Cerebral and cardiovascular dynamics in response to orthostatic stress
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Chapter 3.1

Postural effects on cardiac output and mixed venous oxygen saturation in humans

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Introduction

Normovolemia is the blood volume of healthy individuals and averages ~75 ml·(kg body weight)\(^{-1}\) (258). The effective circulating blood volume refers to the part of the volume within the arterial system effectively perfusing the tissues (3, 241) and it is regulated by the interplay between the circulatory system and the kidneys (83). Changes in the veno-motor tone can increase, or decrease, the capacity of the venous circulation and thereby partially compensate for variations in the effective circulating blood volume. The effective circulating blood volume is assumed to depend mainly on the central blood volume (CBV), that is, the blood available to the heart. Transition from the supine to the upright posture has little effect on the blood pressure and orthostasis is proposed as the operating set point for human cardiovascular function (65). However, in order to maintain blood pressure during standing, an elevated vascular tone is required (111, 182, 219). Cardiac output (CO) is reduced by the postural fall in venous return and CBV (21, 167) with the gravitational displacement of blood to the dependent regions of the body (12, 257). The need for activation of cardiovascular reflexes for circulatory postural adaptation questions whether, in healthy humans, CBV is optimised to support the circulation in the upright position.

A functional definition of ‘normovolemia’ would be the ability to provide the heart with an appropriate CBV, that is cardiac preload (55, 120). However, the usual clinical and hemodynamic parameters are not reliable indices of preload to the heart (28, 210) and an “optimal” volume is neither defined nor is it an easily measurable entity. Hypovolemia may be characterised by a reduced preload to the heart, that is with stroke volume and CO becoming dependent on CBV. The reported increase in CO with volume loading is taken to imply that a patient is preload-responsive (28, 210). Conversely, the intravascular volume may be expanded beyond the volume that can provide for a “maximal” CO at rest. By interpolation between hypo- and hypervolemia, normovolemia may be considered as the point in the cardiac preload-output relationship at which CO does not increase further under circumstances where venous return is unimpeded. We reasoned that in the absence of cardiac
disease, changes in CO itself rather than in central circulatory pressures reflect CBV, and that this holds also for central venous O$_2$ saturation (S$_v$O$_2$) (159, 160, 234). With the hydrostatic indifference point for volume positioned at the level of the pelvis (205), CBV becomes reduced during head-up tilt (HUT), while CO and S$_v$O$_2$ decrease. The extreme values related to a maximal and minimal preload in the same group of subjects have not been identified and the body position that relates to an optimal preload is unknown.

The body position that provides the heart with enough volume to establish a maximal CO at rest was evaluated in volunteers exposed to variations in preload as evoked by displacement of the blood volume to and from the chest by passive tilt at various angles between HUT and head-down tilt (HDT). We hypothesised that changes in CBV are reflected by concurrent changes in S$_v$O$_2$ and CO, and that for both CO and S$_v$O$_2$ a maximum is reached during HDT. The possible appearance of pre-syncopal symptoms during HUT was taken to represent a lower physiologic limit for both variables in healthy humans.

**Methods**

**Subjects**
Nine healthy subjects (one female) were studied after informed consent was given. The study was approved by the Ethical Committee of Copenhagen. The subjects (mean age 29 (range 22-39) years, height 183 (170-191) cm and weight 75 (68-82) kg) showed normal levels of physical fitness without specific training. They had no history of orthostatic fainting and used no medication.

**Pressure Measurements**
Under local anaesthesia (2% lidocaine), a catheter (20 G; internal diameter: 1.0 mm) was placed in the brachial artery (radial artery in one subject) of the non-dominant arm and a balloon-tipped thermodilution catheter (93A-831H-7.5F Baxter Healthcare Corporation, Irvine, CA, USA) was introduced through the left basilic vein under ECG recording. Proper catheter positioning was confirmed by monitoring the pressure waveform and the catheter lumen was continuously flushed with 3 ml isotonic saline per hour. Pressures were measured by Baxter disposable transducers fixed to the left upper arm at the level of the right atrium. Central venous (CVP), pulmonary artery mean pressure (PAMP), pulmonary capillary wedge pressure (PCWP) and mean arterial pressure (MAP) were all measured as the integral over each beat divided by the corresponding interval. Heart rate (HR) was obtained from the pulse pressure interval.

**Cardiac Output**
The thermistor signal was connected to a cardiac output computer (COM-2, Baxter-Edwards). The CO was determined with 10 ml iced 5% glucose solution drawn from a closed automated
injectate delivery system (Baxter-Edwards) and injected linearly over ~3 seconds using a pneumatic pump (114, 119). This approach avoids manual heating of the indicator and improves injection time, consistency in injected volume and linearity of the injection rate (114, 179). Following the passage of the thermodilution curve and after at least 18 seconds, CO was estimated by the COM-2 and analysed with a personal computer via the serial port and an interface box. Finally, the syringe was automatically refilled. Four consecutive injections were executed at random phases of the respiratory cycle over 2 minutes to minimise the influence of ventilation, and CO was expressed as the mean. Each thermodilution curve was visually checked for shape and appearance time before acceptance.

**Mixed Venous Oxygen Saturation**

Blood samples for $S_vO_2$ and arterial $O_2$ saturation ($S_aO_2$), partial pressures for arterial and mixed venous $O_2$ and arterial and mixed venous hemoglobin ($Hb_a$ and $Hb_v$, respectively) concentrations were taken anaerobically in heparinised syringes and analysed immediately on an OSM3 and ABL-4 apparatus (Radiometer, Copenhagen, Denmark) at 37°C.

**Protocol**

After an overnight fast, the subjects were instrumented at 09.00 hours in a room with an ambient temperature of 22°C. Following instrumentation, a test run was performed. After supine rest, periods of tilt at various degrees were interspaced with further periods of supine rest to re-establish control values.

*Head-down tilt.* After 10 min of supine rest, the subjects were tilted passively with shoulder support to a stepwise increasing angle of -5°, -10° and -20° for 10 min each.

*Head-up tilt.* After a further 10 min of supine rest, a passive 30° HUT was performed in 3 seconds on a table provided with a foot support. The subjects remained in this position for 5 min and were subsequently tilted supine. After another 10 min, the subjects were tilted to 70° in 6 s. The tilt was terminated by returning the subject supine after 60 min, or at the subject’s request, or when the systolic blood pressure fell by more than 20 mmHg. Subjects were requested to abstain from movement in order to minimise changes in oxygen consumption ($VO_2$) related to muscle activity. Blood samples were drawn and a series of four thermodilution CO estimates was performed after 5 min in each position of the HDT and HUT 30°, and every 10 min during the sustained HUT 70°.

**Data Analysis and Statistical Procedures**

Systemic vascular resistance was (MAP-CVP)/CO and pulmonary vascular resistance (PAMP-PCWP)/CO. The $VO_2$ was the arterial-venous $O_2$ difference times CO. Values at supine rest prior to 30° HUT were taken as baseline. Apart from CO, data followed a normal distribution and were expressed as mean ± SD. The CO was expressed as median with range. Changes with body position were examined by Student’s t-test with the Ryan-Holm stepdown
Bonferroni adjustment to control the family-wise Type I error-rate (155). Interdependencies were evaluated by the least square method and a P value < 0.05 was taken to represent a statistical significant difference.

Results

The supine and HDT positions were tolerated well, where 70° HUT evoked syncopal symptoms in four subjects (Figure 1). One subject experienced presyncopal symptoms (abdominal discomfort and weakness) without a drop in MAP (92 mmHg) and HR (82 bpm) and was tilted back after 24 min. In three subjects MAP dropped to 42-47 mmHg and HR to 68-87 bpm after 9, 10 and 26 min, respectively, together with the development of presyncopal symptoms. The subjects recovered upon reaching the horizontal position. The median time at 70° HUT was 28 (range 10-66) min allowing for 10 (range 9-14) observations in each subject.

Figure 1.
Cardiac output and mixed venous oxygen saturation during head-up and head-down tilt in 9 healthy young subjects. O: supine; V: head-down tilt; A: head-up tilt. In subjects S1, S3, S6 and S9 arrows indicate presyncopal values. CO: cardiac output; SvO2: mixed venous oxygen saturation.
**Head-down Tilt**

From supine rest to 20° HDT, MAP decreased from 93 ± 9 to 90 ± 9 mmHg with no changes in HR (53 ± 10 bpm). In contrast, PCWP (10.2 ± 2.4 to 11.3 ± 2.5 mmHg; P<0.05) and PAMP (14.8 ± 2.5 to 16.3 ± 2.4 mmHg; P<0.05) increased, with CVP (3.8 ± 1.2 to 4.7 ± 0.5 mmHg; P = 0.08) following the same pattern. The Hb\textsubscript{a} level did not change but the Hb\textsubscript{v} decreased indicating slight hemodilution (Table 1). Despite these indices of an enlarged CBV, CO did not change significantly and S\textsubscript{v}O\textsubscript{2} also remained stable. Accordingly, pulmonary vascular resistance (63.2 ± 15.3 to 62.5 ± 15.5 dyne·sec\textsuperscript{-1}·cm\textsuperscript{-5}) nor systemic vascular resistance (1077 ± 158 to 1108 ± 116 dyne·sec\textsuperscript{-1}·cm\textsuperscript{-5}) or VO\textsubscript{2} (291 ± 47 to 285 ± 47 ml·min\textsuperscript{-1}) varied significantly. The S\textsubscript{v}O\textsubscript{2} was 97.6 ± 0.7% and was not influenced by body position.

**Table 1.**
Cardiac output, arterial and mixed venous O\textsubscript{2} saturation and hemoglobin during head-down tilt

<table>
<thead>
<tr>
<th></th>
<th>HDT -20°</th>
<th>HDT -10°</th>
<th>HDT -5°</th>
<th>Supine</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO (l·min\textsuperscript{-1})</td>
<td>6.2 (5.2-7.5)</td>
<td>6.1 (5.0-8.0)</td>
<td>5.9 (5.2-7.1)</td>
<td>6.1 (5.3-8.7)</td>
</tr>
<tr>
<td>S\textsubscript{v}O\textsubscript{2} (%)</td>
<td>73.9 ± 1.2</td>
<td>74.4 ± 1.7</td>
<td>73.7 ± 2.0</td>
<td>73.6 ± 2.6</td>
</tr>
<tr>
<td>S\textsubscript{a}O\textsubscript{2} (%)</td>
<td>97.6 ± 0.7</td>
<td>97.4 ± 0.7</td>
<td>97.4 ± 0.8</td>
<td>97.6 ± 0.7</td>
</tr>
<tr>
<td>Hb\textsubscript{v} (mmol·l\textsuperscript{-1})</td>
<td>8.6 ± 0.3</td>
<td>8.5 ± 0.4 *</td>
<td>8.6 ± 0.4 *</td>
<td>8.8 ± 0.4</td>
</tr>
<tr>
<td>Hb\textsubscript{a} (mmol·l\textsuperscript{-1})</td>
<td>8.5 ± 0.4</td>
<td>8.5 ± 0.4</td>
<td>8.5 ± 0.3</td>
<td>8.7 ± 0.3</td>
</tr>
</tbody>
</table>

HDT: head-down tilt; CO: thermodilution cardiac output; S\textsubscript{v}O\textsubscript{2}: arterial O\textsubscript{2} saturation; S\textsubscript{a}O\textsubscript{2}: mixed venous O\textsubscript{2} saturation, Hb\textsubscript{a}: arterial hemoglobin; Hb\textsubscript{v}: venous hemoglobin.

Values are expressed as mean ± SD or median with range in parentheses.

Significant difference from supine: * p <0.05.

**Head-up Tilt**

From the supine position to 30° HUT, MAP did not change and CO tended to decrease to 5.3 (3.4-8.1) l·min\textsuperscript{-1} (P = 0.07) while S\textsubscript{a}O\textsubscript{2} remained stable at 72.3 ± 3.0% (Figure 2). From 30° to 70° HUT, CO and S\textsubscript{a}O\textsubscript{2} decreased to, 5.2 (4.6-7.8) l·min\textsuperscript{-1} and 66.1 ± 4.4%, respectively. The MAP did not change but systemic vascular resistance increased (1143 ± 221 to 1317 ± 263 dyne·sec\textsuperscript{-1}·cm\textsuperscript{-5}; P < 0.0001). During 70° HUT, CVP decreased from 4 ± 2 to 2 ± 2 mmHg, PAMP from 14 ± 3 to 11 ± 4 mmHg and PCWP from 9 ± 3 to 2 ± 3 mmHg. The VO\textsubscript{2} increased to 331 ± 65 ml·min\textsuperscript{-1} and remained at that level until the subjects were supine. Just prior to tilting the subjects to the supine position, the CO was 4.7 (3.9-5.6) l·min\textsuperscript{-1} and S\textsubscript{v}O\textsubscript{2} 64.1 ± 3.9%. With resumption of the supine position CO (6.1 (5.6-7.5) l·min\textsuperscript{-1}) and S\textsubscript{v}O\textsubscript{2} (74.4 ± 1.7%) returned to the baseline level.
Figure 2.
Relationship between systemic hemodynamic variables, mixed venous O2 saturation and tilt angle. BP: systolic, mean and diastolic blood pressure; HR: heart rate; CO: cardiac output; SvO2: mixed venous oxygen saturation. Variables are mean ± S.E. # : P<0.05 vs. 0º. Dotted line: supine position; 70ºa: 10 min. head-up tilt 70º; 70ºb: last minute of head-up tilt 70º.

Discussion

It has been proposed that the upright body position is the operating set point for human cardiovascular function (65). The corollary that cardiovascular and fluid regulatory systems seek this “up-right set point” in microgravity constitutes a central hypothesis for studies on
acclimation to microgravity. After a few days in microgravity, blood volume and thus cardiac stroke volume decrease as is the case after prolonged bed rest on earth (299). The finding of an elevated vascular resistance in space agrees with the “upright set-point” hypothesis (298). Our study in healthy humans demonstrates that CO, and in turn $S_{O_2}$, do not increase from supine rest to head-down tilt, a condition in which CBV was assumed to be expanded. Conversely, both CO and $S_{O_2}$ decreased during HUT and were lower by 1.3 l·min⁻¹ and 10%, respectively, when fainting was imminent. These results suggest that the “optimal volume”, defined as the circulating blood volume that can provide for a maximal CO (and in turn $S_{O_2}$), corresponds to the volume that is available to humans in the supine position. This is perhaps a surprising finding as healthy humans spend many hours upright. However, sympathetic tone increases to raise vascular resistance and to maintain blood pressure in the upright position, and it may be considered that the filling state should be optimal under the conditions with the lowest sympathetic tone, that is recumbency. The consequent state of CBV level in the upright body position with a lowered CO and $S_{O_2}$, and also a reduction in cerebral blood velocity and regional cerebral tissue oxygenation (89, 150, 213, 293), can be ameliorated by leg muscle tensing (134, 287) and reflex vasoconstriction with an increase in venous return and thus CO (65, 96, 252). These findings appear contrary to the “upright set-point” hypothesis and point to supine rest as the body position at which resting CO and $S_{O_2}$ are maximal on earth (307).

Table 2.
Mixed venous $O_2$ saturation and cardiac output measured by thermodilution in the 20º head-down and the sustained 70º head-up positions

<table>
<thead>
<tr>
<th>Subject</th>
<th>$S_{O_2}$ (%)</th>
<th>CO (l·min⁻¹)</th>
<th>$S_{O_2}$ (%)</th>
<th>CO (l·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>74.5</td>
<td>6.24</td>
<td>65.5</td>
<td>4.26</td>
</tr>
<tr>
<td>S2</td>
<td>73.9</td>
<td>6.31</td>
<td>59.1</td>
<td>4.27</td>
</tr>
<tr>
<td>S3</td>
<td>74.4</td>
<td>6.12</td>
<td>64.4</td>
<td>4.67</td>
</tr>
<tr>
<td>S4</td>
<td>73.9</td>
<td>6.86</td>
<td>58.9</td>
<td>4.41</td>
</tr>
<tr>
<td>S5</td>
<td>73.6</td>
<td>5.67</td>
<td>71.8</td>
<td>5.56</td>
</tr>
<tr>
<td>S6</td>
<td>71.7</td>
<td>5.18</td>
<td>66.8</td>
<td>4.74</td>
</tr>
<tr>
<td>S7</td>
<td>72.4</td>
<td>6.80</td>
<td>61.4</td>
<td>5.41</td>
</tr>
<tr>
<td>S8</td>
<td>75.0</td>
<td>5.27</td>
<td>62.6</td>
<td>3.90</td>
</tr>
<tr>
<td>S9</td>
<td>75.5</td>
<td>7.47</td>
<td>66.3</td>
<td>5.40</td>
</tr>
<tr>
<td>Average</td>
<td>73.9</td>
<td>6.21</td>
<td>64.1</td>
<td>4.73</td>
</tr>
</tbody>
</table>

CO: cardiac output measured by thermodilution; $S_{O_2}$: mixed venous $O_2$ saturation.

Identification of an “optimal volume” is of clinical interest. A decrease in blood volume may progress to circulatory shock within minutes to hours and the immediate aim is to
re-establish and maintain a blood volume able to provide near normal blood pressure and an adequate CO. On the other hand, deliberately increasing blood volume during surgery may expose patients to a volume overload (120). A “normal” blood volume may be defined as the volume of blood contained within a healthy person. Yet the blood volume varies not only with stature and gender, but also with physical activity (244) and it is not known how an average value for the population applies to the individual. Furthermore, the blood volume is not a readily determined variable. We considered that the blood volume is characterised not only by its size but also by its function as preload to the heart.

From the supine to the upright position ~500 ml of blood is immediately pooled in the venous system (255) with a reduction in CBV of about 25% (167, 257). With a postural reduction in CBV, CO decreases and \( S_vO_2 \) follows CO as a given oxygen uptake has to be extracted from blood exposed to a lower flow. During standing, presyncopal symptoms appear when the CBV is reduced by ~30% (167) associated with a decline in HR in response to increased vagal tone, while sympathetic tone to skeletal muscle ceases leading to a reduction in systemic vascular resistance and MAP (9, 149, 232, 288, 289). Fainting reflects the decrease in cerebral perfusion (161, 293). Conversely, we considered a body position for which both CO and \( S_vO_2 \) would reach maximal values, that is a body position where CO is not limited by the preload to the heart. By tilting the subjects to the head-down position, we found that neither CO nor \( S_vO_2 \) increased. Thus, in humans ‘normovolemia’ may be defined as the circulating blood volume a healthy subject is provided with during supine rest.