Time courses of central hemodynamics during rapid changes in posture

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Sundblad P, Spaak J, Kaijser L. Time courses of central hemodynamics during rapid changes in posture. J Appl Physiol 116: 1182–1188, 2014. First published March 13, 2014; doi:10.1152/japplphysiol.00690.2013.—Changes in posture cause blood volume redistribution, affecting cardiac filling and stroke volume (SV). We hypothesized that the time courses of ventricular filling would differ between the right and left ventricle during a rapid (2 s) tilt and that changes in right ventricular filling pressure would be more swift because of the direct coupling to the systemic circulation. We further hypothesized that the transient imbalance between right and left ventricular filling pressure would influence left ventricular SV changes. Right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), left ventricular stroke volume, heart rate, and arterial pressure were recorded beat-by-beat during rapid tilts from supine to upright positions and back again, during rest and dynamic 100-W leg exercise. RAP changes had a faster time course than PCWP during down-tilts, both during rest and exercise (1 ± 1 vs. 6 ± 2 s and 2 ± 2 vs. 6 ± 2 s, respectively; P < 0.05). This discrepancy caused a transient decrease in the end-diastolic pressure difference between the right and left ventricle. The decreased pressure difference in diastole impeded left ventricular filling because of ventricular interdependence, causing SV to fall transiently. The mechanisms of ventricular interdependence were also involved in reverse during up-tilt, where SV was maintained for 2–3 s despite falling PCWP. Furthermore, the decrease in RAP during up-tilt in the resting condition was biphasic with an initial fast and a second slower component, which might suggest the effect of venous valves. This was not seen during dynamic leg exercise where blood pooling is prevented by the venous muscle pump.

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METHODS

Subjects. Ten men participated in the experiments. Their mean age, weight, and height were 25 yr (range, 22–32 yr), 77 kg (range, 65–89 kg), and 185 cm (range, 175–194 cm), respectively. All were healthy with normal electrocardiograms (ECG), and none were taking prescribed medication. Written informed consent was obtained from all subjects. The Ethics Committee at Huddinge University Hospital approved the experiments.

Protocol. The experiments were conducted at Huddinge University Hospital in the Department of Clinical Physiology. The subjects arrived at the laboratory dressed in shorts and t-shirts at least 2 h after breakfast or lunch. They were familiarized with the experimental setting and then placed on the catheterization table. Under aseptic conditions, a catheter was introduced into the brachial artery and a Swan-Ganz catheter was introduced into the pulmonary artery through a cubital vein. Both catheters were placed in the left arm. The catheters were secured with tape and bandage, and the subject was moved to a tilt table. The tilt table was equipped with a saddle, foot support, and cycle ergometer. It could manually be tilted between supine to upright (80°) within 2 s (16).

Two identical tilt sequences were used during rest and 100-W dynamic exercise. Each sequence started with a 5-min period of supine rest or warm-up pedaling at 100 W. The subjects were then tilted to an upright position (2 s) for another 5-min period and were
then tilted back to supine (2 s). This was repeated five times but with 2-min periods between successive tilts, with the sequence ending in the upright position, giving a total of six up-tilts (supine to upright) and five down-tilts (upright to supine). The initial 5-min periods were longer to allow for cardiac output measurements (see below). The experiments always started with the tilt sequence during rest.

**Measurements.** Throughout the tilt sequences, the following signals were recorded continuously beat-by-beat: heart rate (HR), AP, RAP, PCWP, and hydrostatic height corrections between the level of the heart and the pressure transducers that measured AP, RAP, and PCWP. These variables were recorded and stored at a sampling frequency of 100 Hz using a personal computer-based data collection system (Biopac MP100, with Acqknowledge 3.1 software; Biopac, Goleta, CA).

The invasive pressures were measured with pressure transducers located on a rack beside the tilt table, and the intravascular pressures were transmitted through saline-filled catheters. The Swan-Ganz catheter has one hole at the distal tip and a side-hole located 30 cm proximal to the tip. When this catheter is appropriately placed, pressure can be recorded from the right atrium and the pulmonary artery. The pressure recorded from the side hole of the catheter will be termed right atrial pressure (RAP) throughout this paper. The catheter can be wedged against the vessel wall by inflating a balloon located just proximal to its tip, and this recorded wedge pressure (PCWP) at the distal hole is then equivalent to the left atrial pressure as long as there is no pulmonary venous obstruction. The hydrostatic differences between the heart (axillary line at the level of fourth intercostal space) and the pressure transducers that measured invasive pressure were continuously recorded by use of fluid-filled tubes attached to the subject.

Steady-state cardiac output (CO) was determined by repeated thermodilution. A total of six thermodilutions was performed for each posture during both steady-state rest and steady-state exercise.

**Data analysis.** Heart rate was calculated beat-by-beat from the ECG. Beat-by-beat mean AP (MAP) was calculated by numerical integration. MAP at the heart level was computed at each instant by subtracting brachial pressure from the hydrostatic pressure difference at the heart level recorded in the fluid-filled tubing. Similarly, RAP and PCWP recordings were corrected to the level of the heart.

Beat-by-beat stroke volume (SVp) was derived from the area under the arterial pressure curve, as described by Jellemma et al. (14). In that study, \( SVp \) was computed from \( A_s/z_{280} \), where \( A_s \) is the area under the systolic pressure profile and \( z_{280} \) is the virtual aortic impedance. This method also includes corrections for variations in \( z_{280} \) caused by changes in arterial pressure and HR. \( SVp \) was calculated: \( SVp = \frac{(A_s/z_{280}) \times [1.32 + 0.10 \times (0.28 \times HMAP - 16)]}{2,000} \), where \( HMAP \) is the instantaneous HR (beats/min), HMAP is MAP at the level of the heart in the same beat, and \( z_{280} \) is the calibrated aortic impedance. Stroke volume measurements from thermodilutions (SVt = Q/HR) made during rest and steady-state exercise in supine and upright positions were used to calibrate aortic impedance (2). During tilts, \( z_{280} \) was assumed to change with the same time course as the hydrostatic pressure difference signal measured from the fluid-filled tubing. Beat-by-beat CO was computed as \( SVp \times HR \). HR, MAP, and \( SVp \) can, by definition, not be known until after a cardiac cycle is completed. In the present offline analysis, these data were time corrected to the R-R interval to which they actually corresponded. All offline calculations and averaging were done using customized software developed using LabView 5.0 (National Instruments, Austin, TX).

**Statistics.** The differences between steady-state and dynamic variables were tested statistically using Student’s paired \( t \)-test. When appropriate, Bonferroni corrections for multiple comparisons were made.

**RESULTS.** All ten subjects successfully completed the experiments. In two of the subjects, pressure measurements collected from the Swan-Ganz catheter could not be used because of unreliable wedge pressure recordings after down-tilts during exercise. In the remaining eight subjects, high-quality recordings were obtained. Figs. 1 and 2 show mean group recordings of RAP and PCWP. Time courses were faster for RAP than for PCWP at down-tilts during both rest and exercise (1 \( \pm \) 2 vs. 6 \( \pm \) 2 s and 2 \( \pm \) 2 vs. 6 \( \pm \) 2 s, respectively). Down-tilt caused a transient reduction in the end-diastolic filling pressure difference between the left (LV) and right ventricles (RV) (Fig. 1C). Down-tilt at rest caused a transient reversal in the diastolic pressure difference. This reversal occurred because when the subjects passed through the 30-degree position RAP exceeded PCWP and remained substantially above PCWP for the next several seconds, as can be clearly seen in Fig. 1A. During up-tilts, RAP and PCWP reached the new steady-state simultaneously both during rest (13 \( \pm \) 2 vs. 12 \( \pm \) 2 s) and exercise (7 \( \pm \) 4 vs. 7 \( \pm \) 2 s). However, as shown in Fig. 2, A and B, there was a slower onset of the decrease in PCWP than in RAP, which gave a transient increase in the left-to-right diastolic pressure difference between the ventricles (Fig. 2C) albeit with smaller amplitude compared with the transient decrease seen at down-tilt.

RAP had a slower time course at up-tilt than at down-tilt during rest (Fig. 1A and 2A). There was also a slower time course in RAP at up-tilt during rest than at up-tilt during exercise (Fig. 2, A and B). The difference between steady-state RAP and PCWP increased with exercise compared with the resting condition and was greater in the supine than in the upright position during both rest and exercise (Table 1). The difference in RAP between positions was larger during rest compared with the exercise condition (8 \( \pm \) 1 vs. 5 \( \pm \) 1 mmHg).

HR decreased rapidly during down-tilt, during both rest and exercise, with a small initial increase at rest. The opposite pattern was observed during up-tilt, but HR increased faster at rest than during exercise (7 \( \pm \) 3 vs. 12 \( \pm \) 2 s).

After an initial decrease, left ventricular stroke volume (SV) increased quite rapidly after down-tilt, during both rest and exercise (Fig. 3A). Up-tilt while resting caused a markedly slower decrease in SV than during exercise (13 \( \pm \) 1 vs. 7 \( \pm \) 3 s) and relative to the reciprocal changes seen during down-tilt (Fig. 3, A and B). At rest, there was a time delay of \( \sim \) 3–4 s before SV began to decrease after up-tilt (Fig. 3A).

The time courses for CO were calculated from HR and SV, and were therefore composites of the time courses for these variables. At down-tilt, the time courses for CO reflected the dynamics of SV. Up-tilt, however, produced almost opposite
Fig. 1. Group mean time courses of right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP) in resting and exercising subjects ($n = 8$) during down-tilts (A and B). C: time courses of the difference between PCWP and RAP at the same conditions, assumed to represent the end-diastolic pressure difference between the right and left ventricle. The instant of 30° tilt angle (dashed line) was used for time alignment in the coherent averaging procedure, which largely eliminated random noise and variations due to breathing. D: original recording of RAP and PCWP during a down-tilt.
responses in CO during rest and exercise. At rest, CO initially increased and then gradually fell to a new steady-state level, whereas during exercise, CO initially fell then increased gradually.

Tilting induced transient increases and decreases in AP at down- and up-tilt, respectively. The tilt-induced changes in AP generally abated within 10 s. The amplitudes of these changes were almost twice as large during exercise as at rest. During exercise, down-tilt caused a peak in AP that occurred earlier than during rest (2.0 ± 0.6 vs. 3.5 ± 0.4 s).

**DISCUSSION**

In the present experiments, the time courses of changes in right (RAP) and left (PCWP) atrial pressures and SV during rapid whole body tilts were analyzed. In this paper, RAP and PCWP will often be referred to as right and left ventricular end-diastolic filling pressure, respectively. Despite not measuring the ventricular filling pressure in the ventricles per se, we argue that the pressure gradient from the atria to the ventricle in end diastole is small in young healthy subjects and will not
have significant influence on the conclusions. We found that the transient imbalance between right and left ventricular filling pressure had markedly different effects on SV during exercise vs. rest and during up-tilt vs. down-tilt.

Tilt-induced dynamics of RAP and PCWP and the effects on SV. Under resting conditions, there was a marked difference in the time course of the change in RAP between up- and down-tilts. Down-tilt induced a swift response, where RAP reached a new steady state within 5 s, with a small initial overshoot (Fig. 1A). RAP change during up-tilt included two components: an immediate change that was the converse of the response to down-tilt, although with a reduced amplitude, and a second change with a longer time course (Fig. 2A). The slow component after up-tilt probably arose because of the venous valves preventing immediate pooling of blood in the lower extremities. Dependent veins were subsequently filled by antegrade inflow from arteries via capillaries (13, 20). The fact that the slow component in RAP was absent when subjects were tilted to the upright position during exercise further supports this hypothesis (Fig. 2B). The venous muscle pump, which is active in the legs during cycling, empties the veins with each contraction (15). Therefore, there was considerably less pooling of blood in the lower extremities in the upright position during exercise, and blood was primarily transferred between the thorax and abdomen with changes in posture. Consequently, the difference in steady-state RAP between postures was less during exercise.

Table 1. Steady-state cardiovascular variables at rest and exercise in supine and upright position

<table>
<thead>
<tr>
<th>Variable</th>
<th>Condition</th>
<th>Rest 100 W</th>
<th>Supine</th>
<th>Upright</th>
</tr>
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<tbody>
<tr>
<td>HR, beats/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO, l/min</td>
<td>Supine</td>
<td>10 59 ± 6</td>
<td>72 ± 9*</td>
<td>113 ± 11</td>
</tr>
<tr>
<td></td>
<td>Upright</td>
<td>10 6.8 ± 0.9</td>
<td>5.4 ± 0.8*</td>
<td>15.6 ± 1.6</td>
</tr>
<tr>
<td>SV, ml</td>
<td>Supine</td>
<td>10 116 ± 12</td>
<td>77 ± 15*</td>
<td>139 ± 17</td>
</tr>
<tr>
<td></td>
<td>Upright</td>
<td>10 116 ± 12</td>
<td>77 ± 15*</td>
<td>139 ± 17</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>Supine</td>
<td>9 95 ± 12</td>
<td>98 ± 15</td>
<td>98 ± 12</td>
</tr>
<tr>
<td></td>
<td>Upright</td>
<td>9 137 ± 3.0</td>
<td>181 ± 3.0*</td>
<td>6.6 ± 0.8</td>
</tr>
<tr>
<td>TPR, mmHg min⁻¹</td>
<td>Supine</td>
<td>8 11 ± 2</td>
<td>3 ± 2*</td>
<td>11 ± 2</td>
</tr>
<tr>
<td></td>
<td>Upright</td>
<td>8 15 ± 2</td>
<td>6 ± 2*</td>
<td>20 ± 4</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>Supine</td>
<td>8 15 ± 2</td>
<td>6 ± 2*</td>
<td>20 ± 4</td>
</tr>
<tr>
<td></td>
<td>Upright</td>
<td>8 4 ± 1</td>
<td>2 ± 1*</td>
<td>9 ± 3†</td>
</tr>
<tr>
<td>PCWP-RAP, mmHg</td>
<td>Supine</td>
<td>8 4 ± 1</td>
<td>2 ± 1*</td>
<td>9 ± 3†</td>
</tr>
<tr>
<td></td>
<td>Upright</td>
<td>8 4 ± 1</td>
<td>2 ± 1*</td>
<td>9 ± 3†</td>
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</tbody>
</table>

Values are presented as means ± SD. HR, heart rate; VO₂, O₂ uptake; CO, cardiac output (thermodilution); MAP, mean arterial pressure; TPR, total peripheral resistance; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; PCWP-RAP, the difference between PCWP and RAP. *Significantly different from supine in the same condition; †PCWP-RAP significantly different from rest in the same position.

Fig. 3. Group mean time courses of left ventricular stroke volume (SV) in resting and exercising subjects (n = 10) during down-tilts (A) and up-tilts (B). Dashed line as in Fig. 1.
stretches the LV free wall, making the LV less compliant (23), and 2) when the RV end-diastolic pressure exceeds the LV end-diastolic pressure, the interventricular septum (IVS) is displaced to the left (6, 17). One key aspect of septal displacement is the effect of the pericardium; because it is, in the short term, effectively nondistensible, RV end-diastolic volume can increase only “at the expense” of LV end-diastolic volume in the presence of pericardial constraint (3). Ventricular septum displacement probably gives a more marked effect on LV output than the effect on the LV free wall compliance. The IVS normally bulges to the right because of the higher filling pressure in the LV than in the RV. A prerequisite for leftward motion of the IVS during diastole is that the RV filling pressure exceeds the LV filling pressure (5), which occurred at down-tilt during rest (Fig. 1C).

Similar ventricular interaction, with sudden increase in venous return induced by a release of lower body negative pressure (LBPN), has been shown by Fujimoto et al. (10) They measured ventricular filling pressures in the same way as in the present study and concluded that RV filling pressure transiently impedes LV filling, leading to a drop in left ventricular SV. The effect on SV was fairly small compared with the present study, probably because a slower time course in the release of LBPN (>5 s) and a slower increase in venous return. They concluded that the ventricular interaction in their experimental set-up primarily depended on pericardial constraints.

The difference in time courses between RAP and PCWP remained during exercise. However, RAP did not exceed PCWP with down-tilt during exercise because of the greater difference between steady-state RAP and PCWP (Fig. 1C, Table 1). This implies that the prerequisite for a leftward displacement of the IVS had disappeared and, consequently, there was less decrease in SV at down-tilt during exercise (Fig. 3A). There was still a tilt-induced dip in SV during exercise, however, much smaller (Fig. 3A), which indicated that the transient decrease in the pressure difference during diastole between right and left ventricles (Fig. 1C) caused a decrease in LV compliance, filling, and SV. That the difference between right and left ventricular filling pressures increases during exercise has been demonstrated before (4, 8). In addition, our data show that there was an increased difference between right and left ventricular filling pressures in the supine position compared with the upright position during both rest and exercise.

In up-tilt during rest, the diastolic pressure gradient between the right and left ventricle transiently increased (Fig. 2C), but this did not induce a transient peak in SV. This can be explained in two ways: 1) the magnitude of the sudden decrease in RAP is less at up-tilt than the increase during down-tilt because of the effect of the venous valves as previously discussed and/or 2) the IVS has a convex curvature toward the RV during diastole because of a slightly higher filling pressure in the LV. Therefore, a decrease in RV filling pressure that occurs during up-tilt will not displace the IVS further to the right to the same degree as the leftward movement during down-tilt, because the bending force that is required to displace the already rightward convex IVS further to the right is considerably higher than the force required to displace it to the left (5). However, SV is maintained for several seconds after up-tilt. One explanation could be that there is also ventricular interaction during up-tilts. Figures 2A and 3B indicate that PCWP starts to fall 3–4 s earlier than SV. This suggests that SV is maintained despite a fall in absolute LV filling pressure, because the transiently increased diastolic pressure difference between RV and LV (Fig. 2C) acts to make LV more compliant in the filling phase, i.e., because of ventricular interdependence. Guazzi and coworkers (12) showed in an echocardiography study that, despite a moderate reduction in venous return induced by graded tilt, LV filling and output were maintained, indicating increased LV compliance, probably as the result of decreased RV volume and thus of ventricular interdependence. However, other mechanisms such as decreased afterload and less pericardial constraint and interdependence at the atrial level might also act to maintain SV despite decreased filling pressure. During the course of a few heartbeats, stroke volume from the left ventricle will thus be higher than from the right ventricle, indicating that the pulmonary vessels serve as a blood reservoir during up-tilt (26, 27). It can be noted that maintenance of SV acts to preserve AP in a situation of readjustment to an orthostatic challenge.

Different dynamics in SV after up- and down-tilts during rest have been shown before (26, 27), and the present study explains the underlying mechanisms as being the tilt-induced changes of RAP and PCWP (Fig. 1, A–C), confirming the coupling between SV and venous return in these settings. Down-tilting gave a transient decrease in SV, as discussed above. This dip in SV has also been noted in previous tilting experiments both during rest (1, 26) and exercise (25). The transient decrease in SV after down-tilt at rest noted by Toska et al. (26) was less than that recorded in the present study. This is probably because they tilted subjects between 30° and 0°, whereas in the present study, subjects were tilted between 80° and 0°.

**Tilt-induced changes in heart rate and arterial pressure.** The changes in HR that were seen after tilts are primarily caused by the arterial baroreflex and have been discussed previously in some depth (1, 16, 25, 26, 27).

The initial tilt-induced fluctuations of AP are dependent on 1) the reference point of AP in relation to the hydrostatic indifference point (11), 2) capacitive flows with AP changes (22), and 3) changed efficiency of the venous muscle pump between postures during dynamic leg exercise (9, 15). The return of AP to a new steady state follows reflexive changes in HR and vascular tone.

**Methodological considerations.** Beat-by-beat SV was calculated using a pulse contour technique. This method is fairly reliable when ZAO is calibrated with a separate method to determine CO (2) (in the present experiment, the thermodilution technique was used). However, it has not been evaluated during rapid changes in posture, which induce changes in many cardiovascular variables. Toska and Walløe (26) recently measured beat-by-beat SV with an ultrasound Doppler method during rapid tilts between supine and 30° inclination under resting conditions. Our calculations of SV during both up- and down-tilts show features identical to those obtained from ultrasound Doppler recordings. The different time courses between up-tilt and down-tilt, as well as the initial dip in SV after down-tilt, are the same as those noted by Toska and Walløe (26). These similarities make us confident of the calculations of SV made under resting conditions, but a similar comparison was not possible to conduct with regards to tilts during exercise. Although interpretation of SV during exercise...
must be made with more caution, to our knowledge there is no obvious reason why they should not be as reliable as those performed at rest.

The reference level for RAP and PCWP was taken as the axillary line at the level of the fourth intercostal space (measured parasternally). No consideration was taken of the true location of the ventricles, i.e., the LV is located slightly dorsal to the RV. Our conclusions regarding the discrepancy between the time courses of RAP and PCWP will not be affected by this fact. We noted that the steady-state difference between PCWP and RAP was greater in the supine position during both rest and exercise, and if the reference level for the LV had been placed dorsal to the level of the RV, this would only increase the discrepancy. Therefore, the conclusions made in this study are not affected by the location of the reference levels for RAP and PCWP.

Conclusion. The present study evaluated the central hemodynamics during sudden tilts between upright and supine positions. RAP has a faster time course than PCWP at down-tilts during both rest and exercise. This leads to a transient decrease in the diastolic difference between right and left ventricular filling pressures at down-tilt. The decreased pressure difference impedes LV filling, especially at rest when the RV filling pressure temporarily exceeds the LV filling pressure, displacing the ventricular septum to the left during diastole. In this transient situation, LV filling is markedly impaired and consequently SV falls. Similar hemodynamic factors are probably also involved during up-tilt, when SV is maintained for 2–3 s despite falling LV filling pressure.

The decrease in RAP during up-tilt in the resting condition was biphasic with an initial fast and a second slower component, which might suggest the effect of venous valves. The slow component was not seen during dynamic leg exercise when blood pooling in the legs is prevented by the muscle pump.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
Author contributions: P.S. conception and design of research; P.S. and L.K. performed experiments; P.S. and J.S. analyzed data; P.S. and J.S. interpreted data; P.S. and J.S. edited and revised manuscript; P.S. and J.S. approved final version of manuscript.

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