Maintaining cerebral blood flow
Bronzwaer, A.-S.G.T.

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4.2

The cerebrovascular response to lower body negative pressure versus head-up tilt

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ABSTRACT

Lower body negative pressure (LBNP) has been proposed as a MRI compatible surrogate for orthostatic stress. Although the effects of LBNP on cerebral hemodynamic behavior have been considered to reflect those of orthostatic stress, a direct comparison with actual orthostasis is lacking. We assessed the effects of LBNP (-50 mmHg) versus head-up tilt (HUT; at 70°) in 10 healthy subjects (5 female) on transcranial Doppler determined cerebral blood flow velocity (CBFv) in the middle cerebral artery and cerebral perfusion pressure (CPP) as estimated from the blood pressure signal (finger plethysmography). CPP was maintained during LBNP but decreased after 2 min in response to HUT leading to a ~15% difference in CPP between LBNP and HUT (p≤0.020). Mean CBFv initially decreased similarly in response to LBNP and for HUT but from minute 3 on, the decline became ~50% smaller (p≤0.029) during LBNP. The reduction in end-tidal PCO₂ was comparable but with an earlier return towards baseline values in response to LBNP but not during HUT (p=0.008). We consider the larger decrease in CBFv during HUT versus LBNP attributable to the pronounced reduction in end-tidal PCO₂ and to gravitational influences on CPP and this should be taken into account when applying LBNP as an MRI compatible orthostatic stress modality.
INTRODUCTION

Orthostatic stress elicits a gravitational shift of blood away from the upper towards the lower parts of the body. The postural decline in arterial pressure at the level of the brain is subsequently being counteracted by a cerebrovascular autoregulatory adaptive response. Nevertheless, steady-state cerebral blood flow velocity (CBFv) as determined by transcranial Doppler (TCD) and cortical oxygenation decrease when changing from the supine to the upright body position. If the postural reduction in cerebral perfusion is substantial, the mismatch between cerebral oxygen demand vs. supply results in a transient loss of consciousness. Passive head-up tilt (HUT) is a commonly used orthostatic stress test, for example employed for the evaluation of patients with syncope of unknown origin. Cerebral hemodynamics are then often monitored by TCD which measures CBFv in a large brain-feeding artery as a proxy for cerebral blood flow (CBF).

Advances in functional MRI techniques have enabled the measurement of not only cerebral blood flow but also volume and oxygenation at the brain tissue level which would provide a more complete insight into the cerebral hemodynamic response to orthostatic stress. Evaluating the cerebrovascular orthostatic response with MRI is, however, challenging because either active standing or passive HUT is incompatible with the horizontal and static setup of an MRI scanner. Lower body negative pressure (LBNP) has the potential to serve as an MRI compatible surrogate of orthostatic stress as it reduces central blood volume while the subject remains in the supine body position. Although the effects of LBNP on cerebral hemodynamic behavior have been considered to reflect those elicited by orthostatic stress, a direct comparison with actual orthostasis is not available. The present study aimed to provide a formal comparison of the systemic and cerebrovascular responses to LBNP (-50 mmHg) versus HUT (70°) in young healthy volunteers.

METHODS

Subjects

Ten healthy, non-smoking subjects (5 female), with a median (range) age of 22 (19-26) years, height of 174 (166-177) cm and weight 69 (55-77) kg with no history of fainting and/or cardiac arrhythmia nor taking cardiovascular medication participated in this study. Phase of menstrual cycle was not accounted for. Subjects abstained from heavy exercise and caffeinated beverages for at least 5 h prior to the experiments, that were conducted in a temperature-controlled laboratory (20-22°C) at the same time of the day.
(12 to 4 pm). The institutional Medical Ethics Committee approved the study protocol and both oral and written informed consent was obtained from all participants.

**Experimental protocol**

Measurements were performed with subjects in the supine position on a manually operated tilt table (Dr. Kaiser Medizintechnik, Bad Hersfeld, Germany). Following instrumentation, the lower body was positioned inside the LBNP box and sealed at the level of the iliac crest. The study protocol consisted of a 5 min baseline period followed by either a 5-min period of LBNP (-50 mmHg) or a 5 min period of HUT (70°). All participants underwent both LBNP and HUT. As these experiments were part of a larger study program, LBNP and HUT were applied in a fixed order starting with LBNP. To prevent a downward shift of the body into the LBNP box disrupting the tight air sealing with loss of sub-atmospheric pressure, the LBNP box was supplied with a saddle. During HUT, subjects were instructed not to tense their legs while their body was restraint to the table by straps. The transition to -50 mmHg LBNP or 70° HUT was established within 10 s. The safety guidelines of the protocol determined that LBNP and HUT would both be terminated in case of (pre-)syncopal symptoms including sweating, light-headedness, nausea, blurred vision and/or signs meeting one or more of the following criteria: systolic arterial pressure (SAP) below 80 mmHg, or rapid drop (SAP by ≥20 mmHg·min⁻¹, diastolic arterial pressure (DAP) by ≥10 mmHg·min⁻¹), and drop in HR by ≥15 bpm.

**Measurements**

Continuous blood pressure (BP) was measured non-invasively by finger plethysmography with the cuff placed around the middle phalanx of the non-dominant hand placed at heart level (Nexfin, Edwards Lifesciences BMEYE, the Netherlands). Left ventricular stroke volume (SV) was determined by a pulse contour method (Nexfin CO-trek, Edwards Lifesciences BMEYE, Amsterdam, the Netherlands) that has been validated against thermodilution measurements. Cardiac output (CO) was calculated as SV times HR and total peripheral resistance (TPR) was the ratio between mean arterial pressure (MAP) and CO. End-tidal CO₂ partial pressure (PetCO₂) was monitored through a nasal cannula connected to a capnograph (Datex Normocap 200, Helsinki, Finland). Changes in CBFv were followed in the proximal segment of the middle cerebral artery (MCA) by means of TCD (DWL Multidop X4, Sipplingen, Germany). The left MCA was insonated through the temporal window just above the zygomatic arch at a depth of 40–60 mm with a pulsed 2 MHz probe. After signal optimization, the probe was immobilized by a head-band.

**Data Analysis**

All signals were inspected and artefacts removed. Blood pressure at the level of the MCA (BPbrain) was estimated by subtracting the hydrostatic column between the level of the
left atrium and the insonation point of the TCD probe (present during HUT only), from BP at heart level (BP<sub>heart</sub>). Cerebral perfusion pressure (CPP) was approximated as the difference between BP<sub>brain</sub> and critical closing pressure (CrCP; the pressure inside a blood vessel below which the vessel will collapse and blood flow ceases<sup>193</sup>), see Figure 4.2.1. The instantaneous relationship between first harmonic filtered BP<sub>brain</sub> and CBFv waveforms was used to estimate CrCP for each cardiac cycle.<sup>194</sup> CrCP could then be obtained by extrapolation of the linear regression CBFv = a x BP<sub>brain</sub> + b where CrCP equals BP<sub>brain</sub> at zero CBFv: CrCP = -b/a.<sup>193-195</sup> The resistance area product (RAP) was estimated as measure for cerebrovascular resistance by the inverse of the aforementioned linear regression slope (RAP = 1/a). In contrast to other measures of cerebrovascular resistance, the RAP takes the CrCP into account and has therefore the potential to convey more information about the cerebral circulation.<sup>193,196</sup>

**Statistical Analysis**

Data were analyzed with Sigmaplot (version 11.0, Systat Software Inc., USA) and are presented as mean ± SEM. Two-way repeated measures ANOVA was used to identify differences in both systemic and cerebrovascular parameters between LBNP/HUT and time of exposure (including the first minute after termination or tilt back). Upon identification of a significant interaction, multiple comparisons were made using Holm-Sidak’s post hoc analysis. A p-value less than 0.05 was considered to indicate a statistically significant difference.
Figure 4.2.1. Stepwise calculation of cerebral perfusion pressure (CPP) from blood pressure at heart level (BP\textsubscript{heart}). BP at brain level (BP\textsubscript{brain}) is estimated by accounting for the hydrostatic column between heart and brain. The critical closing pressure (CrCP) is derived from the zero-flow pressure intercept by linear regression analysis of instantaneous mean CBFv-mean BP\textsubscript{brain} relationships in which the pressure-axis intercept equals CrCP. The driving pressure of the brain is approximated by the CPP as the difference between BP\textsubscript{brain} and CrCP. The larger reduction in CrCP during HUT vs. LBNP incorporates the influence of the hydrostatic column on BP\textsubscript{brain} that is present during HUT but not LBNP.
RESULTS

Rest

Baseline systemic and cerebrovascular parameters were comparable for LBNP and HUT, except for BP and TPR which were lower prior to LBNP (p≤0.002; Table 4.2.1 and Table 4.2.2).

Table 4.2.1. Systemic and cerebrovascular response to lower body negative pressure.

<table>
<thead>
<tr>
<th></th>
<th>LBPN</th>
<th>baseline</th>
<th>1st min</th>
<th>2nd min</th>
<th>3rd min</th>
<th>4th min</th>
<th>5th min</th>
<th>post</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean BP&lt;sub&gt;heart&lt;/sub&gt; (mmHg)</td>
<td>87 ± 13*</td>
<td>87 ± 12</td>
<td>85 ± 14</td>
<td>87 ± 12</td>
<td>86 ± 11</td>
<td>84 ± 12</td>
<td>88 ± 13</td>
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<tr>
<td>mean BP&lt;sub&gt;brain&lt;/sub&gt; (mmHg)</td>
<td>87 ± 13*</td>
<td>87 ± 12</td>
<td>85 ± 14</td>
<td>87 ± 12</td>
<td>86 ± 11</td>
<td>84 ± 12</td>
<td>88 ± 13</td>
<td></td>
</tr>
<tr>
<td>mean CBFv (cm·s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>68 ± 7</td>
<td>59 ± 7&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>61 ± 10&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>64 ± 7</td>
<td>62 ± 6&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>62 ± 4&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>67 ± 5</td>
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<td>CPP (mmHg)</td>
<td>71 ± 11</td>
<td>79 ± 14&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>76 ± 14</td>
<td>78 ± 13</td>
<td>77 ± 10</td>
<td>76 ± 13</td>
<td>68 ± 11</td>
<td></td>
</tr>
<tr>
<td>RAP (mmHg·cm&lt;sup&gt;-1&lt;/sup&gt;·s)</td>
<td>1.06 ± 0.16</td>
<td>1.34 ± 0.25&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>1.27 ± 0.27&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>1.21 ± 0.18&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>1.25 ± 0.18&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>1.22 ± 0.19&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>1.07 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>CrCP (mmHg)</td>
<td>17 ± 14</td>
<td>9 ± 17&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>10 ± 16&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>10 ± 19&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>9 ± 17&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>8 ± 16&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>20 ± 12</td>
<td></td>
</tr>
<tr>
<td>HR (beats·min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>67 ± 15</td>
<td>77 ± 11&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>83 ± 13&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>85 ± 11&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>87 ± 12&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>89 ± 11&lt;sup&gt;‡&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>SV (mL)</td>
<td>109 ± 16</td>
<td>84 ± 17&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>82 ± 16&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>80 ± 13&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>79 ± 15&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>76 ± 15&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>106 ± 13</td>
<td></td>
</tr>
<tr>
<td>CO (L·min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>7.2 ± 1.2</td>
<td>6.5 ± 1.1&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>6.7 ± 1.3&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>6.8 ± 1.3&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>6.7 ± 1.3&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>7.1 ± 1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPR (dyn·s·cm&lt;sup&gt;-5&lt;/sup&gt;)</td>
<td>987 ± 186&lt;sup&gt;‡&lt;/sup&gt; 1111 ± 270&lt;sup&gt;‡&lt;/sup&gt; 1052 ± 259</td>
<td>1065 ± 249&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>1038 ± 221</td>
<td>1035 ± 214</td>
<td>1025 ± 200</td>
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<td></td>
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<tr>
<td>PetCO&lt;sub&gt;2&lt;/sub&gt; (mmHg)</td>
<td>39.4 ± 2.9</td>
<td>35.7 ± 4.2&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>35.2 ± 5.3&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>36.2 ± 5.0&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>36.0 ± 4.9&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>37.3 ± 4.3</td>
<td>39.2 ± 2.9</td>
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</tbody>
</table>

Data are presented as mean ± SEM. BP, blood pressure; CBFv, cerebral blood flow velocity; RAP, resistance area product; CrCP, critical closing pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; PetCO<sub>2</sub>, end-tidal carbon dioxide partial pressure. ‡p<0.05 vs. baseline; *p<0.05 vs. baseline prior to LBNP (see Table 4.2.1).

Table 4.2.2. Systemic and cerebrovascular response to head-up tilt.

<table>
<thead>
<tr>
<th></th>
<th>HUT</th>
<th>baseline</th>
<th>1st min</th>
<th>2nd min</th>
<th>3rd min</th>
<th>4th min</th>
<th>5th min</th>
<th>post</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean BP&lt;sub&gt;heart&lt;/sub&gt; (mmHg)</td>
<td>95 ± 14*</td>
<td>95 ± 15</td>
<td>98 ± 20</td>
<td>94 ± 17</td>
<td>94 ± 15</td>
<td>94 ± 15</td>
<td>93 ± 13</td>
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<tr>
<td>mean BP&lt;sub&gt;brain&lt;/sub&gt; (mmHg)</td>
<td>95 ± 14*</td>
<td>77 ± 16&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>80 ± 20&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>76 ± 17&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>76 ± 15&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>76 ± 15&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>94 ± 13</td>
<td></td>
</tr>
<tr>
<td>mean CBFv (cm·s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>70 ± 10</td>
<td>63 ± 14&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>63 ± 11&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>62 ± 8&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>60 ± 8&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>60 ± 8&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>68 ± 10</td>
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<tr>
<td>CPP (mmHg)</td>
<td>83 ± 13</td>
<td>80 ± 15</td>
<td>84 ± 11</td>
<td>78 ± 7&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>77 ± 8&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>79 ± 9&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>77 ± 16&lt;sup&gt;‡&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>RAP (mmHg·cm&lt;sup&gt;-1&lt;/sup&gt;·s)</td>
<td>1.24 ± 0.29</td>
<td>1.38 ± 0.31&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>1.41 ± 0.24&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>1.33 ± 0.23</td>
<td>1.36 ± 0.26</td>
<td>1.39 ± 0.23&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>1.20 ± 0.28</td>
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<tr>
<td>CrCP (mmHg)</td>
<td>13 ± 13</td>
<td>-2 ± 13&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>-3 ± 15&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>-1 ± 14&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>1 ± 14&lt;sup&gt;‡&lt;/sup&gt;</td>
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<td>19 ± 14&lt;sup&gt;‡&lt;/sup&gt;</td>
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<td>HR (beats·min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>65 ± 10</td>
<td>78 ± 10&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>81 ± 8&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>84 ± 10&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>82 ± 10&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>82 ± 11&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>66 ± 11</td>
<td></td>
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<tr>
<td>SV (mL)</td>
<td>114 ± 18</td>
<td>84 ± 14&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>83 ± 13&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>84 ± 14&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>83 ± 15&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>84 ± 17&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>115 ± 18</td>
<td></td>
</tr>
<tr>
<td>CO (L·min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>7.2 ± 0.8</td>
<td>6.5 ± 0.8&lt;sup‡&lt;/sup&gt;</td>
<td>6.6 ± 0.8&lt;sup‡&lt;/sup&gt;</td>
<td>6.7 ± 0.9&lt;sup‡&lt;/sup&gt;</td>
<td>6.7 ± 1.1&lt;sup‡&lt;/sup&gt;</td>
<td>6.8 ± 1.0&lt;sup‡&lt;/sup&gt;</td>
<td>7.5 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>TPR (dyn·s·cm&lt;sup&gt;-5&lt;/sup&gt;)</td>
<td>1081 ± 214* 1195 ± 291&lt;sup&gt;‡&lt;/sup&gt; 1242 ± 369&lt;sup&gt;‡&lt;/sup&gt; 1129 ± 312</td>
<td>1170 ± 311</td>
<td>1162 ± 302</td>
<td>1024 ± 181</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PetCO&lt;sub&gt;2&lt;/sub&gt; (mmHg)</td>
<td>39.7 ± 3.2</td>
<td>36.8 ± 2.6&lt;sup‡&lt;/sup&gt;</td>
<td>36.8 ± 2.0&lt;sup‡&lt;/sup&gt;</td>
<td>36.1 ± 2.5&lt;sup‡&lt;/sup&gt;</td>
<td>35.8 ± 3.1&lt;sup‡&lt;/sup&gt;</td>
<td>36.4 ± 2.7&lt;sup‡&lt;/sup&gt;</td>
<td>38.8 ± 1.5</td>
<td></td>
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</tbody>
</table>

Data are presented as mean ± SEM. For abbreviations see Table 4.2.1. ‡p<0.05 vs. baseline; *p<0.05 vs. baseline prior to LBNP (see Table 4.2.1).
**Systemic circulation**

Mean BP<sub>heart</sub> was maintained in response to both LBNP and HUT with similar changes in HR, SV, CO and TPR (Figure 4.2.2). An overshoot in CO was observed after tilt back but not after termination of LBNP (p=0.007).

![Graph showing the changes in systemic response to 5 min LBNP and 70° HUT](image)

**Figure 4.2.2.** Change in systemic response to 5 min LBNP (black circles) and 70° HUT (grey triangles). BP<sub>heart</sub>, blood pressure at heart level; SV, stroke volume; HR, heart rate; CO, cardiac output. ‡p<0.05 vs. rest; *p<0.05 LBNP vs. HUT

**Cerebrovascular circulation**

After stabilization following the transition from supine to the upright tilted position, CPP differed between LBNP and HUT (p≤0.020; Figure 4.2.3A), predominantly by a reduction in CPP during HUT. The initial increase in RAP was 70% smaller in response to HUT vs. LBNP (p=0.002). The trend of a higher RAP during the remaining period of LBNP vs. HUT (apparent in Figure 4.2.3B) did not reach statistical significance. Mean CBFv initially decreased similarly in response to LBNP and for HUT but from minute 3 on, the decline in mean CBFv was ~50% smaller (p≤0.006) during LBNP (see Figure 4.2.3C). PetCO<sub>2</sub> initially declined similarly in response to LBNP and HUT with an early rise towards baseline values during LBNP but not during HUT (p=0.021; Figure 4.2.3D).
The cerebrovascular response to LBNP versus head-up tilt

Figure 4.2.3. Change in cerebrovascular response to 5 min LBNP (black circles) or 70° HUT (grey triangles). CPP, cerebral perfusion pressure; RAP, resistance area product; CBFv, cerebral blood flow velocity; PetCO2, end-tidal CO2; #p<0.05 vs. rest; *p<0.05 LBNP vs. HUT.

DISCUSSION

The present study assessed the cerebrovascular response to LBNP versus the clinical customary but MRI-incompatible tilt-table test. The novel finding of the study is a ~50% smaller decline in mean CBFv during LBNP compared to HUT from min 3 on, concurrent to similar systemic hemodynamic responses throughout the respective challenges. We consider this difference attributable to the larger reduction in PetCO2 together with hydrostatic effects on the cerebral circulation as will be addressed.

Systemic circulation

Both LBNP and HUT reduce venous return and thus central blood volume by pooling of blood in the lower parts of the body.197,198 Musgrave et al. found that LBNP at -40 mmHg produces a 500-600 ml shift of blood to the legs,199 quantitatively similar to the volume shift observed by the upright posture or 70° HUT.116,147,200 Both LBNP and HUT produce a similar decline in thoracic volume and increase in pelvic and leg volume as measured with impedance plethysmography.201 The current finding that -50 mmHg LBNP and 70° HUT leads to similar changes in HR, SV, and thus CO without arterial hypotension conforms to data from previous studies.202-204 The finding by Taneja et al.201 of a larger increase in HR during 70° HUT compared to -50 mmHg LBNP may be related to the ramp
protocol used and subjects did not act as their own control. Overall, the present and previous findings support the contention that 70° HUT and -50 mmHg LBNP evoke a similar degree of central hypovolemia with comparable systemic hemodynamic responses.

**Influence of PetCO₂**

The maximal reduction in PetCO₂ was comparable for LBNP and HUT, but the time course differed markedly, that is: a progressive decline with HUT versus a sharp decrease followed by a gradual return to baseline values with LBNP. The CO₂ reactivity of the brain vasculature implies on average a ~3.5% change in CBFv per mmHg PetCO₂ in the normocapnic range.⁷⁹,²⁰⁵ Accordingly, the dissimilarity in PetCO₂ response between LBNP and HUT appears to result in a concomitant differential response in mean CBFv (Figure 4.2.3, lower panel). Nevertheless, PetCO₂ is a valid proxy for changes in arterial PCO₂ (which affects CBFv) as long as the premise of a stable ventilation-perfusion (V̇̇E/Q̇̇) ratio is met. The implication is that in a fixed body position PetCO₂ tracks changes in arterial PCO₂ but when assuming the upright position, Q decreases and its distribution over the lung changes, while V̇̇E increases.²⁰⁶-²⁰⁹ With the transition from the supine to the upright position, air expired from the basal alveoli is diluted by that from the relatively underperfused apical alveoli,²⁰⁸,²¹⁰ and in healthy humans the V̇̇E/Q̇̇ ratio increases ~50% from supine to upright.²¹¹,²¹² In the present study the reduction in CO in response to LBNP and HUT was comparable. However, LBNP plays only a minor role in affecting regional ventilatory parameters when compared with gravity.²¹³ In addition, during HUT a hydrostatic pressure gradient develops down the lungs with an influence on the distribution of blood over the lungs.²⁰⁷ Hence, the V̇̇E/Q̇̇ mismatch is assumed being larger during HUT vs. LBNP which results in enhanced overestimation of the postural decline in arterial CO₂ by PetCO₂. We therefore consider the difference in arterial PCO₂ between LBNP and HUT being smaller than the difference expressed by PetCO₂. This indicates that the larger reduction in CBFv during HUT vs. LBNP cannot solely be attributed to the difference in PetCO₂.

**Hydrostatic pressure effects**

Raising the head above heart level during 70° HUT but not during LBNP, creates an estimated 15-20 mmHg hydrostatic pressure difference between the aortic arch and large cerebral vessels with a ~20% decline in mean BPbrain. The effective CPP is, however, not equal to BPbrain but influenced by intracranial pressure (ICP) and vasomotor tone.²¹⁴ In the present paper these factors are represented by the critical closing pressure; CrCP.¹⁹³,¹⁹⁵ The decline in CrCP in response to both LBNP and HUT is consistent with findings during the early phase of tilt.²¹⁵ The larger decrease in CrCP during HUT versus LBNP might
be the result of a larger decline in ICP by reductions in cerebrospinal fluid and blood volume when assuming the upright posture.\textsuperscript{216,217} The decline in ICP varied from \(~4\) to \(~10\) mmHg in response to standing,\textsuperscript{218} and 70° HUT.\textsuperscript{219,220} It has as yet not been evaluated whether and to what degree ICP changes in response to LBNP.

The time course of CBFv, PetCO\(_2\) and CPP suggests that the instantaneous increase in CPP during LBNP was initially counteracted by a reduction in PetCO\(_2\). The difference in CBFv between LBNP and HUT from minute 3 onwards was, however, concomitant to a difference in PetCO\(_2\) and CPP, suggesting a separate effect of CPP on CBFv. According to the concept of the cerebral autoregulation (CA), different values for CPP within a certain arterial pressure range should not affect cerebral perfusion much.\textsuperscript{221} However, the concept of CA as a flat plateau has been challenged.\textsuperscript{65,222,223} In fact, maintaining constant CBF with increasing mean BP would require an infinite gain that is generally not operative in humans.\textsuperscript{8,12,224} Taken together, CPP may well have contributed to the small difference in CBFv between LBNP and HUT, even with the pressure difference within what has been indicated as the autoregulatory range.\textsuperscript{225}

**Limitations**

Potential limitations inherent to the study design should be considered. The driving pressure of the brain cannot easily be determined in healthy humans because measurement of parameters such as the ICP requires an invasive procedure. In this study we estimated the CPP, as proxy for the brain’s driving pressure, by taking the hydrostatic height difference,\textsuperscript{226,227} and the CrCP as a representation of ICP into account.\textsuperscript{193,214,228} There is an ongoing debate on whether BP at heart vs. brain level approximates the driving pressure for the brain more closely. For the blood flow regulation of the brain, its inflow pressure as well as the venous and cerebrospinal fluid pressures decline in proportion to the vertical distance to the heart.\textsuperscript{219,229,230} The transition from the supine to the upright body position instantaneously creates a hydrostatic column resulting in an on average \(~20\) mmHg decline in carotid arterial pressure with a corresponding reduction in arterial pressure within the brain.\textsuperscript{231} During posture change, ICP was reported to decline in the few subjects in whom it has been measured,\textsuperscript{218-220,232} and we therefore expect that CrCP, as a surrogate of ICP, declines during HUT. Data on ICP during LBNP are to the best of our knowledge not available. If not corrected for the hydrostatic height difference, CrCP increases rather than decreases in response to HUT (Figure 4.2.4), which seems unlikely.\textsuperscript{215} Taken together arterial blood pressure at the level of the brain cannot be set equal to peripherally measured BP when the head is positioned above heart level. Accordingly, arterial pressure at brain level took into account the vertical distance between the apex of the heart and the location of the TCD probe.
TCD was used to monitor changes in CBF. This technique has been widely used under the assumption that the cross-sectional area of the insonated vessel is maintained during the measurement. Possible changes in the diameter of the MCA by enhanced sympathetic activity or alterations in PCO₂ could modulate cerebral blood velocity independently from cerebral blood flow. Increases in sympathetic outflow by baroreflex activation in response to LBNP do not alter MCA diameter,¹⁰⁸ and MCA diameter remains relatively constant during the small deviations in PetCO₂²₃₃,²₃₄ and arterial pressure,²₃⁵ as observed in the present study. In addition, TCD was the readout modality for both HUT as well as for LBNP and, therefore, only different behavior of MCA diameter would impact our conclusions which we consider unlikely.

During LBNP a saddle prevented a downward shift of the body during the application of sub-atmospheric pressure. During HUT, we coached the subjects to avoid leg tensing to minimize variations in venous return and SV response to central hypovolemia. The
magnitude of the change in SV did not differ between HUT vs. LBNP rendering an effect on venous return less likely.

**Conclusion**

The present study showed differences in the cerebrovascular response to LBNP versus HUT despite similar changes in systemic hemodynamics. The prolonged reduction in CBFv following HUT as compared to LBNP seems to be attributed to PetCO₂ and to gravitational effects on CPP. We therefore consider the effect of a posture change important for cerebrovascular behavior when humans are subjected to orthostatic stress. This cannot be simulated by supine LBNP and should therefore be taken into account when employing LBNP as MRI compatible alternative for head-up tilt.