Circulatory and Respiratory Responses to Lower Body Negative Pressure in Man

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Abstract Circulatory and ventilatory responses to lower body negative pressure (LBNP) were simultaneously investigated in 8 healthy men before, during, and after the application of -20, -40, and -60 mmHg pressure. Minute ventilation ($V_e$) decreased during LBNP due to a fall in respiratory frequency with sustained tidal volume. The cardiac output ($Q$) was reduced in proportion to the applied LBNP exposure, while $V_e$ decreased to almost the same level at all LBNP applications. In spite of decreased $V_e$, end-tidal $P_{O_2}$ and $P_{CO_2}$ were increased and decreased, respectively, indicating a relative alveolar hyperventilation. The ventilation equivalent for $O_2$ ($\dot{V}_e/\dot{V}_{O_2}$) increased, while the cardiac output equivalent for $O_2$ ($\dot{Q}/\dot{V}_{O_2}$) decreased. The relation between $\dot{V}_e/\dot{V}_{O_2}$ and $\dot{Q}/\dot{V}_{O_2}$ showed a significant negative correlation ($r = -0.93$, $p<0.01$). The veno-arterial $CO_2$ concentration difference ($C_{v\ O_2} - C_{a\ O_2}$) increased with LBNP, due to a fall in $C_{a\ CO_2}$ with constant $C_{v\ CO_2}$. The constant $C_{v\ CO_2}$ indicated a constant tissue acid-base balance. These observations suggest the existence of a ventilatory mechanism improving the efficiency of respiration in order to compensate for the sustained LBNP depression of $Q$ at a given gas exchange.

Key words: lower body negative pressure, baroreceptors, cardiac output, ventilation, (a-\bar{v})O$_2$ difference.

The application of negative pressure to the lower body (LBNP) induces pooling of the blood in these areas, thus decreasing venous return to the heart. This is an accepted simulation of the effects of quiet stading or upright tilting (WOLTHUIS et al., 1974; FREY and HOFFLER, 1988).

A decrease in cardiac output ($\dot{Q}$), stroke volume (SV), pulse pressure and

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central blood volume develop during LBNP (Murray et al., 1968; Wolthuis et al., 1974; Frey and Hoffler, 1988). Most investigators measured these circulatory variables with invasive techniques. These invasive approaches alter orthostatic tolerance in normal man (Wolthuis et al., 1974) and thus decrease the tolerance to LBNP exposure. LBNP could be tolerated much longer and more comfortably when no intravascular instrumentation was used during the application (Stevens and Lamb, 1965).

Early observation of respiratory variables was performed by Dowell et al. (1969), who used arterial catheters for simultaneous circulatory variables. No significant change of ventilation (Ven) was found by Dowell et al. (1969), who used LBNP with −40 mmHg for one hour, or by Loepky et al. (1978), who used LBNP at high altitude and at the same time intravascular instrumentation. Thus physiological reactances cannot be excluded in their investigations. Simultaneous and non-invasive recording of respiratory and circulatory variables during LBNP have not been published yet, to the best of our knowledge.

The object of the present study was first, to measure both circulatory and respiratory variables during LBNP with noninvasive methods; second, to analyze the simultaneously obtained cardiopulmonary responses.

MATERIALS AND METHODS

Subjects and Equipment. Eight healthy males volunteered for this study. The statistics (mean ± S.D.) of their physical characteristics were: age, 29.1 ± 3.0 year; height, 171.8 ± 3.1 cm; weight, 64.7 ± 5.4 kg. All subjects had a medical examination, and none were on medication. The study procedures and protocol were approved by the local ethics committee and conformed to the Helsinki Declaration. Informed consent was obtained in writing from all volunteers. Each subject conducted a trial run to become familiar with the equipment.

The LBNP device was built according to the specifications described by Stevens and Lamb (1965). A rubber seal was fixed from 10 cm below the iliac crest; we could thus exclude any disturbance for abdominal respiratory movement. The desired negative pressure could be achieved within a few seconds and the level was continuously measured by a pressure transducer (TMI, Tokyo) connected to the inside of the box. The magnitude of the vacuum was regulated by adjusting an electric pressure regulator (Rico Co., Tokyo).

Measurements. From the electrodes placed on the anterior chest wall, ECG was recorded by a cardiac telemeter (Cardiosuper San-Ei 2E 31A, Tokyo). The heart rate (HR) was monitored continuously from the R-R interval. Respiratory flow and end expiratory gas tensions (PETO₂ and PECO₂) were measured with a respiratory hot-wire flowmeter (RF-2, Minato Med. Sci., Ltd.) and an expired gas monitor (San-Ei, 1H 21A, Tokyo), respectively. Tidal volume (VT), inspiratory and expiratory duration (Tᵢ and Tₑ) were electrically computed from the obtained respiratory flow signal. Expired air gas was collected into a Douglas bag through

Japanese Journal of Physiology
CARDIOPULMONARY RESPONSE TO LBNP

a one-way valve, and minute O₂ uptake (\( \dot{V}_{O₂} \)) and CO₂ output (\( \dot{V}_{CO₂} \)) were calculated. Oxyhemoglobin saturation of the arterial blood (\( S_{aO₂} \)) was also measured by an ear oximeter (Biox III, Ohmeda).

Stroke volume (SV) and cardiac output (\( \dot{Q} \)) were automatically determined from the electrode signals with a Minnesota Impedance Cardiograph (model 304-A). Four stainless steel strips of 5 mm width and of 0.1 mm thickness were arranged around the neck and the chest wall of the subjects, constituting the tetrapolar electrode system of an impedance cardiograph. This system is fully described by MIYAMOTO et al. (1981), and its validity and accuracy are also well confirmed by other investigators (MUZI et al., 1985; DU QUESNAY et al., 1987). The systolic (\( BP_s \)) and diastolic arterial blood pressure (\( BP_d \)) were measured with a sphygmomanometer with Korotkoff sound sensor, and mean arterial pressure (\( MAP = BP_d + 1/3 (BP_s - BP_d) \)), pulse pressure (PP), and total peripheral vascular resistance (TPVR = MAP/\( \dot{Q} \)) were subsequently calculated.

The following derived variables were calculated from the measurements: minute ventilation (\( \dot{V}E = \dot{V}T \times \) respiratory frequency, \( f \)), gas exchange ratio (\( \dot{V}_{CO₂}/\dot{V}_{O₂} = R \)), ventilation (\( \dot{V}E/\dot{V}_{O₂} \) and \( \dot{V}E/\dot{V}_{CO₂} \)), and cardiac output equivalents (\( \dot{Q}/\dot{V}_{O₂} \) and \( \dot{Q}/\dot{V}_{CO₂} \)), as well as (\( a-v \))O₂ and (\( v-a \))CO₂ content difference derived from the Fick equation. We also calculated \( Ca_{CO₂} \) with the following quadratic equation (MIYAMURA and HONDA, 1978):
\[
C_{CO₂} = -0.00243(P_{CO₂})^2 + 0.657P_{CO₂} + 23.6.
\]

**Experimental protocol.** The subject was positioned in LBNP device in the supine position and a rubber seal was placed around the lower abdomen. The subjects rested in the recumbent position for 30 min before the LBNP exposure. After recording of a 5-min control period at ambient pressure, three levels of negative pressure (-20, -40, and -60 mmHg) were applied for 5 min with 30-min intervals. Observations were continued for 3 min following each LBNP exposure. Respiratory flow, HR, SV, and \( \dot{Q} \) were recorded before, during and after each LBNP test. The expired air was collected for 3 min before the start, the last 3 min during LBNP, and after LBNP application. Blood pressure was also measured before, at 0.5, 2.5, and 4.5 min during, and at 0.5 and 2.5 min after LBNP.

**Data analysis.** The distribution of each population of data was shown to be approximately Gaussian, so a paired Student’s \( t \)-test was chosen for statistical analysis. In all cases, a \( p \) value less than 0.05 was required to achieve statistical significance.

**RESULTS**

**Respiratory responses**

Just after application of LBNP, \( PET_{O₂} \) and \( PET_{CO₂} \) immediately increased and decreased, respectively, in proportion to the magnitude of the negative pressure (Fig. 1). Later in the LBNP phase, \( PET_{O₂} \) gradually returned to the control level,
but PETCO₂ was maintained low. VT was rather constant during LBNP at all three levels (Fig. 1). The respiratory frequency (f) decreased significantly, accompanied by a slight increase in TI and TE. The magnitude of the f depression, however, was not directly related to the level of LBNP (Fig. 1). The low f and nearly unchanged

*Japanese Journal of Physiology*
CARDIOPULMONARY RESPONSE TO LBNP

VT were consistent with a reduction of $\dot{V}E$ during LBNP (Fig. 1).

Circulatory responses

SV and $Q$ decreased rapidly during LBNP in all subjects, whereas HR increased progressively. These changes were proportional to the applied LBNP (Fig. 1). The BPs fell significantly, while BPD rose, so PP was reduced significantly and proportional to the LBNP exposure (Fig. 2). However, MAP was well maintained at the control level of all LBNP (Fig. 2). A significant increase in TPVR was found, and the increments were related to the intensity of the negative pressure applied (Fig. 2).

Metabolic and cardiopulmonary responses

The $\dot{V}O_2$ decreased by 14, 15, and 18% and $\dot{V}CO_2$ by 13, 13, and 17% below the control level, at three LBNP levels, respectively (Table 1). The ventilatory quotient ($R$) was found unchanged during LBNP due to parallel changes in $\dot{V}O_2$ and $\dot{V}CO_2$ (Table 1). Both the $(a-\bar{v})O_2$ and $(\bar{v}-a)CO_2$ concentration differences

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Table 1. Effects of 3 levels of LBNP on metabolism, ventilation, and cardiac equivalent for O₂ and CO₂, (a-v)O₂ and (v-a)CO₂ difference.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>LBNP</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \dot{V}_O_2 )</td>
<td>(ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−20)</td>
<td>249.7 ± 38.9</td>
<td>215.8 ± 28.8**</td>
<td>261.3 ± 30.5**</td>
</tr>
<tr>
<td>(−40)</td>
<td>235.7 ± 44.6</td>
<td>199.5 ± 28.1**</td>
<td>265.3 ± 33.2**</td>
</tr>
<tr>
<td>(−60)</td>
<td>234.8 ± 45.2</td>
<td>193.0 ± 33.4**</td>
<td>275.0 ± 43.4**</td>
</tr>
<tr>
<td>( \dot{V}_{CO_2} )</td>
<td>(ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−20)</td>
<td>186.8 ± 28.7</td>
<td>162.3 ± 17.6**</td>
<td>189.6 ± 23.8**</td>
</tr>
<tr>
<td>(−40)</td>
<td>175.0 ± 37.7</td>
<td>153.5 ± 28.2**</td>
<td>195.7 ± 36.1**</td>
</tr>
<tr>
<td>(−60)</td>
<td>179.3 ± 37.8</td>
<td>148.8 ± 29.8*</td>
<td>200.8 ± 38.5**</td>
</tr>
<tr>
<td>( R )</td>
<td>(−20)</td>
<td>0.75 ± 0.07</td>
<td>0.76 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>(−40)</td>
<td>0.74 ± 0.08</td>
<td>0.77 ± 0.07</td>
</tr>
<tr>
<td></td>
<td>(−60)</td>
<td>0.76 ± 0.08</td>
<td>0.77 ± 0.06</td>
</tr>
<tr>
<td>( \dot{V}<em>E/\dot{V}</em>{O_2} )</td>
<td>(−20)</td>
<td>31.86 ± 5.09</td>
<td>33.80 ± 6.76**</td>
</tr>
<tr>
<td></td>
<td>(−40)</td>
<td>32.73 ± 5.30</td>
<td>35.18 ± 5.67**</td>
</tr>
<tr>
<td></td>
<td>(−60)</td>
<td>33.20 ± 4.83</td>
<td>36.10 ± 4.23*</td>
</tr>
<tr>
<td>( \dot{V}<em>E/\dot{V}</em>{CO_2} )</td>
<td>(−20)</td>
<td>42.38 ± 4.42</td>
<td>44.39 ± 4.94**</td>
</tr>
<tr>
<td></td>
<td>(−40)</td>
<td>43.28 ± 6.04</td>
<td>45.96 ± 6.76*</td>
</tr>
<tr>
<td></td>
<td>(−60)</td>
<td>43.55 ± 4.14</td>
<td>47.02 ± 6.02**</td>
</tr>
<tr>
<td>( \dot{Q}/\dot{V}_{O_2} )</td>
<td>(−20)</td>
<td>23.14 ± 3.28</td>
<td>21.36 ± 3.02</td>
</tr>
<tr>
<td></td>
<td>(−40)</td>
<td>22.87 ± 3.85</td>
<td>18.67 ± 3.75*</td>
</tr>
<tr>
<td></td>
<td>(−60)</td>
<td>23.77 ± 3.61</td>
<td>16.78 ± 3.91**</td>
</tr>
<tr>
<td>( \dot{Q}/\dot{V}_{CO_2} )</td>
<td>(−20)</td>
<td>31.20 ± 6.27</td>
<td>28.32 ± 4.01</td>
</tr>
<tr>
<td></td>
<td>(−40)</td>
<td>31.21 ± 6.71</td>
<td>24.40 ± 5.09**</td>
</tr>
<tr>
<td></td>
<td>(−60)</td>
<td>31.47 ± 5.84</td>
<td>21.76 ± 4.61**</td>
</tr>
<tr>
<td>(a-v)O₂ differ.</td>
<td>(−20)</td>
<td>44 ± 6</td>
<td>48 ± 8</td>
</tr>
<tr>
<td></td>
<td>(−40)</td>
<td>45 ± 6</td>
<td>56 ± 13*</td>
</tr>
<tr>
<td></td>
<td>(−60)</td>
<td>43 ± 6</td>
<td>63 ± 16**</td>
</tr>
<tr>
<td>(v-a)CO₂ differ.</td>
<td>(−20)</td>
<td>33 ± 6</td>
<td>36 ± 6</td>
</tr>
<tr>
<td></td>
<td>(−40)</td>
<td>33 ± 6</td>
<td>42 ± 10*</td>
</tr>
<tr>
<td></td>
<td>(−60)</td>
<td>33 ± 6</td>
<td>48 ± 11**</td>
</tr>
</tbody>
</table>

Values are means ± S.D. \( \dot{Q} \), cardiac output; \( \dot{V}_E \), minute ventilation; \( R \), respiratory exchange ratio. \( \dot{V}_E/\dot{V}_{O_2} \) and \( \dot{V}_E/\dot{V}_{CO_2} \), ventilation equivalent for O₂ and CO₂. \( \dot{Q}/\dot{V}_{O_2} \) and \( \dot{Q}/\dot{V}_{CO_2} \), cardiac output equivalent for O₂ and CO₂. (a-v)O₂ and (v-a)CO₂ differences were calculated by Fick equation. **\( p < 0.05 \), ***\( p < 0.01 \). Significantly different from the control level.

*Japanese Journal of Physiology*
increased significantly in parallel with the intensity of LBNP (Table 1). The mixed venous CO₂ concentration (CvCO₂) was maintained at the control level of all LBNP exposures (Table 3). The ventilation (VE/VO₂ and VE/VCO₂) and cardiac output (Q/VO₂ and Q/VCO₂) equivalents increased and decreased proportionally to the intensity of LBNP, respectively (Table 1). The SaO₂ alteration followed the PETO₂ changes (Fig. 1).

Recovery responses
Most variables returned to the control level either immediately or within 3 min after release of LBNP (Figs. 1, 2, and Table 1).

DISCUSSION
Circulatory responses. Our LBNP application elicited rapid and significant reductions in SV and Q, as was also found by others (STEVENS and LAMB, 1965; WOLTHUIS et al., 1974). The reduction in Q is primarily due to a shift of central blood to the legs and pelvic regions (STEVENS and LAMB, 1965; MAINS et al., 1968; MUSGRAVE et al., 1971; MONTGOMERY et al., 1977). In spite of a marked fall in Q, the MAP was kept constant at control level, resulting in a rapid and significant increase in TPVR (Fig. 2) as reported earlier (STEVENS and LAMB, 1965; MURRAY et al., 1968; FREY and HOFFLER, 1988). The fall in PP may have caused tachycardia, probably through deactivation of the cardiac-sinus baroreceptors (EAD et al., 1952). The BPs and PP fall must be due to reduced venous return caused by LBNP, and according to Starling’s law of the heart we expected the reduced SV actually observed.

Our subjects had neither any incidence of syncopal episodes, nor any marked, initial elevation in HR during LBNP. Subjects responding with a marked rise in HR and a lesser increase in TPVR during LBNP tend to have lower tolerance to LBNP exposure (STEVENS and LAMB, 1965). However our subjects showed a high peripheral vascular tone, well-maintained MAP, and relatively slowly increasing HR during LBNP. Q decreased rapidly in the early phase and was then maintained relatively constant during LBNP (Fig. 1). Thus no further pooling of blood took place in the lower body regions. Simultaneously, HR and TPVR were increased, and MAP was rather constant. In addition, our fall in PCO₂ must correspond to a fall in arterial PCO₂, which can cause a venoconstriction (CRUZ et al., 1976). Such a general venoconstriction is probably an important factor in the protection of the body against an excessive fall in Q.

Cardiopulmonary responses. LBNP induced a rapid and significant fall in VE. This result may be explainable with one or more of the following hypotheses.

The cardiodynamic hypothesis: A possible mechanism contributing to the fall in VE could be the fall in Q during LBNP. JONES et al. (1981) reported that reduction of Q, induced by cardiac pacing, caused a fall in VE, VCO₂, and PETCO₂ and an elevation in PETO₂. Our results coincided with their data. BROWN et al. (1976) found a decreased CO₂ flux to the lungs of human treated with propranolol; this resulted
in decreased $\dot{Q}$ and a hypopnea. It was suggested that right ventricular strain acts as a controller of ventilation and provides a link between $\dot{Q}$ and pulmonary ventilation. The decrements in central venous pressure (CVP) and right atrial pressure during LBNP may affect right ventricular function due to a reduction in pulmonary blood flow and in the volume of the pulmonary capillary bed (Zechman et al., 1967; Dowell et al., 1969). Other investigators found decreased CVP (by 3–7 mmHg) during LBNP in the range from −10 to −60 mmHg (Stevens and Lamb, 1965; Murray et al., 1968; Rowell et al., 1972; Katkov et al., 1987). Johnson et al. (1973) noted a decrease in right atrial pressure during moderate LBNP. All this information points to a close matching of the respiratory and the cardiovascular events as expressed in the cardiodynamic hypothesis (Wasserman et al., 1974).

Assuming this hypothesis to be the explanation of our results, we must expect proportionality between the respiratory and circulatory alterations. The latter was changed proportionally to the intensity of the LBNP exposure. However, $\dot{V}E$ only fell by 12% at all levels (Table 2). Accordingly, the ventilatory fall during LBNP may not be completely explainable by cardiodynamics. Thus we must consider other possibilities.

Hemorrhage hypothesis: The physiological responses to LBNP are similar to those of acute hemorrhage. In the cat, ventilation increased during hemorrhage, which was accompanied by hypotension and stimulation of the carotid body chemoreceptors (D'Silva et al., 1966). Our MAP was well maintained and ventilation was reduced during LBNP, and our data exclude hypoxia, so the fall in $\dot{V}E$ cannot be related to this mechanism.

Optimization hypothesis: The $PETCO_2$ decreased and $PETO_2$ rose during LBNP. Peripheral chemoreceptor and central chemosensation may have been suppressed by increased $PO_2$ and by decreased $PACO_2$. However, a constant, minimal suction in the pelvic region may also have reduced the intrapulmonic pressure, and thus improved the efficiency of the respiratory work (Poon, 1987). Thus the mechanical efficiency of the lungs induced by gravity in standing man, seems to be operating also during LBNP, even here where direct influence from high LBNP application

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Table 2. Maximal changes in $\dot{Q}$ and $\dot{V}E$ during 3 different levels of LBNP.

<table>
<thead>
<tr>
<th>LBNP (mmHg)</th>
<th>$\dot{Q}$(l/min)</th>
<th>Peak-response</th>
<th>Decrement in %</th>
<th>$\dot{V}E$(l/min)</th>
<th>Peak-response</th>
<th>Decrement in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
<td>5.73±0.94</td>
<td>4.23±0.97**</td>
<td>26</td>
<td>7.86±1.11</td>
<td>6.88±1.53*</td>
<td>12</td>
</tr>
<tr>
<td>-40</td>
<td>5.29±0.82</td>
<td>3.48±0.58**</td>
<td>34</td>
<td>7.63±1.38</td>
<td>6.88±1.60*</td>
<td>12</td>
</tr>
<tr>
<td>-60</td>
<td>5.48±0.74</td>
<td>2.93±0.76**</td>
<td>46</td>
<td>7.94±1.68</td>
<td>6.85±1.56*</td>
<td>13</td>
</tr>
</tbody>
</table>

Values are means±S.D. $\dot{Q}$, cardiac output; $\dot{V}E$, minute ventilation. *$p<0.05$, **$p<0.01$. Significantly different from the control level.
CARDIOPULMONARY RESPONSE TO LBNP

We hereby assume with Poon (1987) that the respiratory control system minimizes the net cost of the conflicting chemical and mechanical demands. For standing position (or LBNP exposure), it is cost-effective to be hypocapnic. Further studies are necessary in order to explain how the respiratory control system optimizes the cost of breathing.

On the other hand, although the $\dot{V}_E$ decreased in absolute terms as mentioned above, we found a relative hyperventilation (i.e., a rise in $\dot{V}_E/\dot{V}_{CO_2}$ corresponding to the fall in end-tidal $P_{CO_2}$) during LBNP. While cardiac output equivalent decreased inversely with the negative pressure (Table 1), the reciprocal values of the cardiac output equivalents (i.e., the values of $C_{AO_2} - C_{VO_2}$ and $C_{vCO_2} - C_{aCO_2}$) increased. These results were due to a fall in $C_{aCO_2}$ (Table 3). The constant $CO_2$ concentration in the mixed venous blood (Table 3), suggests that tissue $CO_2$ concentration as well as tissue pH might also be constant. Hereby the acid-base balance in the tissues could be maintained, whereas that of the arterial blood varies. This constant $C_{vCO_2}$ may owe to increased ventilation equivalent during LBNP. We further found that the ventilatory equivalent increased proportionally to decreased circulatory equivalent during LBNP (Fig. 3, $p<0.01$). These observations indicate the

Fig. 3. The relation between ventilation and cardiac output equivalents for $O_2$ and $CO_2$ ($\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$, and $Q/\dot{V}_{O_2}$ and $Q/\dot{V}_{CO_2}$, respectively) at 3 levels of LBNP.
existence of a ventilatory mechanism to counteract the sustained depression of $\dot{Q}$ caused by LBNP.

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REFERENCES


51: 1103–1107.


