Responses of muscle sympathetic nerve activity to lower body positive pressure

QI FU, YOSHIKI SUGIYAMA, ATSUNORI KAMIYA, A. S. M. SHAMSUZZAMAN, AND TADAAKI MANO
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Fu, Qi, Yoshi Sugiyma, Atsunori Kamiya, A. S. M. Shamsuzzaman, and Tadaaki Mano. Responses of muscle sympathetic nerve activity to lower body positive pressure. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H1254–H1259, 1998.—To evaluate the response of vasomotor sympathetic nerve activity to lower body positive pressure (LBPP), muscle sympathetic nerve activity (MSNA) was microneurographically recorded from the tibial nerve in 10 healthy young men, along with hemodynamic variables and echocardiogram, during exposure to incremental LBPP at 10, 20, and 30 mmHg in the supine position. MSNA was suppressed to a similar extent (27%) at 10- and 20-mmHg LBPP. However, at 30-mmHg LBPP, MSNA tended to increase but was still nearly at the control value. Mean arterial pressure was elevated (11%), total peripheral resistance markedly increased (36%), and stroke volume and cardiac output tended to decrease at 30-mmHg LBPP. Heart rate remained unchanged throughout the procedures. Left atrial dimension significantly increased during 10- and 30-mmHg LBPP, indicating an increased cardiac filling. These results suggest that the inhibitory effect of the cardiopulmonary baroreflex on MSNA at 10- and 20-mmHg LBPP could be counteracted by the sympathoexcitatory effect of the intramuscular pressure-sensitive mechanoreflex at 30-mmHg LBPP. However, the increment of total peripheral resistance at 30-mmHg LBPP may not depend exclusively on this small enhancement of MSNA to graded LBPP as well as to determine the possible underlying mechanisms.

Consequently, we adopted these techniques to test the following hypotheses: 1) low levels of LBPP (i.e., 10 and 20 mmHg) can result in a suppression of MSNA via a cardiopulmonary baroreflex, and 2) a higher level of LBPP (i.e., 30 mmHg) can increase MSNA by activation of intramuscular pressure-sensitive receptors.

METHODS

Subjects. Ten healthy young men, 23.9 ± 2.0 (SE) yr old, 57.5 ± 2.3 kg body wt (body fat <20%), and 170.2 ± 1.7 cm height, were recruited among undergraduate students at Nagoya University. All had a negative history of cardiovascular, kidney, or other diseases. All subjects denied taking any medication at the time of study. All abstained from alcohol and caffeine use 24 h before the procedure, and all reported no recent use of tobacco or other pharmacological agents. The subjects were informed of the purpose and the procedures used in the study and gave their consent to participate in the experiment. The study was conducted under the guidelines proposed by the Japan Microneurography Society and was approved by the Human Research Committee of the Research Institute of Environmental Medicine, Nagoya University.

Experimental protocol and procedures. All experiments were carried out with the subject supine and dressed in shorts and in a room with an ambient temperature of 25–27°C. MSNA was recorded microneurographically from the tibial nerve at the popliteal fossa. Respiration curves derived from nasal airflow with a thermistor, precordial electrocardiogram (ECG) from the CM5 lead, and blood pressure (mmHg) waves obtained by a tonometry method (model BP-508S, Colin Electronics, Komaki, Japan) were simultaneously recorded. Impedance pneumography (model AI-601G, Nihon Kohden, Tokyo, Japan) was used to measure transthoracic impedance (ZT) for the estimation of stroke volume (SV; ml/beat). The echocardiographic technique was used to observe the change in left atrial dimension (LAD, mm). Having rested for >30 min, the subject was asked to breathe synchronously to an electronic metronome set at a frequency of 0.25 Hz. After the control data for MSNA, ECG, blood pressure, respiration, and ZT were recorded for 5 min, LBPP was applied progressively at 10, 20, and then 30 mmHg and returned to 0 mmHg. Each step lasted for 6 min. LAD was measured at control and 10- and 30-mmHg LBPP.

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All variables were monitored continuously throughout the procedures and stored on a DAT recorder (model PC216Ax, 8-channel, double-speed, Sony Precision Instruments, Tokyo, Japn).

LBPP. Graded LBPP was applied distally to the subject’s iliac crest by sealing the subject within a customized pressure box at the level of the iliac crest. Pressure was regulated within the LBPP chamber by controlling valves that adjusted the airflow into the chamber with the help of a computer using a closed-loop servomechanism. The pressure applied was read via a pressure transducer connected to the inside of the chamber.

Recording of MSNA. MSNA was recorded from the tibial nerve at the popliteal fossa by a microneurographic technique using a tungsten microelectrode with a tip diameter of ~1 µm and an electrode impedance of 2–5 MΩ (model 26-05-1, Frederic Haer, Bowdoinham, ME). Nerve signals were fed through a high-input impedance preamplifier with a 500- to 5,000-Hz band-pass filter. MSNA was then full-wave rectified and integrated with a time constant of 0.1 s. The identification of MSNA was based on the presence of the following characteristics reported previously elsewhere (25): 1) pulse-synchronous and rhythmic efferent burst discharges, 2) afferent activity evoked by tapping of the appropriate muscle but not in response to a gentle skin touch, 3) modulation by respiration, and 4) enhancement by maneuvers increasing intrathoracic pressure, such as the Valsalva maneuver.

Atrial dimension by echocardiography. Echocardiography was performed (model SSA-270A, Toshiba Medical Systems, Tokyo, Japn) at control and 10- and 30-mmHg LBPP. LAD (mm) and left atrial area (cm²) were measured by time motion (T-MSNA), arbitrary units; NE, not examined; PRU, peripheral resistance units. *P < 0.05 vs. control; †P < 0.02 vs. control; ‡P < 0.001 vs. control.

RESULTS

Complete data were obtained in all studies. There were no untoward effects from the study, and none of the subjects complained of any discomfort during the experiment. The results presented in Table 1 and Figs. 1–3.

MSNA demonstrated a three-phase response to progressive increases in LBPP: phase 1 occurred at 10- mmHg LBPP and was characterized by significant decreases (27%) in burst rate (3.9 bursts/min), burst

<table>
<thead>
<tr>
<th>SBP, mmHg</th>
<th>Control</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP, mmHg</td>
<td>120.5 ± 2.4</td>
<td>118.2 ± 2.4</td>
<td>123.6 ± 2.3</td>
<td>128.4 ± 3.0*</td>
<td>119.6 ± 1.8</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>63.0 ± 2.5</td>
<td>62.7 ± 2.4</td>
<td>66.5 ± 2.6</td>
<td>73.6 ± 3.2†</td>
<td>62.6 ± 1.9</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>82.1 ± 2.1</td>
<td>80.6 ± 2.3</td>
<td>84.9 ± 2.4</td>
<td>91.3 ± 3.2†</td>
<td>84.0 ± 1.6</td>
</tr>
<tr>
<td>SV, ml/beat</td>
<td>58.6 ± 2.6</td>
<td>58.8 ± 2.5</td>
<td>58.5 ± 2.2</td>
<td>58.7 ± 2.6</td>
<td>59.1 ± 2.5</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>71.9 ± 11.2</td>
<td>70.2 ± 9.3</td>
<td>60.8 ± 7.1</td>
<td>58.3 ± 9.4</td>
<td>70.8 ± 8.2</td>
</tr>
<tr>
<td>Z0, Ω</td>
<td>26.2 ± 1.3</td>
<td>25.8 ± 1.2</td>
<td>25.5 ± 1.2</td>
<td>25.6 ± 1.2</td>
<td>26.0 ± 1.3</td>
</tr>
<tr>
<td>TPR, PRU</td>
<td>22.6 ± 2.8</td>
<td>22.4 ± 2.8</td>
<td>26.2 ± 2.3</td>
<td>30.7 ± 3.3*</td>
<td>22.5 ± 2.6</td>
</tr>
<tr>
<td>MSNA</td>
<td>14.2 ± 1.5</td>
<td>10.3 ± 1.2*</td>
<td>10.3 ± 1.4*</td>
<td>12.9 ± 1.4</td>
<td>14.7 ± 1.3</td>
</tr>
<tr>
<td>BR, bursts/min</td>
<td>24.1 ± 2.7</td>
<td>17.8 ± 2.2*</td>
<td>17.6 ± 2.4*</td>
<td>22.0 ± 2.0</td>
<td>25.2 ± 2.3</td>
</tr>
<tr>
<td>T-MSNA, AU/min</td>
<td>134.2 ± 18.1</td>
<td>90.7 ± 12.2</td>
<td>92.1 ± 20.4</td>
<td>142.2 ± 34.0</td>
<td>150.8 ± 27.3</td>
</tr>
<tr>
<td>LAD, mm</td>
<td>27.1 ± 0.5</td>
<td>30.3 ± 0.7</td>
<td>NE</td>
<td>29.8 ± 1.0*</td>
<td>NE</td>
</tr>
</tbody>
</table>

Values are means ± SE. Control, 0 mmHg; LBPP, lower body positive pressure; MSNA, muscle sympathetic nerve activity; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; Z0, transthoracic impedance; TPR, total peripheral resistance; BR, burst rate; BI, burst incidence; T-MSNA, total activity; LAD, left atrial dimension; AU, arbitrary units; NE, not examined; PRU, peripheral resistance units. *P < 0.05 vs. control; †P < 0.01 vs. control.
incidence (6.3 bursts/100 heartbeats), and T-MSNA (43.5 AU/min); phase 2 occurred at 20-mmHg LBPP and was characterized by a plateauing of the MSNA response; phase 3 occurred at 30-mmHg LBPP and was characterized by a trend toward an increase in MSNA. Systolic and diastolic blood pressure were significantly raised by 7% (8 mmHg) and 17% (11 mmHg), respectively, at 30-mmHg LBPP. MAP was increased by 11% (10 mmHg) at the same chamber pressure. SV and CO tended to fall by ~20%, and there was a 36% statistically significant rise in TPR at 30-mmHg LBPP. HR remained unchanged during the procedures. LAD was significantly increased at 10- and 30-mmHg LBPP (12 and 10% increment, respectively).

DISCUSSION

The major finding from this investigation was the suppressive response of MSNA to a low level of LBPP such as 10 or 20 mmHg, whereas the MSNA response tended to increase at 30 mmHg, but still not far beyond the control value.

Changes in MSNA during LBPP. At 10-mmHg LBPP, MSNA was suppressed. LAD measured by echocardiography was larger than in the control condition, indicating an increase in cardiac filling (central blood volume). Systemic blood pressure did not change significantly. In previous investigations, central venous pressure has been described to increase at 5- to 20-mmHg LBPP, which will elevate cardiac filling and load the cardiopulmonary baroreceptors (21, 23). Therefore, we consider that the significant decrease in MSNA at 10-mmHg
LBPP in our study might be related to cardiopulmonary baroreceptor loading. LBPP induces a translocation of blood volume from the lower body to the thoracic compartment. Although the amount of blood shifted during LBPP in healthy normovolemic subjects in the supine position was small, it would selectively load the cardiopulmonary baroreceptors (2, 21). The cardiopulmonary baroreceptors convey tonic afferent nerve traffic to the cardiovascular center and inhibit efferent sympathetic nerve activity to muscle (3, 11, 24).

However, MSNA tended to increase at 30-mmHg LBPP compared with the low level of LBPP, even though the difference was not statistically significant. LBPP >20 mmHg has been suggested to stimulate intramuscular pressure-sensitive receptors (21). The presence of these intramuscular receptors, which are linked to the group III and/or IV afferent nerve fibers, could increase afferent nerve traffic via dorsal spinal root pathways (10, 13), integrate with the cardiovascular center (14, 15), and result in a sustained rise in TPR (5, 9, 26) as well as arterial pressure (6–8, 18). This increase in TPR or arterial pressure is thought to be due to the activation of vasomotor sympathetic nerve activity without activation of central command mechanisms (26). On the other hand, cardiopulmonary and arterial baroreceptors were loaded at 30-mmHg LBPP, because LAD was larger and systemic blood pressure was higher than the control values. These baroreceptor loadings had a suppressive effect on MSNA. If all these factors are taken into consideration, the baroreflex-mediated suppressive response of MSNA could be counteracted by the excitatory effect of the intramuscular pressure-sensitive receptor activation (21).

Mechanisms of an increase in TPR during LBPP. MAP is a product of TPR and CO. Our results demonstrated that 30-mmHg LBPP failed to produce any increase in SV or CO. On the contrary, mean values of SV and CO tended to decline by ~20% at the highest LBPP. Despite this, a substantial increase in MAP was obtained. This would suggest that the significant increase in MAP at 30-mmHg LBPP was the result of a marked increase in TPR, referring to an increase in afterload. The effect of LBPP on the redistribution of blood volume in a supine position is small (2), and the main physiological effect at >30-mmHg LBPP is an increase in afterload.

There are some possibilities for the mechanisms of a marked increase in TPR during LBPP. One possibility is an enhancement of vasomotor sympathetic nerve activity due to the intramuscular pressure-sensitive mechanoreflex (21). In the present study, MSNA at 30-mmHg LBPP tended to increase compared with that at lower levels of LBPP, even though it was still nearly the control level. Therefore, we cannot conclude that the increase in TPR during 30-mmHg LBPP is mainly due to an increase in vasomotor sympathetic nerve activity. Besides the possibility of a neurally mediated increase in TPR, a second mechanism is a mechanical increase in TPR by LBPP itself. Extramural pressure of the vessels in the lower part of the body increases in parallel with the level of LBPP. The increase in local extramural pressure may partly contribute to the increase in TPR during LBPP. This results from Laplace's law (19). A third possibility may be a hormone-related increment in TPR under 30-mmHg LBPP. Although we did not measure plasma renin activity and ANG II in our study, it has been reported that LBPP can stimulate the renin-angiotensin-aldosterone axis (12). Therefore, an elevation in ANG II, which has a vasoconstrictive effect, can contribute to an increase in TPR during LBPP.

TPR increased during LBPP, especially at the highest chamber pressure, and CO tended to decrease. CO is obtained from the product of SV and HR, and in the present study HR remained unchanged throughout application of LBPP. Therefore, CO displayed a response parallel to that of SV. Three factors can influence SV: preload, myocardial contractility, and afterload. Among them, afterload plays the most important and determinant role. There was an increase in preload under the graded LBPP, but it could be totally offset by the opposing effect of increased afterload. These combined effects may have resulted in a trend toward a decrease in SV and CO.
A role for MSNA in hemodynamic homeostasis during LBPP. MSNA controls the peripheral vascular resistance to preserve hemodynamic homeostasis in the face of perturbation in the cardiovascular system. In previous studies, MSNA was suppressed during head-out water immersion (16) and head-down tilt (17), which cause an increase in cardiac filling because of hydrostatic pressure on the lower part of the body and/or a cephalad fluid shift. This suppression of MSNA is thought to buffer the hypertensive effect of the increased cardiac filling by reducing the peripheral vascular resistance. At a low level of LBPP (<20 mmHg) we observed a suppression of MSNA as well as an enlargement of cardiac dimension. Therefore, the suppression of MSNA at a low level of LBPP may contribute to a decrease in vascular resistance to maintain blood pressure homeostasis against the translocation of blood volume to the thorax.

On the other hand, the response of MSNA to >30-mmHg LBPP may have a different pathophysiological relevance. The tendency for an enhanced MSNA response may partly contribute to an increased TPR and result in an elevation of systemic blood pressure. The elevated systemic perfusion pressure can adjust the CO and the distribution of blood flow to the organs. This may help to maintain blood supply to the exercising muscles, since an increase in intramuscular pressure is observed during exercise (1). Moreover, it is also important in the initial treatment of patients with hypovolemic shock by redistributing the reduced blood volume to the vital organs. To elucidate the role of MSNA in hemodynamic homeostasis during higher-level LBPP, the contribution of MSNA to increases in TPR and systemic blood pressure should be evaluated in future studies.

In conclusion, MSNA was suppressed by 10- and 20-mmHg LBPP. The mechanism might be as follows: <20-mmHg LBPP could selectively load the cardiopulmonary baroreceptors via translocation of blood volume from the lower body, which in turn would inhibit MSNA. On the other hand, the response of MSNA to 30-mmHg LBPP tended to increase but without statistical significance, with a marked increase in TPR. The sympathoexcitatory effect of the intramuscular pressure-sensitive mechanoreflex may have offset the baroreflex-mediated suppressive response of MSNA during LBPP. However, the increase in TPR at 30-mmHg LBPP may not depend exclusively on this small enhancement of MSNA but may be also partly due to an increase in local extramural pressure and an increase in ANG II.

Perspectives. This study represents the first description of MSNA in response to graded LBPP. The response of MSNA to LBPP is interpreted as the interaction of the sympathoexcitatory effect of the cardiopulmonary baroreflex and the sympathoexcitatory effect of the intramuscular pressure-sensitive mechanoreflex. However, in this study we could not clarify the role of MSNA in an increase in TPR and systemic blood pressure. The cardiovascular function and its underlying physiological mechanisms, including the role of MSNA, during LBPP are still unclear, because LBPP affects many systems, such as the cardiopulmonary baroreflex, arterial baroreflex, and intramuscular pressure-sensitive mechanoreflex, as well as the renin-angiotensin-aldosterone system, at different pressure levels. Therefore, further studies are needed to clarify 1) the potential contribution of the increased response of MSNA to the increment in TPR and systemic blood pressure at higher LBPP, 2) characteristics of the intramuscular pressure-sensitive mechanoreceptor-muscle sympathetic nerve reflex and its physiological relevance, 3) characteristics of the arterial baroreceptor-muscle sympathetic nerve reflex, and 4) the effect of humoral regulation on cardiovascular and related autonomic functions.

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