Cerebral and cardiovascular dynamics in response to orthostatic stress
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Chapter 3.2

Stroke volume of the heart and thoracic fluid content during head-up and-down tilt in humans

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Introduction

In the surgical patient, a decrease in the central blood volume (CBV) by the accumulation of blood in dependent parts of the body becomes a problem, in particular when regional anaesthesia paralyses venous tone during procedures that squeeze the lower caval vein, as with lower abdominal surgery requiring an extended body position. In addition, the surgical patient becomes vulnerable when required to remain motionless if the intervention is carried out in a position where venous return and the CBV are compromised. Vasovagal episodes are regularly reported during procedures on the shoulder using local anaesthesia and with the patient sitting upright. The initial cardiovascular response to hemorrhage is similar to that derived from observations in patients, and from experiments in which the CBV is reduced by lower body negative pressure or prolonged orthostatic stress like passive head-up tilt (HUT) (50, 128, 247). Under these conditions, the effect of gravity on the cardiovascular system is changed with a reflex increase in sympathetic tonus to the heart and blood vessels (182, 225). During HUT, the CBV is decreased by venous pooling in the legs (167) and stroke volume (SV) decreases (206), that is SV may become dependent on the filling of the heart (230) although during HUT, SV is supported by sympathetic activation (16, 168, 182, 225). Under such circumstances, the Frank-Starling relationship is examined with vascular pressures to indicate pre-load to the heart, with resulting curvilinear functions (72, 146, 148).

The Frank-Starling law of the heart was established in an animal preparation (261), but it is also accepted widely to apply to the function of the heart in the intact organism. In parallel with the length-tension diagram for skeletal muscles, the “law of the heart” states that SV depends on the diastolic volume (123, 324). However, most often, SV or cardiac output (CO) is related to central venous (CVP), mean pulmonary artery (MPAP), or pulmonary artery wedge (PAWP) pressures (148, 204). The implicit assumption is that pressure changes in parallel with the CBV, but in some cases the reverse may be true. For example, during a Valsalva manoeuvre, compression of the central vessels restrains venous return and, in turn, SV (213). In patients, there may be no correlation between SV and central pressures, whereas there is a tight relation between SV and the filling of the heart (276).
In addition, in humans subjected to lower body negative pressure as a supine model of orthostatic stress, there is a larger change in left ventricular volume for a given range of central vascular pressures in athletes than in control subjects, i.e. the compliance of the heart is enhanced with endurance training (146, 148) as confirmed with thoracic electrical admittance of thoracic fluid content (TA) during HUT (191). Nevertheless, in dogs submitted to graded caval vein occlusion during autonomic blockade, the relationship between stroke work and the end-diastolic length or chamber volume of the heart is linear (72). The hypothesis of this study was that, even with an intact autonomic system, changes in SV relate to those in thoracic fluid content rather than to the concomitant changes in central vascular pressures during manipulation of the CBV. In addition, for SV, we evaluated changes in CO against those in TA and central vascular pressures.

**Methods**

Nine healthy, non-smoking, untrained subjects (one female) without orthostatic intolerance participated in the study. Their median age was 29 (range 22-39) years, height 183 (170-191) cm, and weight 75 (68-82) kg. Informed consent was obtained and the study was approved by the Ethics Committee of Copenhagen.

**Experimental Protocol**

The subjects reported to the laboratory in the morning after an overnight fast. Instrumentation began at 09.00 hours in a room at 22º C, while the subjects were laying on a motor-driven tilt-table. A test run was performed to familiarise the subject with the protocol and in order to manipulate the CBV, they were requested to lay still, i.e. not to activate the muscle pump. Thirty minutes of rest was followed by 20 min of supine control to establish baseline values. Thereafter, 20º head-down tilt (HDT) was assumed for 5 min with support for the shoulders and, after further 20 min of supine rest, 70º HUT was established with support for the feet. The HUT was terminated at the subject’s request, or if the systolic pressure fell by more than 20 mmHg.

**Measurements**

The subjects were instrumented with electrocardiogram (ECG) electrodes (Q-10-25) and, under local anaesthesia (2% lidocaine), a catheter (20 G; internal diameter:1.0 mm) was placed in the brachial artery of the non-dominant arm. A pulmonary artery catheter (93A-831H-7.5F, Baxter Healthcare Corporation, Irvine, CA) was introduced through a percutaneous sheath in the basilic vein of the left arm, with ECG monitoring, and the position of the catheter was confirmed by monitoring the characteristic pressure waveforms. Mean arterial pressure (MAP), PAWP, MPAP, and CVP were measured with Uniflow transducers (Baxter Healthcare Corporation, Irvine, CA).
Corporation, Irvine, CA) calibrated and zeroed at the level of the right atrium in the mid-axillary line, fastened to the subject and connected to a pressure monitoring system (Dialogue 2000, Copenhagen, Denmark). The catheter lumens were continuously flushed with 3 ml isotonic saline per hour and, at both the beginning and end of the recording, it was ascertained that the natural frequencies for the pressure systems were > 15 Hz for arterial pressure and > 8 Hz for the central vascular pressures (64).

**Cardiac Output**
A COM-2 apparatus (Baxter Edwards Critical Care, Irvine CA) was used to compute CO. Four injections of 10 ml ice-cooled (<10° C) 5% glucose solution were provided with a computer-controlled injectate pump within 3 min, separated by at least 36 seconds (119). The injectate was delivered through the proximal port of the pulmonary artery catheter in ~ 2 seconds and the syringe was refilled automatically using a closed injection system (CO-set, Baxter Edwards Critical Care). The injections were made at random phases of the respiratory cycle as ascertained with no systemic difference between measurements when assessed by two-way analysis of variance. An interface box provided electric isolation.

**Thoracic Electrical Admittance**
Thoracic electrical admittance was measured with 200 mA at 100 kHz (C-Guard, Danmeter, Odense, Denmark). After the skin was cleaned with alcohol swabs, pairs of electrodes (Q-10-25) were placed behind the right sternocleidomastoid muscle and corresponding to the upper left ribs in the midaxillary line, with each pair placed with an internal distance of 5 cm (253). This electrode placement was also used when a correlation with changes in the CBV was evaluated (87, 98, 205). The outer two electrodes provided the electrical field, while the inner pair was sensing; such an evaluation of the CBV shows a correlation with the volume deficit during hemorrhage and following reperfusion in the pig that approaches 1.0 (130), and allows for prediction of hypotension when the CBV is reduced, e.g. during HUT (206), lower body negative pressure (41), syncope (189), and hemodialysis (42).

**Analysis**
Pressure waveforms were recorded on a polygraph (Graphtec WR7700, Japan), A/D converted at 100 Hz by a PC and stored for off-line analysis. The stability of the signals was verified by examining heart rate (HR), systolic, mean and diastolic arterial pressures, MPAP and CVP before and after each thermodilution estimate of CO. If any variable differed more than 10% from the mean of the series, the series was rejected (115). After data reduction, beat-to-beat mean values for all pressures were derived as the integral over one beat divided by the corresponding beat interval. Values for TA, MAP, HR, CVP and MPAP were averaged over 10 seconds for each minute. The end-expiratory PAWP was taken as an index of left ventricular end-diastolic pressure and HR was derived from the arterial pulse pressure.
interval. SV was the ratio of CO and HR, and both CO and SV represent the average of the four determinations made every 10 min. In addition, CVP was taken as an estimate of pericardial surface pressure, while PAWP-CVP expressed the left ventricular transmural end-diastolic pressure (279).

SV and CO were related to the grouped means of CVP, MPAP, PAWP, (PAWP-CVP) and TA, respectively. Relationships between SV and central pressures as well as between SV and changes in TA were evaluated by linear and non-linear least-square regression to predict a curve of "best fit" to each set of data and they are presented as means ± SD. Changes related to posture were compared by using repeated measurements ANOVA on ranks, with Dunnett post hoc test for multiple comparisons, and a P value < 0.05 was taken to indicate a statistically significant difference.

Results

HR, MAP, CVP, TA, SV and CO did not change significantly from the supine position to 20° HDT, whereas PAWP and MPAP increased (Table 1). During 20 min of HUT, MAP remained stable, whereas HR increased and CVP, MPAP, PAWP, SV, CO and TA decreased. However, from 20 to 50 min of HUT, the central vascular pressures did not change significantly, whereas both SV and CO decreased further. When the tilt was discontinued, all variables returned to the baseline levels, except for TA, which remained lower than that prior to the tilt. The relationships between SV and CO versus central pressures and PAWP-CVP were non-linear (Figure 1). In contrast, the relationships between SV and CO versus TA were linear: SV = - 572 + 23501 × TA (Standard error (SE) 7.3; R² = 0.93) and CO = - 7.3 + 454 × TA (SE 0.31; R² = 0.89) (Figure 2).
Table 1
Hemodynamic variables during posture changes

<table>
<thead>
<tr>
<th></th>
<th>Supine start</th>
<th>HDT</th>
<th>HUT 20 min</th>
<th>HUT 50 min</th>
<th>Supine end</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>53 ± 10</td>
<td>53 ± 10</td>
<td>86 ± 18 ‡</td>
<td>92 ± 12 ‡</td>
<td>62 ± 17</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>93 ± 9</td>
<td>90 ± 9</td>
<td>93 ± 10</td>
<td>91 ± 19</td>
<td>92 ± 17</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>3.6 ± 0.9</td>
<td>4.7 ± 1.6</td>
<td>0.9 ± 1.4 ‡</td>
<td>0.9 ± 1.7 ‡</td>
<td>3.9 ± 1.4</td>
</tr>
<tr>
<td>MPAP (mmHg)</td>
<td>13.9 ± 2.7</td>
<td>16.1 ± 2.5 *</td>
<td>9.3 ± 3.8 †</td>
<td>9 ± 3 †</td>
<td>14.3 ± 2.8</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>8.8 ± 3.4</td>
<td>11.3 ± 2.5 *</td>
<td>0.7 ± 3.3 ‡</td>
<td>0.8 ± 2.8 ‡</td>
<td>9.6 ± 3.3</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>112 ± 18</td>
<td>118 ± 15</td>
<td>65 ± 25 †</td>
<td>48 ± 22 †</td>
<td>113 ± 22</td>
</tr>
<tr>
<td>CO (l min⁻¹)</td>
<td>6.4 ± 1.3</td>
<td>6.4 ± 1.0</td>
<td>4.9 ± 0.6 *</td>
<td>4.4 ± 1.0 *</td>
<td>6.4 ± 1.0</td>
</tr>
<tr>
<td>TA (S·10⁻³)</td>
<td>30.8 ± 7.1</td>
<td>30.5 ± 6.9</td>
<td>26.7 ± 6.8 *</td>
<td>26.4 ± 6.7 *</td>
<td>28.7 ± 7.2 *</td>
</tr>
</tbody>
</table>

HR: heart rate; MAP: mean arterial pressure; CVP: right atrial pressure; MPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; SV: stroke volume; CO: cardiac output; TA: thoracic admittance.
Values expressed as mean ± S.D. vs. supine: * P<0.05, † P<0.01, ‡ P<0.001

Discussion

This investigation evaluated the relationship between SV of the heart and thoracic fluid content versus central vascular pressures for filling of the heart. The assumption was that, even with an intact autonomic system, changes in SV induced by manipulation of the CBV relate more clearly to those in thoracic fluid content than to the concomitant changes in central vascular pressures. There was a linear relationship between SV and the thoracic fluid content, as also established for the CBV (62). In contrast, HDT was associated with an increase in MPAP and PAWP, although the thoracic fluid content did not change significantly and, equally, SV remained stable. Conversely, during sustained HUT, SV decreased together with the thoracic fluid content, although the central pressures stabilised.

In an isolated heart, the larger the diastolic volume of the heart (within physiological limits), the greater the energy of its contraction (261). For larger volumes, the SV-diastolic volume relationship, in parallel with the length-tension diagram for skeletal muscle, reaches a saturation point, i.e. a larger cardiac volume is not associated with an increase in SV. Equally, during supine rest, the CBV is large enough to establish a maximal SV (88). However, the relationship between SV and TA was affected by prolonged tilting, in that TA did not
re-establish the resting value when the subjects were tilted down, i.e. it takes some time before
the oedema developed in the legs is recruited to the central circulation (167). On the other
hand, SV was re-established immediately in the supine position. The implication is that, in the
supine position, a saturation point for the filling of the heart is reached and that, after about
1 hour of supine rest, the CBV is somewhat larger than needed for maintaining a maximal SV
at rest.

Figure 1.
Stroke volume and central vascular pressures. HDT: 20º head down tilt; HUT: 70º head-up tilt (in minutes); SUPstart: prior to HUT; SUPend: supine after tilt
back; SV: stroke volume; CVP: central venous pressure; MPAP: mean pulmonary arterial pressure; PAWP: pulmonary artery capillary pressure. Values are
mean ± SE.
**Study limitations**

There are potential limitations to the present study. The mechanisms responsible for the compensation of intravascular fluid shifts in humans remain speculative because little information is available regarding the amount of fluid shifted and the hemodynamics of the venous and pulmonary parts of the circulation (255). A limitation of central pressures recording during transition to the upright posture is that the position of the transducers may change relative to that of the heart that in itself moves caudally. However, during sustained HUT, when there was a reduction in SV and thereby CO for a given central pressure, the position of the transducers relative to the heart is maintained. Equally, evaluations during supine rest before and after the tilt are not biased.

![Figure 2](image_url)

During HDT, the moderate rise in intracardiac pressures was not followed by an increase in SV or TA. We consider it unlikely that this would be due to insufficient time allowed for transfer of the HDT related augmentation in venous return to an increase in SV for the HDT position. We recognise that the filling of the heart by the augmentation in venous return during acute HDT may have been antagonised by pericardial constraint. In dogs, the pericardium modulates biventricular compensatory responses to acute atrial volume changes (136) and, in healthy humans, pericardial constraint may be important for determining the maximal dilatation in response to volume infusion (156, 204). However, acute hypovolemia induced by furosemide does not alter the slope or zero intercept of the curve relating PAWP to left ventricular diastolic volume determined by echocardiography, rendering a short-term change in pericardial distensibility less likely (204). In this study the relationship between SV and PAWP-CVP, as an expression of LV transmural end-diastolic pressure (279) did not support a role for pericardial constraint during HDT (Figure 1).
During HUT, HR increased considerably while SV became reduced, indicating carotid baroreceptor unloading (56). The increase in HR did not balance the decrease in SV and there was a substantial reduction in CO. The maintenance of MAP indicated appropriate enhancement of vasomotor tone related to increased carotid baroreflex responsiveness in response to the HUT-induced central hypovolemia (191). Excitation of the sympathetic nervous system during HUT (16, 168), as exemplified by the increase in HR (202), would be assumed to increase SV for a given central pressure (233). However, the reverse was established with a decrease in SV for a given central vascular pressure during sustained HUT. The relationship between SV and TA was maintained and sympatho-excitation during HUT may affect the relationship between pressure and volume within the central vessels (151), i.e. a given pressure gradually corresponded to a smaller volume.

We did not control for either contractility or afterload, and the SV-TA curve represents only an approximation to the Frank-Starling relationship of the heart (72). Rather, the data correspond to the integrated response with intact autonomic cardiovascular control.

Conclusions

During both HUT and HDT, SV of the heart changed more clearly with the thoracic fluid content than with the concomitant changes in central vascular pressures. Thus with maximal resting values for SV and CO established in the supine position, HDT was associated with an increase in central filling pressures, while, during sustained hypovolemia, SV decreased although central pressures remained stable. These findings confirm that the function of the heart relates to its volume rather than to its so-called filling pressures. The implication is that, for the assessment of pre-load to the heart, central vascular pressures can be substituted by an evaluation of the CBV by electrical admittance, or ideally, of the heart, e.g. by echocardiography.