Role of central circulatory factors in the fat-free mass-maximal aerobic capacity relation across age

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Hunt, Brian E., Kevin P. Davy, Pamela P. Jones, Christopher A. DeSouza, Rachael E. Van Pelt, Hirofumi Tanaka, and Douglas R. Seals. Role of central circulatory factors in the fat-free mass-maximal aerobic capacity relation across age. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H1178–H1182, 1998.—Fat-free mass (FFM) (primarily skeletal muscle mass) is related to maximal aerobic capacity among healthy humans across the adult age range. The basis for this physiological association is assumed to be a direct relation between skeletal muscle mass and its capacity to consume oxygen. We tested the alternative hypothesis that FFM exerts its influence on maximal aerobic capacity in part via an association with central circulatory function. To do so, we analyzed data from 103 healthy sedentary adults aged 18–75 yr. FFM was strongly and positively related to maximal oxygen consumption (r = 0.80, P < 0.001). FFM was also strongly and positively related to supine resting levels of blood volume (r = 0.79, P < 0.001) and stroke volume (r = 0.75, P < 0.001). Statistically controlling for the collective influences of blood volume and stroke volume abolished the tight relation between FFM and maximal oxygen consumption (r = 0.12, not significant). These results indicate that 1) FFM may be an important physiological determinant of blood volume and stroke volume among healthy sedentary adult humans of varying age; and 2) this relation between FFM and central circulatory function appears to represent the primary physiological basis for the strong association between FFM and maximal aerobic capacity in this population. Our findings suggest that sarcopenia (loss of skeletal muscle mass with aging) may contribute to the age-related decline in maximal aerobic capacity primarily via reductions in blood volume and stroke volume rather than a direct effect on the oxygen-consuming potential of muscle per se.

blood volume; stroke volume; maximal oxygen consumption

FAT-FREE MASS (FFM) (primarily skeletal muscle mass) is related to maximal aerobic capacity among healthy humans across the adult age range (3, 32). The physiological basis for this association is assumed to be a direct relation between skeletal muscle mass and its capacity to consume oxygen for energy metabolism (14, 18, 32).

However, FFM also may be related to central circulatory factors known to influence maximal aerobic capacity. Indeed, the measurement of FFM via hydrodensitometry includes blood volume. Consistent with this idea, we (7, 21) and others (3, 22) have observed that FFM is strongly related to blood volume among sedentary adult humans of different ages. Because blood volume can exert an important influence on left ventricular stroke volume (6, 15, 31), it is possible that FFM acts as a determinant of stroke volume in this population. Moreover, we have recently shown that supine stroke volume at rest is a strong physiological correlate of maximal oxygen consumption in young and older healthy sedentary adults (19). Therefore, it is possible that FFM may be linked to maximal aerobic capacity, at least in part, via this central circulatory mechanism, rather than solely through a permissive influence on peripheral oxygen utilization as currently assumed (14, 18, 32).

Accordingly, in the present study we tested this alternative hypothesis. To do so, we determined the relations among FFM, supine resting levels of blood volume and stroke volume, and maximal aerobic capacity among sedentary healthy adult humans varying in age. We then attempted to statistically “partial out” the potential influences of blood volume and stroke volume on FFM and reexamine the relation between FFM and maximal aerobic capacity independent of these effects.

METHODS

Subjects. Data from 103 sedentary subjects (25 men and 78 women) in whom FFM and maximal oxygen consumption recently had been measured in our laboratory were included in the data analysis. FFM and blood volume data were available on 80 subjects (41 men and 39 women) and FFM and stroke volume data on 58 subjects (25 men and 33 women). Fifty-one subjects were over the median age of 48 (7 men and 44 women). Thirty-five women were postmenopausal: 16 were using hormone replacement and 19 were nonusers. All premenopausal women were eumenorrheic as assessed by self-report and were studied during the early follicular phase of their menstrual cycle. Subjects ranged in age from 18 to 75 yr and from 31 to 78 kg in FFM. Other physical characteristics are described in Table 1. All subjects were free of overt cardiovascular disease as assessed by medical history. Subjects over the age of 50 yr were further evaluated for clinical evidence of cardiovascular disease with a physical examination and electrocardiograms during rest and maximal exercise. Exclusion criteria included S-T segment depression/elevation >1 mm from baseline, chest pain, shortness of breath/wheezing, leg cramping or intermittent claudication, systolic blood pressure >260 mmHg or diastolic blood pressure >115 mmHg, etc. (4). No subject reported using medication other than hormone replacement, and premenopausal women were not using oral contraceptives. All subjects were nonsmokers.
Body mass and composition. Total body mass was measured to the nearest 0.1 kg on a physician’s balance scale. Total body density was determined by hydrodensitometry with residual volume measured by nitrogen dilution (34). Body fat percentage was calculated using the equation of Brozek (2). Fat mass and FFM were calculated from the percentage of body fat and total body mass.

Blood volume and systemic hemodynamics. Measurements were performed under quiet resting conditions after a 12-h overnight fast with subjects in the supine position. Blood volume was determined by methods described in detail previously by our laboratory (7, 21, 30). Plasma volume was measured using a modified Evans blue dye technique. Blood volume was calculated from plasma volume and the simultaneous determination of venous hematocrit (in triplicate). Hematocrit of the venous sample was corrected for peripheral sampling (0.91) and for trapped plasma (0.96). Arterial blood pressure was determined by sphygmomanometry using procedures established by the American Heart Association and described previously (29). Cardiac output was estimated using a semiautomated acetylene rebreathing technique as recently described by our laboratory (19, 20). Briefly, subjects began rebreathing a 1.0-liter gas mixture containing 1.0% C2H2, 5.0% He, 45.0% O2, 49% N2 after they had reached steady-state levels of minute ventilation, oxygen consumption, and heart rate. Cardiac output was calculated from the exponential disappearance of acetylene from the rebreathing bag during three rebreathing trials. This technique has excellent day-to-day reproducibility in our laboratory (r = 0.98) (20). Stroke volume was calculated from cardiac output and heart rate (electrocardiogram tracing). Systemic vascular resistance was calculated by dividing mean arterial pressure by cardiac output.

Maximal aerobic capacity. Maximal oxygen consumption was determined via open-circuit spirometry during treadmill exercise as described previously (11, 19, 21) and was used as a measure of maximal aerobic capacity. Subjects walked on a motorized treadmill at a constant speed with increasing grade every 2 min until subjective exhaustion. Subjects satisfied at least three of the following criteria for attainment of maximal oxygen consumption: 1) a plateau in oxygen consumption (~100 ml) with increasing exercise intensity; 2) a respiratory exchange ratio >1.1; 3) achievement of age-predicted maximal heart rate; and 4) perceived exertion >18 on Borg Scale. Maximal heart rate was determined during the last minute of exercise. The product of maximal heart rate and supine stroke volume at rest was used as an estimate of maximal cardiac output (31).

Data analysis. Pair-wise univariate correlation and regression analyses were performed to determine the simple relations between variables of interest in the pooled data set (n = 103), as well as within gender and age subgroups. Multivariate analyses were performed only within the subgroup of subjects in whom all variables of interest were measured (n = 27). Specifically, to determine whether blood volume and stroke volume underlie the strong association between FFM and maximal oxygen consumption, semipartial correlation analysis was used to statistically partial out the effects of blood volume and stroke volume on FFM. Multiple stepwise regression analysis also was performed to determine the relative importance of each variable in predicting maximal oxygen consumption as indicated by the respective beta weights (β). All relations of interest were similar in postmenopausal women using compared with those not using chronic estrogen supplementation as we have reported previously (19, 21). Significance was set a priori at P < 0.05.

RESULTS

Univariate analyses in pooled subjects. FFM was strongly and positively related to maximal oxygen consumption (r = 0.80, P < 0.001) (Fig. 1). Supine resting levels of blood volume (r = 0.75, P < 0.001), stroke volume (r = 0.75, P < 0.001), and estimated maximal cardiac output (r = 0.84, P < 0.001) also were significantly correlated with maximal oxygen consumption.

FFM was strongly and positively related to supine resting levels of blood volume (r = 0.79, P < 0.001) and stroke volume (r = 0.75, P < 0.001) (Fig. 2). Blood volume and stroke volume also were significantly correlated (r = 0.53, P < 0.001). FFM also was strongly related to cardiac output (r = 0.72, P < 0.001) and more modestly related to diastolic (r = 0.35, P < 0.002) and mean (r = 0.25, P < 0.03) arterial blood pressures and to systemic vascular resistance (r = −0.38, P < 0.01); there was no relation with heart rate or systolic blood pressure.

FFM was related to maximal oxygen consumption in both men (r = 0.54) and women (r = 0.44) and in the young (r = 0.87) and older (r = 0.69) subjects (P < 0.01–0.001). FFM and supine resting levels of blood volume were related in males (r = 0.49) and females.

Table 1. Selected subject characteristics

<table>
<thead>
<tr>
<th>n</th>
<th>Age yr</th>
<th>Body mass, kg</th>
<th>Height, m</th>
<th>% Body fat</th>
<th>Fat-free mass, kg</th>
<th>SBP, mmHg</th>
<th>DBP, mmHg</th>
<th>HR rest, beats/min</th>
<th>VO2 max, l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>103</td>
<td>47 ± 2</td>
<td>65.3 ± 1.3</td>
<td>1.67 ± 0.01</td>
<td>30 ± 1</td>
<td>47.5 ± 0.9</td>
<td>117 ± 2</td>
<td>74 ± 1</td>
<td>64 ± 1</td>
<td>2.1 ± 0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, number of subjects. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR rest, resting heart rate; VO2 max, maximal oxygen consumption.
(r = 0.48) and in the young (r = 0.80) and older (r = 0.74) subjects (P < 0.01–001). FFM and stroke volume were related in men (r = 0.61) and women (r = 0.58), as well as in the young (r = 0.67) and older (r = 0.82) subjects (all P < 0.001).

Univariate and multivariate analyses in subgroup with common measures. In the subgroup of subjects with measures of all four key dependent variables (n = 27), the univariate correlation between FFM and maximal oxygen consumption was identical to that observed in the pooled population (r = 0.80, P < 0.001). Similarly, supine resting levels of blood volume (r = 0.81, P < 0.001) and stroke volume (r = 0.64, P < 0.01) also were strongly related to FFM in this subgroup.

After statistically accounting for the collective influence of blood volume and stroke volume through the use of semipartial regression analysis, FFM and maximal oxygen consumption no longer were significantly related (r = 0.12, P = 0.22). Consistent with this observation, multiple stepwise regression analysis revealed that although FFM entered the equation first (rY,1 = 0.80), based on its β-weight (β = 0.238), it was the least important of the three variables in predicting maximal oxygen consumption. In contrast, stroke volume entered the multiple regression equation second (rY,2 = 0.87) but had the strongest influence on predicting maximal oxygen consumption based on its high β-weight (β = 0.509). Blood volume entered the equation last (rY,23 = 0.89) but had a greater impact on predicting maximal oxygen consumption based on its β-weight (β = 0.293) than did FFM.

**DISCUSSION**

The main findings of the present investigation are as follows. First, our results confirm the strong relation between maximal oxygen consumption and FFM among healthy adult men and women varying in age. Second, our data establish that FFM is an important physiological correlate of supine resting levels of blood volume and stroke volume in this population. Third, the present results demonstrate that the strong association between maximal oxygen consumption and FFM in this population is largely dependent on the influences of blood volume and stroke volume rather than solely attributable to factors related to peripheral oxygen demand and utilization as previously assumed (14, 18, 32).

FFM and maximal oxygen consumption. In the present study, FFM accounted for >60% of the variance in maximal oxygen consumption among our subjects (Fig. 1), which agrees with previous observations (3, 33). Historically, it has been assumed that the physiological basis for this association between FFM and maximal oxygen consumption is a direct relation between the size of the skeletal muscle mass and its capacity for producing mechanical work (i.e., generating oxygen demand) and/or consuming oxygen (14, 32). The present findings introduce a new concept concerning this association, that FFM exerts its permissive influence on maximal aerobic capacity primarily via an effect on central circulatory function involving blood volume and stroke volume. This is supported by the facts that 1) blood volume and stroke volume both correlated with FFM (r = 0.79 and r = 0.75, respectively) as well as with maximal oxygen consumption (r = 0.75 and 0.75); 2) when the collective influences of blood volume and stroke volume were accounted for statistically using semipartial regression analysis, the strong positive relation between FFM and maximal oxygen consumption (r = 0.80, P < 0.001) was abolished (r = 0.12, not significant); and 3) the β-weights generated by the multiple stepwise regression analysis demonstrated that both stroke volume and blood volume had a greater effect on maximal oxygen consumption than did FFM per se.

Our findings are consistent with the concept that the key limitation for maximal oxygen consumption in adult humans resides in the ability of the heart and central circulation to deliver oxygen to active muscle. As such, our data support two earlier lines of evidence concerning this idea: 1) that several acute experimental perturbations (e.g., blood doping; erythropoietin use) (9, 10) and chronic conditions/states (e.g., sex-related differences in hemoglobin) (1, 24) affect maximal oxygen consumption, independent of changes/differences in the oxygen-consuming potential of skeletal muscle, and 2) that a relatively small fraction of the total muscle mass (<50%) is required to attain maximal oxygen consumption in most individuals (28).

Thus, although factors directly linked to peripheral oxygen utilization may contribute to the FFM-maximal oxygen consumption relation in humans, the present findings indicate that this association is based to a large extent on the relations between FFM and these
central circulatory determinants of maximal aerobic capacity.

Several considerations should be noted in the interpretation of the present data. First, our results are based on a retrospective analysis of data rather than a prospective study design. Second, measurements of all four key dependent variables (FFM, maximal oxygen consumption, stroke volume, and blood volume) were obtained in only 27 of 103 subjects and thus may not be representative of the larger sample. However, we believe this is not likely due to the fact that the univariate relations in the subgroup were very similar to those in the larger sample. Third, the intercorrelations among the key dependent variables clearly make statistical efforts to determine their independent contribution to the FFM-maximal oxygen consumption relation difficult. Our combined use of semipartial correlation analysis and examination of the β-weight values from the multiple stepwise regression analysis was intended to address this issue as much as is possible. Nevertheless, this approach does not completely eliminate the potential effects of these interrelations.

FFM and blood volume. The present data showing a strong positive relation between FFM and blood volume in sedentary adults varying in age (Fig. 2) confirm the recent observations of our laboratory (7, 21) and the previous findings of others (3, 22). This relation is likely due in part to the fundamental physiological association between FFM and total body water. The latter is supported by our recent findings of a high correlation between FFM and plasma volume among healthy sedentary adult females (21). However, this coupling between FFM and plasma volume does not appear to explain the entire relation between FFM and blood volume because we have observed a similarly strong relation between FFM and estimated erythrocyte volume (21).

FFM and stroke volume. In the present study, FFM accounted for ~50% of the total variance in left ventricular stroke volume (Fig. 2). There are at least three possible mechanisms linking FFM and stroke volume in our subjects.

One possibility is blood volume. Strandell (31) previously observed that among older subjects those with the highest levels of blood volume also had the highest supine stroke volumes at rest. Moreover, Granath and Strandell (15) reported a correlation of \( r = 0.68 \) between resting blood volume and stroke volume measured during submaximal dynamic exercise in a group of healthy older adults. In the present study, we found a correlation of \( r = 0.53 \) between supine resting levels of blood volume and stroke volume. This modest relation (explaining only ~25% of the variance), coupled with the fact that the correlation between FFM and stroke volume was only slightly reduced after accounting for the influence of blood volume, suggests that the latter does not explain the major portion of the FFM-stroke volume relation among our subjects.

Another possibility is that stroke volume is related to FFM via an effect of body size on left ventricular cavity dimension. The latter was not measured in the present study. However, the fact that FFM was strongly related to body surface area in the present study (\( r = 0.80 \)) and that body surface area, in turn, correlated strongly with stroke volume (\( r = 0.71 \)) is consistent with this concept.

Finally, it is also possible that FFM is associated with stroke volume via a relation with left ventricular afterload. However, the fact that FFM was only weakly related to mean arterial blood pressure (\( r = 0.25 \)) among our subjects suggests that this factor did not play a major role.

Physiological significance: possible relevance for sarcopenia and aging. Sarcopenia refers to the loss of skeletal muscle mass with advancing age in adult humans and recently has been an intense focus of interest in gerontology and geriatric medicine (13, 27). The primary emphasis of research efforts to date concerning sarcopenia has been on skeletal muscle metabolism, strength, and motor function (12, 17, 23). By extending our understanding of the fundamental relations among FFM, central circulatory function, and maximal aerobic capacity, the present findings may provide new insight concerning the physiological significance of sarcopenia for human aging.

For example, maximal aerobic capacity decreases progressively with advancing age in humans (5, 14, 16) and is thought to contribute importantly to the declines in physical work and exercise capacities, independence, and quality of life in older adults (11, 16, 18). Age-related reductions in FFM (sarcopenia) are thought to be an important factor in the marked decline in maximal aerobic capacity with aging by limiting the capacity for oxygen utilization by active skeletal muscle (12, 14, 32, 33). The present findings introduce the possibility that age-associated reductions in FFM may play a critical role in the declines in maximal aerobic capacity through an effect independent of peripheral oxygen demand and utilization, namely, decreases in blood volume and stroke volume. This idea is consistent with the fact that blood volume and stroke volume are key determinants of maximal aerobic capacity in healthy humans (3, 5, 8, 25, 30) and contribute to the declines observed with advancing age (7, 8, 25).

The present findings provide insight into the nature of mechanisms (central circulatory versus peripheral oxygen consuming) through which FFM may be linked to age-related declines in maximal aerobic capacity in sedentary humans (i.e., FFM-dependent influences). It is important to emphasize, however, that recently Proctor and Joyner (26) demonstrated a FFM-independent influence in the decline in maximal aerobic capacity across age in endurance-trained men and women. Specifically, they found that maximal oxygen consumption per unit skeletal muscle mass was lower in the older compared with the young adult athletes, which they attributed to reductions in maximal oxygen delivery. Thus, taken together, our results and those of Proctor and Joyner (26) suggest that central circulatory factors that are both related to and independent of FFM...
may contribute to age-associated reductions in maximal aerobic capacity in healthy adult humans.

In conclusion, the results of the present study confirm the association between FFM and maximal oxygen consumption among healthy men and women of increasing age. Our data also support the concept that FFM is strongly related to both blood volume and stroke volume in this population. Most importantly, the present findings indicate that this relation between FFM and central circulatory function appears to represent the primary physiological basis for the strong association between FFM and maximal aerobic capacity. As such, our results suggest that the physiological significance of sarcopenia for human aging is not limited to effects on skeletal muscle per se but rather extends importantly to central circulatory regulation of functional capacity.

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