Leg mass and lower body negative pressure tolerance in men and women

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Lawler, Lori A., John R. Halliwill, Joelene M. Summer, Michael J. Joyner, and Sharon L. Mulvagh. Leg mass and lower body negative pressure tolerance in men and women. J. Appl. Physiol. 85(4): 1471–1475, 1998.—To explore the hypothesis that lower body muscle mass correlates with orthostatic tolerance, 18 healthy volunteers (age 18–48 yr; 10 men, 8 women) underwent a graded lower body negative pressure (LBNP) protocol consisting of six, 5-min stages of suction up to 60 mmHg in 10-mmHg increments. Forearm blood flow, heart rate, and blood pressure were measured, and forearm vascular resistance was calculated. Leg muscle mass was assessed by dual-energy X-ray absorptiometry. All subjects received standard intravenous hydration for at least 8 h before the study. Six men and four women completed all stages of LBNP. Four men and four women developed presyncopeal symptoms, including marked bradycardia and/or hypotension, at LBNP levels of 30 mmHg (n = 2; 1 man, 1 woman), 40 mmHg (n = 2; 1 man, 1 woman), and 50 mmHg (n = 4; 2 men, 2 women). The presyncopeal subjects had leg muscle masses ranging from 19.5 to 25.2 kg in men and from 11.7 to 16.6 kg in women. In subjects who completed all stages of LBNP, leg muscle mass ranged from 17.5 to 24.1 kg in men and from 10.4 to 18.0 kg in women. Leg muscle mass did not differ between presyncopeal subjects and those who completed the protocol. Furthermore, there were no differences in the hemodynamic responses to LBNP between subjects with low vs. high leg mass. These data suggest that leg muscle mass is not a critical determinant of LBNP tolerance in otherwise healthy men and women.

correlation between LBNP tolerance and leg compliance between endurance-trained and untrained men. A complimentary observation by Lightfoot et al. (9) is that LBNP tolerance increases after 12 wk of resistance training. Lightfoot et al. also found greater LBNP tolerance in subjects who participated in chronic resistance training. These results suggest that both short- and long-term interventions that alter leg muscle mass can change LBNP tolerance. However, it is unknown what impact leg muscle mass has on orthostatic tolerance in the absence of interventions that alter leg muscle mass. We hypothesized that, without alteration of leg muscle mass by use of acute or chronic interventions, leg muscle mass would be correlated with LBNP tolerance (i.e., more muscle in the legs allows for higher LBNP tolerance).

To test this hypothesis, we retrospectively analyzed data from 18 healthy volunteers (age 18–48 yr; 10 men, 8 women) who underwent sequential graded LBNP up to 60 mmHg, as part of a recent investigation (5). Leg muscle mass was assessed by dual-energy X-ray absorptiometry (DEXA). Our data suggest that leg muscle mass is not a critical determinant of LBNP tolerance in otherwise healthy men and women.

METHODS

Subjects. Eighteen healthy, nonobese subjects (8 women, 10 men) who were between the ages of 18 and 48 yr and had a wide range of fitness levels (maximal oxygen uptake (V\textsubscript{O}\textsubscript{2max}) 29.6–59.3 ml·kg\textsuperscript{-1}·min\textsuperscript{-1}) were studied. All subjects were nonsmokers, were not taking any medications, had no history of syncope, and had no abnormal findings on physical examination. Female subjects had a negative pregnancy test, and the date of the last menstrual period was recorded. The Institutional Review Board approved the study. Each subject gave written informed consent before participating in the study.

Subject monitoring. During the study, heart rate was monitored by using a five-lead electrocardiogram. Arterial pressure was monitored noninvasively on a beat-to-beat basis by using a Finapres blood pressure monitor (model 2300, Ohmeda, Englewood, CO).

Determination of lean muscle mass. DEXA (Total Body Analysis, ver. 3.6y, Lunar, Madison, WI) was used to estimate regional (lower body) muscle mass (at a medium scan speed of ~25 min). This technique, which has long been recognized for its effectiveness in measuring bone density, has also demonstrated excellent precision in the measurement of bone-free lean tissue (i.e., muscle) and fat. Bony landmark sites described by Heymsfield et al. (6) were used to obtain the summed lower extremity (appendicular) muscle mass (i.e., bone-free lean tissue for both legs; in kilograms). The Lunar DEXA instrument is calibrated monthly by using a series of}

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meat blocks of known composition. Body surface area was determined by using a standard nomogram.

LBNP. LBNP was used to cause incremental venous pooling in the lower extremities. Subjects were in the supine position and sealed at the iliac crest level into an airtight box. Subjects were supported within the LBNP box by a mounted bike seat but had no foot support. Gradual vacuum-pump suction was applied continuously and sequentially at levels of 10, 20, 30, 50, and 60 mmHg for 5 min at each level. The graded LBNP protocol results in progressive increases in sym pathetically mediated vasoconstriction manifested by reduced flow in limb skeletal muscle beds and tachycardia. Negative pressure was terminated if the subject displayed presyncopal signs or symptoms, including bradycardia (heart rate <60 beats/min), hypotension (systolic blood pressure <80 mmHg), nausea, or lightheadedness.

Forearm blood flow (FBF). FBF was measured by using venous occlusion plethysmography with mercury-in-Silastic strain gauges and is expressed as milliliters per milliliter tissue per minute (4). During measurements of FBF, blood flow to the hand was excluded by inflation of a wrist cuff to 250 mmHg. The upper arm cuff collecting pressure was 50 mmHg, and both cuffs were inflated for 7.5 of 15-s intervals (4 flows/min). The gauge and cuffs were applied to the subject’s right arm only, and measurements were made during the last 3 min of each segment of the protocol.

Left ventricular end-diastolic diameter (LVEDD). Two-dimensional guided M-mode transthoracic images were obtained from the left parasternal position by using a Sonus 1500 cardiac ultrasound machine (Hewlett-Packard, Andover, MA) equipped with a 2.5-MHz transducer. Transducer positioning was optimized to obtain the least oblique image at the midventricular short-axis, papillary muscle level. At least five consecutive cardiac cycles were recorded onto 0.5-in. sVHS tape, with subsequent off-line digitization and measurement (Nova Microsonics) of LVEDD and left ventricular end-systolic diameter. This measurement was used as an indication of ventricular volume, a stimulus for the unloading of cardiopulmonary receptors. The assumption was that LBNP would evoke increased venous pooling, reduce venous return, and cause LVEDD to fall (7, 14).

Protocol

\( \dot{V}O_2 \) and body composition for leg muscle mass were determined on a protocol-familiarization and screening day that, on average, occurred within 13 wk of the study. Subjects were instructed to maintain their normal activities and to not initiate new exercise regimens during this time period. Subject compliance was ascertained on a regular basis by interview. The night before the LBNP study, subjects were admitted to the General Clinical Research Center, given a standard meal, and hydrated intravenously (saline, 125 ml/h) overnight. The next morning, the subject was positioned in the LBNP box and instrumented for heart rate, blood pressure, and FBF measurements. Baseline measurements were followed by six 5-min stages of LBNP, increasing by 10 mmHg at each stage. Echocardiographic and physiological measurements were acquired during the final 3 min of each stage. LBNP was terminated if presyncopal symptoms and/or signs (i.e., bradycardia, nausea, dyspnea, and so on) occurred.

Data Analysis

Data were digitized and stored on computer at 1,000 Hz. Data were analyzed off line with signal processing software (Windaq, Dataq Instruments, Akron, OH). After the heart rate and R-R intervals were determined from the electrocardiogram, the data were decimated to 100 Hz for derivation of arterial pressure and blood flow. Mean arterial pressure was derived from the arterial pressure waveform. Forearm blood flow was determined from the derivative of the forearm plethysmogram. Forearm vascular resistance was calculated as mean arterial pressure/forearm blood flow and is expressed as units (actual units: mmHg·dl tissue·min·ml⁻¹).

Those subjects who completed all stages of the protocol are referred to as finishers throughout the paper and those who

### Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Finishing Status</th>
<th>LBNP Stage Tolerated, mmHg</th>
<th>Leg Muscle Mass, kg</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>Body Surface Area, m²</th>
<th>Body Fat, %</th>
<th>( \dot{V}O_2 )max, ml·kg⁻¹·min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male nonfinishers (4)</td>
<td></td>
<td>22.4</td>
<td>186</td>
<td>100</td>
<td>2.25</td>
<td>40.9</td>
<td>59.3</td>
</tr>
<tr>
<td>Male finishers (6)</td>
<td></td>
<td>22.1</td>
<td>186</td>
<td>92</td>
<td>2.16</td>
<td>45.2</td>
<td>51.8</td>
</tr>
<tr>
<td>Female nonfinishers (4)</td>
<td></td>
<td>25.2</td>
<td>191</td>
<td>99</td>
<td>2.3</td>
<td>46.7</td>
<td>44.7</td>
</tr>
<tr>
<td>Female finishers (4)</td>
<td></td>
<td>19.5</td>
<td>190</td>
<td>74</td>
<td>2.01</td>
<td>48.0</td>
<td>44.7</td>
</tr>
<tr>
<td>Means ± SE</td>
<td></td>
<td>22.3 ± 1.2</td>
<td>188 ± 1</td>
<td>91 ± 6</td>
<td>2.18 ± 0.6</td>
<td>48.3 ± 5.6</td>
<td></td>
</tr>
<tr>
<td>Male nonfinishers (4)</td>
<td></td>
<td>20.7</td>
<td>178</td>
<td>72</td>
<td>1.85</td>
<td>55.5</td>
<td>57.5</td>
</tr>
<tr>
<td>Male finishers (6)</td>
<td></td>
<td>22</td>
<td>189</td>
<td>83</td>
<td>2.07</td>
<td>57.5</td>
<td>38.7</td>
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<tr>
<td>Female nonfinishers (4)</td>
<td></td>
<td>19.9</td>
<td>184</td>
<td>84</td>
<td>2.05</td>
<td>43.6</td>
<td>45.8</td>
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<tr>
<td>Female finishers (4)</td>
<td></td>
<td>24.1</td>
<td>195</td>
<td>105</td>
<td>2.37</td>
<td>43.6</td>
<td>51.8</td>
</tr>
<tr>
<td>Means ± SE</td>
<td></td>
<td>20.3 ± 0.4</td>
<td>182 ± 4</td>
<td>82 ± 5</td>
<td>2.00 ± 0.8</td>
<td>48.7 ± 3.0</td>
<td></td>
</tr>
<tr>
<td>Male nonfinishers (4)</td>
<td></td>
<td>16.3</td>
<td>170</td>
<td>66</td>
<td>1.76</td>
<td>32.6</td>
<td>46.4</td>
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<tr>
<td>Male finishers (6)</td>
<td></td>
<td>15</td>
<td>166</td>
<td>70</td>
<td>1.78</td>
<td>40.9</td>
<td>46.4</td>
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<tr>
<td>Female nonfinishers (4)</td>
<td></td>
<td>11.7</td>
<td>157</td>
<td>58</td>
<td>1.58</td>
<td>43.7</td>
<td>43.7</td>
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<tr>
<td>Female finishers (4)</td>
<td></td>
<td>16.6</td>
<td>175</td>
<td>63</td>
<td>1.75</td>
<td>46.9</td>
<td>46.9</td>
</tr>
<tr>
<td>Means ± SE</td>
<td></td>
<td>14.9 ± 1.1</td>
<td>167 ± 4</td>
<td>64 ± 3</td>
<td>1.71 ± 0.5</td>
<td>42.4 ± 3.3</td>
<td></td>
</tr>
<tr>
<td>Male nonfinishers (4)</td>
<td></td>
<td>18</td>
<td>163</td>
<td>67</td>
<td>1.74</td>
<td>52.9</td>
<td>52.9</td>
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<tr>
<td>Male finishers (6)</td>
<td></td>
<td>10.4</td>
<td>159</td>
<td>62</td>
<td>1.64</td>
<td>28.6</td>
<td>28.6</td>
</tr>
<tr>
<td>Female nonfinishers (4)</td>
<td></td>
<td>12.4</td>
<td>166</td>
<td>66</td>
<td>1.73</td>
<td>36.3</td>
<td>36.3</td>
</tr>
<tr>
<td>Female finishers (4)</td>
<td></td>
<td>13.8</td>
<td>162</td>
<td>58</td>
<td>1.63</td>
<td>39.4</td>
<td>39.4</td>
</tr>
<tr>
<td>Means ± SE</td>
<td></td>
<td>13.7 ± 1.6</td>
<td>163 ± 1</td>
<td>63 ± 2</td>
<td>1.69 ± 0.3</td>
<td>39.3 ± 5.1</td>
<td></td>
</tr>
</tbody>
</table>

Nos. in parentheses are no. of subjects. LBNP, lower body negative pressure; \( \dot{V}O_2 \)max, maximal O₂ consumption.
did not complete the protocol as nonfinishers. Demographic and physiological data were analyzed by using a two-way analysis of variance (gender, finishing status). Further analysis of the response to LBNP was analyzed with the subjects divided arbitrarily into “low”-leg-mass (low group) and “high”-leg-mass groups (high group), defined as follows. The high group contained men with >21 kg leg muscle mass (mean 23.2 ± 0.6 kg) and women with >14 kg leg muscle mass (mean 16.5 ± 0.6 kg). The low group contained men with <21 kg leg muscle mass (mean 19.0 ± 0.6 kg) and women with <14 kg leg muscle mass (mean 12.1 ± 0.7 kg). The cutoffs were chosen to create groups with an equal number of men and women in each group. Repeated-measures analysis of variance was used to compare responses to LBNP between these groups. For this analysis, data at 40 mmHg LBNP and above were excluded because of the decreasing number of subjects. Data are expressed as means ± SE.

**RESULTS**

The individual and group characteristics of subjects classified according to protocol completion are in Table 1. Six men and four women completed each stage of LBNP (finishers). Finishers had leg muscle masses averaging 20.3 ± 1.1 kg in men and 13.7 ± 1.6 kg in women. Four men and four women developed presyncopeal symptoms at LBNP levels ranging from 30 to 50 mmHg (nonfinishers). At 30 and 40 mmHg, one man and one woman became presyncopeal at each stage. At LBNP of 50 mmHg, two men and two women developed signs and/or symptoms of syncope. Nonfinishers had leg muscle masses averaging 22.3 ± 1.2 kg in men and 14.9 ± 1.1 kg in women. There were no differences between finishers and nonfinishers in fitness level (V˙O₂max), age, height, weight, body surface area, or leg muscle mass regardless of gender (see Table 1).

The development of presyncopeal signs or symptoms is a rather subjective experimental end point; thus we further explored the effect of leg muscle mass by assessing the hemodynamic responses to graded LBNP. Accordingly, we divided our subjects into two groups on the basis of their leg muscle mass to facilitate analysis. The high group contained men with >21 kg leg muscle mass and women with >14 kg leg muscle mass. The low group contained men with <21 kg leg muscle mass and women with <14 kg leg muscle mass. The low group contained men with <21 kg leg muscle mass and women with <14 kg leg muscle mass. Figure 1 shows the heart rate, mean arterial pressure, forearm vascular resistance, and LVEDD responses to LBNP in both the high and low groups. With graded LBNP, mean arterial pressure and LVEDD fell, whereas heart rate and forearm vascular resistance increased (all P < 0.05 vs. baseline). However, there were no differences in these responses between the high and the low groups (P > 0.05 between groups for all variables).

One additional observation worth noting is that three of the four female finishers were in the follicular phase of the menstrual cycle. By contrast, two of the female nonfinishers were in the luteal phase, one was in the follicular phase, and the menstrual phase of the remaining subject could not be determined clinically because of hysterectomy.

**DISCUSSION**

The major finding in our study is that there is no apparent relationship between leg muscle mass and LBNP tolerance in subjects who have not undergone an intervention designed to cause short- or long-term changes in their leg muscle mass.

We initially hypothesized a direct relationship between leg muscle mass and the ability to withstand LBNP. The rationale was that less muscle mass would
lead to greater venous pooling during LBNP, resulting in less venous return, and the subject would fail to tolerate suction. However, subjects with less leg muscle mass did not show an increased propensity to become syncopal during LBNP. Also, subjects with less muscle mass did not display differences in any of the hemodynamic responses to LBNP that we recorded (Fig. 1).

Interestingly, three of four female finishers were in the follicular phase of their menstrual cycle. This trend suggests a possible relationship between hormone levels (e.g., estrogen) and orthostatic tolerance. One potential link is nitric oxide. It is currently thought that estrogen can increase the synthesis of nitric oxide (8). Because estrogen levels during the follicular phase are relatively lower than during other phases of the menstrual cycle, estrogen- and/or nitric oxide-mediated vasodilation might be attenuated during the follicular phase, leading to increased orthostatic tolerance.

Prior Studies

These observations contrast with those of Convertino et al. (2), who concluded that muscle mass is a key determinant of venous compliance. They suggested that more muscle mass provides structural support that decreases leg compliance. A study done by Buckey et al. (1) proposed that compliance in the deep veins of the legs is dependent on the surrounding skeletal muscle, because these veins have little sympathetic innervation and little vascular smooth muscle. An additional study that assessed the effects of altered muscle mass on orthostatic responses was done by Lightfoot et al. (9). This group studied subjects who underwent short-term and chronic, upper and lower body resistance training. They concluded that more muscle mass was associated with greater orthostatic tolerance. Another study done by Tatro et al. (13) demonstrated that muscle hypertrophy was associated with reduced leg compliance in five of seven subjects but that it did not affect LBNP tolerance. This observation suggests that muscle may correlate with compliance but not necessarily orthostatic tolerance. The effect of muscle mass on orthostatic tolerance is evident in other studies implementing a loss of muscle mass. Convertino and colleagues (3) suggest that muscular atrophy caused by bed rest increases venous compliance and might contribute to orthostatic intolerance in some individuals.

Perspectives

When the present results from this cross-sectional study are evaluated in the context of previous studies on this issue, an important caveat is reemphasized. Ludwig and Convertino (10) have indicated that, whereas general overall ideas of which factors are involved in the determination of a physiological outcome can be postulated on the basis of average responses, individual differences restrict prediction on a subject-to-subject basis. This concept may explain why interventions that alter muscle mass can also alter orthostatic tolerance in the same individual but may not be predictive of orthostatic tolerance on a cross-sectional basis in a group of subjects studied at a single time point. How can we reconcile our observation demonstrating no relationship between muscle mass and orthostatic tolerance with the previous work on muscle loss and muscle gain?

We speculate that when muscle mass is either lost or gained, the inelastic fascia surrounding the muscle compartment does not adapt quickly to the change in muscle mass. If so, acute loss of muscle would result in more space within the compartment available for blood pooling, whereas acute gain would result in less space. However, we suspect chronic changes in muscle mass lead to compensatory (corresponding) changes in the fascial space and return to normal the potential space for blood pooling. It should be noted that these concepts come from our studies in subjects whose muscle mass is in the normal range. Whether the proposed relationship holds at the extremes of muscle mass (hypertrophy or atrophy) remains to be determined.

Our failure to observe differences in orthostatic responses between subjects with high and low leg mass is not necessarily surprising when one considers that various mechanisms like arterial and cardiopulmonary baroreflexes are integrally involved in the control of arterial pressure. If all of these mechanisms operated identically in all subjects, it is possible that individuals with high muscle mass and decreased leg compliance would show greater orthostatic tolerance. In this context, our results suggest that leg compliance and pooling appear to be only minor contributing factors to orthostatic tolerance when other mechanisms are functional.

Conclusions

In individuals not undergoing interventions specifically associated with alterations in muscle mass (e.g., bed rest or resistance training), leg muscle mass does not appear to be a major determinant of LBNP tolerance in either men or women. The effects of hormones associated with different stages of the menstrual cycle (e.g., estrogen) and orthostatic tolerance with the previous work on women's LBNP tolerance deserve further investigation.

We sincerely thank those who helped us in acquiring and analyzing the data for this study: Barbara Manahan, Deborah Doherty, Dr. Robin A. Horn, and Dr. Stacey A. Vlahakis. Tamara J. Eickhoff deserves thanks for technical assistance and recruiting of subjects, as does Darrell L. Loeffler for technical assistance. We also thank each subject for participating in our study.

This study was supported by National Institutes of Health Grants M01-RR-00086, RR-00086-24, NS-32552-01, and HL-46493; the Glen L. and Lyra M. Ebling Cardiology Research Endowment; and the Mayo Foundation.

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Received 21 Jan 1998; accepted in final form 18 May 1998.

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