yr, P = 0.55) or in women (slope = −0.0014 ± 0.0010 RER units/yr, P = 0.17), indicating that age did not affect the subjects’ ability to give maximal effort during the test.

Resting VO2. Cardiovascular function was assessed at a separate occasion, and at least 1 wk after the initial exercise test, another exercise test was performed to measure Q max, VO2 max, HR max, and maximal exercise blood pressures. Q max was determined noninvasively using closed-circuit acetylene rebreathing during treadmill exercise, as described in detail previously (25, 30). After the subjects performed a few minutes of warm-up exercise, the treadmill speed and grade were progressively increased to the lowest settings found to elicit VO2 max during the initial VO2 max test. In general, larger increments in speed and grade were used for subjects with greater fitness so that the duration of exercise before maximal exercise (~4–6 min) was not a function of fitness. This protocol allowed us to avoid the potentially confounding effect of test duration on measured Q max and maximum stroke volume (SV max) (17). VO2 was monitored continuously (as described above), and, when the VO2 was at or near the previously measured VO2 max value, blood pressure was measured by auscultation, and the subject was switched from the open-circuit VO2 measurement system to a closed-circuit rebreathing system containing a mixture of 0.5% C2H2, 10% He, 45% O2, and 44.5% N2 for measurement of cardiac output. End-tidal gas concentrations were monitored using a capillary sampling line attached to the mouthpiece and a Perkin-Elmer mass spectrometer (MGA 1100), which was interfaced to a computer. The calculation of cardiac output was based on the exponential decay of end-tidal C2H2 concentrations across 8–10 serial breaths. Tests in which HR max was <85% of age-predicted HR max (220 – age) were deemed submaximal (8) and were not included in the analyses for the present report. VO2 max and HR max values from the cardiac output test were slightly but not significantly lower than those measured in the initial VO2 max test (VO2 max: difference = 13 ± 10 ml/min, P = 0.20; HR max: difference = 1.6 ± 0.9 beats/min, P = 0.10). VO2 max, HR max, and maximal blood pressure data obtained from the cardiac output test were used for outcome analyses, since they were collected in the same test as the cardiac output data, and this made it possible to elucidate the mechanisms underlying the age- and gender-related differences in VO2 max, SV max, a-VO2 max, maximal exercise total peripheral resistance (TPR max), and maximal exercise mean blood pressure (MBP max) were calculated using standard equations, as described previously (25).

Statistics. Mixed-model analysis of variance was used to assess whether the rates of age-associated decline in VO2 max and its determinants were different between men and women (as indicated by an interaction between age and gender). Linear regression was used for analyses of relationships among quantitative variables. Error terms are presented as standard errors (SEs), unless noted otherwise. Analyses were performed at an alpha error rate of 0.05. SAS software (SAS version 8, SAS Institute, Cary, NC) was used for all analyses.

RESULTS

Subject characteristics. Characteristics of the subjects are presented in Table 1. The low VO2 max values reflect the older, sedentary state of the subjects. Although the men were slightly older than the women, on average, this difference was small relative to the wide age range in both groups. As would be expected, men were heavier, taller, and had a greater average VO2 max than women.

Age-associated decline in cardiovascular capacity: effects of gender. Inverse relationships between age and VO2 max were evident in both men (~57 ± 5 ml·min−1·yr−1; P < 0.0001) and women (~23 ± 2 ml·min−1·yr−1; P < 0.0001), but the slope of this relationship was twofold steeper (P < 0.0001) in men than in women (Fig. 1). The gender difference in the relationship between age and aerobic capacity was also evident when VO2 max was expressed relative to body weight (men: ~0.51 ± 0.08 ml·kg−1·min−1·yr−1; P < 0.0001; women: ~0.22 ± 0.04 ml·kg−1·min−1·yr−1; P < 0.0001; P = 0.0006 for comparison between men and women). We also analyzed VO2 max data as percentages of the estimated values for 60-yr-old men and women (where the estimated values for 60 yr olds were calculated from the regression equations depicted in Fig. 1A). Despite this adjustment to account for the higher starting values seen in men, the results were similar in that the slope of

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
<th>All Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>83</td>
<td>33</td>
<td>116</td>
</tr>
<tr>
<td>Age, yr</td>
<td>72 ± 8</td>
<td>76 ± 9*</td>
<td>73 ± 9</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>65.2 ± 11.9</td>
<td>82.7 ± 11.8*</td>
<td>70.4 ± 14.2</td>
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<td>Height, cm</td>
<td>160.6 ± 5.9</td>
<td>174.7 ± 5.3*</td>
<td>164.6 ± 8.5</td>
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<tr>
<td>BMI, kg/m2</td>
<td>25.3 ± 4.5</td>
<td>27.2 ± 3.7</td>
<td>25.9 ± 4.3</td>
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<tr>
<td>Resting HR, beats/min</td>
<td>74 ± 10</td>
<td>73 ± 11</td>
<td>74 ± 10</td>
</tr>
<tr>
<td>Resting SBP, mmHg</td>
<td>130 ± 21.4</td>
<td>134 ± 17</td>
<td>131 ± 20</td>
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<td>Resting DBP, mmHg</td>
<td>78 ± 10</td>
<td>79 ± 11</td>
<td>78 ± 10</td>
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<tr>
<td>Cholesterol, mg/dl</td>
<td>207 ± 47</td>
<td>225 ± 106</td>
<td>212 ± 68</td>
</tr>
<tr>
<td>LDL-C, mg/dl</td>
<td>122 ± 28</td>
<td>113 ± 27</td>
<td>121 ± 28</td>
</tr>
<tr>
<td>HDL-C, mg/dl</td>
<td>57 ± 13</td>
<td>45 ± 9*</td>
<td>53 ± 13</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>143 ± 82</td>
<td>152 ± 80</td>
<td>146 ± 82</td>
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<td>VO2 max, ml/min</td>
<td>1,232 ± 259</td>
<td>1,758 ± 542*</td>
<td>1,385 ± 433</td>
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<tr>
<td>VO2 max, ml·kg−1·min−1</td>
<td>19.1 ± 3.6</td>
<td>21.4 ± 6.3</td>
<td>19.7 ± 4.6</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of subjects. Lipid data are missing on 3 men and 4 women. BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; VO2 max, maximal oxygen uptake. *P ≤ 0.05 vs. women.
Normalizing Q˙max for body surface area (men: -1.32 ± 0.23%/yr, P < 0.0001; women -0.87 ± 0.23%/yr, P = 0.0003; P = 0.24 for comparison between men and women). Although SV during maximal exercise was greater in men than in women (94.0 ± 2.9 vs. 66.7 ± 1.8 ml, respectively; P < 0.0001), it was not related to age in women, men, or in the combined group (all P values ≥ 0.33) (Fig. 3). Normalization of SVmax for differences in body surface area decreased the magnitude of difference between men and women. However, the difference was still significant (47.3 ± 1.6 vs. 39.9 ± 0.9 ml/m² in men and women, respectively; P < 0.0001). An inverse relationship between age and HRmax was present for the group as a whole (−1.3 ± 0.2 beats·min⁻¹·yr⁻¹); however, this relationship was not significantly influenced by gender (P = 0.40) (Fig. 3).

Hemodynamic determinants of the decline in aerobic capacity. The independent contribution of each hemodynamic determinant of the age-associated decline in V˙O₂ max was quantified by calculating V˙O₂ max values that should have resulted from differences in one hemodynamic factor while holding the value(s) for the other factor(s) constant (V˙O₂ max = Qmax × a-vDo₂). For example, to determine how much of the observed −57 ml·min⁻¹·yr⁻¹ slope in V˙O₂ max in the men was due to the relationship between age and V˙O₂ max was still steeper (P = 0.03) in men (−2.1 ± 0.2%/yr; P < 0.0001) than in women (−1.5 ± 0.2%/yr; P < 0.0001) (Fig. 1).

There was a gender-specific, inverse relationship between age and Qₑ max in these older subjects, with men showing a steeper (P = 0.01) slope than women (men: −215 ± 50 ml·min⁻¹·yr⁻¹, P = 0.0002; women: −87 ± 25 ml·min⁻¹·yr⁻¹, P = 0.0009) (Fig. 2). The gender difference in the age vs. Qₑ max slopes was still evident (P = 0.03) after normalizing Qₑ max for body surface area (men: −95 ± 26 ml·min⁻¹·m⁻²·yr⁻¹, P = 0.001; women: −35 ± 14 ml·min⁻¹·m⁻²·yr⁻¹, P = 0.02). When Qₑ max was expressed in relative terms as a percentage of the estimated Qₑ max for 60 yr olds (using the same approach as described above for V˙O₂ max), men: −1.25 ± 0.29%/yr, P = 0.0003; women: −0.77 ± 0.22%/yr, P = 0.009), the gender difference in the slopes for the relationships between age and Qₑ max was no longer significant (P = 0.23, Fig. 2).

a-vDo₂ and age were inversely related (men: −0.22 ± 0.04 ml·dl⁻¹·yr⁻¹, P < 0.0001; women: −0.12 ± 0.03 ml·dl⁻¹·yr⁻¹, P = 0.0003). The aging effect in men tended to be greater than that in women (P = 0.08; Fig. 3).
AERobic capacity and its determinants in aging

Fig. 3. Associations between age and arteriovenous oxygen content difference (a-vDO2; A), maximum heart rate (HRmax; B), and maximum stroke volume (SVmax; C). Solid circles and solid lines = men; open circles and dashed lines = women. *P ≤ 0.05 for slope vs. zero. †P ≤ 0.05 for slope in men vs. slope in women.

age-related differences in Qmax, the relationship between age, and the product of the observed Qmax values and a fixed value for a-vDO2, was assessed (where the fixed value for a-vDO2 was the estimated value for subjects in the midpoint of the age range, i.e., 76 yr). In men, the portion of the age vs. VO2max slope that was estimated to be exclusively due to reductions in Qmax was −28 ± 7 mL·min⁻¹·yr⁻¹ (P = 0.0002), and the portion that was estimated to be due to reductions in a-vDO2 was −30 ± 5 mL·min⁻¹·yr⁻¹ (P < 0.0001). This suggests that decreases in Qmax and a-vDO2 contribute equally to the age-related decline in VO2max. Likewise, in women, the portions of the slope for the age vs. VO2max relationship that were estimated to be exclusively due to Qmax (−10 ± 3 mL·min⁻¹·yr⁻¹, P = 0.0009) and to a-vDO2 (−12 ± 3 mL·min⁻¹·yr⁻¹, P = 0.0003) were similar. None of the age vs. VO2max relationships were attributable to age-related variation in SVmax in either men (P = 0.33) or women (P = 0.93). Therefore, the portions of the slopes in the age vs. VO2max relationships for men and women that were due to decreases in Qmax were entirely due to age-associated decrements in HRmax (men: −19 ± 4 mL·min⁻¹·yr⁻¹, P < 0.0001; women: −10 ± 1 mL·min⁻¹·yr⁻¹, P < 0.0001).

TPRmax was related to age in both men (8.4 ± 3.0 dyn·s⁻¹·cm⁻²·yr⁻¹, P = 0.01) and women (16.5 ± 3.1 dyn·s⁻¹·cm⁻²·yr⁻¹, P < 0.0001), and the slopes for the relationships in men and women were not statistically different (P = 0.12). In contrast, men and women were different (P = 0.003) with respect to the relationship between age and MBPmax. In women, we found a positive relationship between age and MBPmax (0.6 ± 0.2 mmHg/yr, P = 0.0006), while in men, MBPmax was not associated with age (P = 0.18).

Discussion

The purpose of the present study was, first, to obtain information regarding the physiological basis for the reduction in VO2max after the age of 60 yr in sedentary men and women, and to assess the relative contribution of cardiac output and a-vDO2 to the deterioration of VO2max in advancing age. Second, we sought to determine whether gender influences the age-associated decline in VO2max after the age of 60 yr and to explore the physiological basis for gender-related differences. Results from the present study provide evidence that, in 60- to 92-yr-old subjects, the age-related decrease in VO2max is attributable to decrements in both Qmax and a-vDO2 and that HRmax is solely responsible for the decline in Qmax. Since the age-associated decline in Qmax was accompanied by an age-related increase in TPRmax in both men and women, MBPmax did not decline with age, and even increased with age in women. Another important finding of the present study is that, although the rate of age-associated decline in VO2max, Qmax, and maximal a-vDO2 is greater in men than in women, the relative contribution of Qmax and a-vDO2 to the decline in aerobic power appears to be similar for men and women.

Most previous studies have reported that the age-related decline in VO2max is attributable to reductions in both a-vDO2 and Qmax. a-vDO2 has been shown, unequivocally, to decrease with advancing age in 18- to 75-yr-old subjects (1, 14, 18, 19), and our findings in subjects as old as 92 yr are consistent with most other investigators (1, 11, 13, 14, 19) and show a significant decline in Qmax with increasing age. Furthermore, we did not observe any evidence that SVmax increases with age.
to compensate for the decrease in HR\textsubscript{max} and prevent a decrease in Q\textsubscript{max}.

The lack of an age-associated change in SV\textsubscript{max} reported in the present study may appear contradictory to a previous report from our laboratory (19) in which we found that 60- to 72-yr-old sedentary men and women had a lower SV\textsubscript{max} than 20 to 31 yr olds. One explanation is that the data from the earlier report reflect the changes in SV\textsubscript{max} that occur during the early and middle decades of adulthood, while data from the present study reflect changes that occur in the later decades of life. It is plausible, therefore, that SV\textsubscript{max} decreases with age until late adulthood, after which the decline in SV\textsubscript{max} ceases.

A greater age-associated decline in VO\textsubscript{2 max} in men, compared with women, has been reported by others (3, 7, 12, 13, 26, 29), and our findings confirm these previous reports. Furthermore, our data suggest that the decrease in VO\textsubscript{2 max} is likely to be accelerated after the age of 60 yr. Although men have higher VO\textsubscript{2 max} values than women through most of the adult lifespan, the greater age-associated decrements in VO\textsubscript{2 max} in men should eventually result in the elimination of this gender-specific difference in advanced age. In fact, based on our data, the regression lines for men and women intersect at age 94 yr, only slightly beyond the age of the oldest individuals in the present study. Our data show that both the greater decline in Q\textsubscript{max} and the greater decline in a-vDO\textsubscript{2} in men than in women account for the gender-specific difference in the rate at which VO\textsubscript{2 max} declines with advancing age. Most previous studies have reported the annual age-associated decline in VO\textsubscript{2 max} to be 24 to 35 ml\textcdot min\textsuperscript{-1}\textcdot yr\textsuperscript{-1} in sedentary men (12, 21, 22) and 13 to 16 ml\textcdot min\textsuperscript{-1}\textcdot yr\textsuperscript{-1} in sedentary women (12, 23, 28). These age-related declines are much slower than the respective 57 ± 5 and 23 ± 2 ml\textcdot min\textsuperscript{-1}\textcdot yr\textsuperscript{-1} decrements seen in the present study. One explanation for this apparent discrepancy is that we did not study young individuals, and many of the subjects in our study were older than those in the previous studies. The upper age range for the previous studies was 75–84 yr, and, furthermore, there were only a few subjects in the upper end of the age spectrum (12, 21–23, 28). In contrast, 31 of our 100 subjects were 80–92 yr of age. It is plausible, therefore, that the greater decline in aerobic capacity may reflect a greater proportion of very old subjects who, by virtue of their old age, had mild frailty and physical inactivity. Thus very old men and women may exhibit more rapid deterioration in physiological function than their younger counterparts.

The age-associated decline in VO\textsubscript{2 max} is commonly described as a fixed percent per decade (11, 19, 22, 23, 28, 29). Mathematically, this suggests that the absolute reduction in VO\textsubscript{2 max} per decade should progressively decrease as people age. Despite this premise that the absolute decline in VO\textsubscript{2 max} should decrease with increasing age, the comparison of our data on very old subjects with that reported in the literature for 20- to 84-yr-old subjects (12, 21–23, 28) suggests otherwise, i.e., the rate of age-associated decline in VO\textsubscript{2 max} increases with age rather than decreases. In support of this notion, a recent comparison of longitudinal changes in VO\textsubscript{2 max} among subjects from a wide age range (8) indicated that the 8-yr decline in VO\textsubscript{2 max} is much greater in men and women over 60 yr old (~50 and 24 ml\textcdot min\textsuperscript{-1}\textcdot yr\textsuperscript{-1}, respectively) than it is in 30–39 yr olds (~17 and 13 ml\textcdot min\textsuperscript{-1}\textcdot yr\textsuperscript{-1}, respectively).

The reason for the more rapid decline in VO\textsubscript{2 max}, Q\textsubscript{max}, and a-vDO\textsubscript{2} among men compared with women is not clear. One possibility is that the men decline at a greater rate, simply because they have greater absolute cardiovascular functional capacity to begin with. To address this possibility, we calculated VO\textsubscript{2 max}, Q\textsubscript{max}, and a-vDO\textsubscript{2} as percentages of the values that would be expected for the average 60-yr-old man and woman. Despite this normalization of men and women to a uniform starting value, the men still demonstrated a more rapid age-associated deterioration in VO\textsubscript{2 max} than women. In contrast, the declines in Q\textsubscript{max} and a-vDO\textsubscript{2}, when expressed relative to age 60-yr values, were no longer significantly different between men and women. Although the relative declines in Q\textsubscript{max} and a-vDO\textsubscript{2} are not statistically significantly different between men and women (P = 0.23 and P = 0.24, respectively), we may have lacked the statistical power to detect significance for these outcomes, since they are responsible for the age-related decline in VO\textsubscript{2 max}. It seems that at least some of the more rapid decline in maximal cardiovascular function in men is due to initially greater function, and some is due to other factors. One factor could be a greater age-associated decline in inotropic sensitivity to β-adrenergic agonist in men than in women, which is partly due to a greater β-adrenergic-stimulated increase in left ventricular systolic function in younger men than in younger women (31).

Another potential explanation for gender differences in the decline in cardiovascular function is that older men decrease their physical activity levels more than women as they age. Although we do not have leisure time physical activity data to assess this possibility in the present study, this explanation seems unlikely, since population-based data from the Minnesota Heart Survey suggest that women decrease their leisure time physical activity levels more than men (9). It is also important to recognize that the main type of physical activity that has a tangible effect on VO\textsubscript{2 max} is structured vigorous endurance exercise. Because the men and women in the present study were specifically selected as individuals who did not participate in endurance training, it is unlikely that differential changes in other, nonendurance-training activities between men and women could explain the gender differences in the rate of VO\textsubscript{2 max} decline. It has been reported that variations in habitual physical activity only account for ≤5% of the variation in VO\textsubscript{2 max} among elderly men and women (27).

Although the absolute age-related declines in VO\textsubscript{2 max}, a-vDO\textsubscript{2}, Q\textsubscript{max}, and HR\textsubscript{max} were greater in men than in women, we found that the age-associated reductions in Q\textsubscript{max} and a-vDO\textsubscript{2} contributed equally to the age-associated declines in VO\textsubscript{2 max} for men and women. Furthermore, the entire age-associated decline in Q\textsubscript{max} was attributable to decreases in HR\textsubscript{max} for both men and women. These data suggest that aging of the skeletal muscle and of the central cardiovascular system contribute equally to the decline in aerobic capacity with advancing age during the later stages of life and that this is true for both men and women.

The VO\textsubscript{2 max} values of individuals in the upper end of the age range studied were extremely low. In fact, the average VO\textsubscript{2 max} for the oldest two men and the oldest two women was only 971 and 820 ml/min (13.0 and 13.6 ml\textcdot kg\textsuperscript{-1}\textcdot min\textsuperscript{-1}), respectively. To put this into perspective, the energy expenditure required for these elderly subjects to stand statically (16) would require ~50% of VO\textsubscript{2 max}. This serious deficiency in cardiovascular function in very old men and women illustrates the importance of interventions known to increase VO\textsubscript{2 max}, such as exercise.
training, to delay the age at which cardiorespiratory fitness becomes so limiting that an individual can no longer function independently in activities of daily living.

Several limitations should be considered when interpreting the results of the present study. First, young subjects and those with clinical evidence of heart disease were not included in our study. The findings, therefore, are only applicable to individuals in the later decades of life who are free from clinical heart disease. Second, some of the older men and women had mild to moderate frailty, which may have affected the results. However, because the prevalence of physical frailty increases with age, the data on our oldest subjects more closely represent the elderly population than it would have if we had excluded all frail subjects. Third, although we specifically recruited individuals who did not perform habitual structured exercise, it is quite conceivable that the older subjects were less active in their daily living than the younger subjects, and this could have contributed to the decline in aerobic capacity, independent of the effects of aging per se. Another limitation is that undetected coronary disease may have been present in some participants, despite the relatively thorough screening process used in the present study (6). Because the frequency of occult heart disease increases with age and is more common in older men than in older women (6), coronary disease might have been partly responsible for the more rapid decline in VO2 max seen in our older subjects, compared with younger subjects, and it might have also been partly responsible for the greater rate of decline seen in men than in women. Lastly, we used a cross-sectional design, which has inherent limitations related to the inability to draw all of the subjects from the same population. While it cannot be known if this limitation affected our results, it is noteworthy that our cross-sectional estimates of the rate of decline in the present study are similar to those recently reported from a longitudinal study (8).

In summary, findings from the present study suggest that, after the age of 60 yr, VO2 max decreases with age due to reductions in both Q max and a-vDO2 and that these reductions occur more rapidly in men than in women. Furthermore, the age-related declines in Q max and a-vDO2 contribute equally to the age-associated reductions in VO2 max in men and women. The age-related decline in Q max is due to decreases in HR max with no significant effect of age on maximal exercise stroke volume. Because the rates of decline in VO2 max and its physiological determinants are considerably greater in older men than in older women, the gender-associated differences tend to dissipate in the later decades of life.

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Current affiliation for R. J. Spina: Department of Kinesiology, San Francisco State University, San Francisco, CA 94132.

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