Noninvasive cardiac output measurement in orthostasis: pulse contour analysis compared with acetylene rebreathing

W. J. STOK, R. C. O. STRINGER, AND J. M. KAREMAKER
Academic Medical Center, Department of Physiology, University of Amsterdam, 1105AZ Amsterdam, The Netherlands

Stok, W. J., R. C. O. Stringer, and J. M. Karemaker. Noninvasive cardiac output measurement in orthostasis: pulse contour analysis compared with acetylene rebreathing. J. Appl. Physiol. 87(6): 2266–2273, 1999.—We tested the reliability of noninvasive cardiac output (CO) measurement in different body positions by pulse contour analysis (COpc) by using a transmission line model (K. H. Wesseling, B. De Wit, J. A. P. Weber, and N. T. Smith, Adv. Cardiol. Phys. 5, Suppl. II: 16–52, 1983). Acetylene rebreathing (COrebr) was used as a reference method. Twelve subjects (age 21–34 yr) were studied: 1) six in whom COrebr and COpc were measured in the standing and 6° head-down tilt (HDT) positions and 2) six in whom CO was measured in the 30° HDT, supine, 30° head-up-tilt (HUT), and 70° HUT postures on a tilt table. The COrebr-to-COpc ratio in (near) the supine position during rebreathing was used as the calibration factor for COpc measurements. Calibrated COpc (COcal-sup) consistently overestimated CO in the upright posture. The drop in CO with upright posture was underestimated by ~50%. COcal-sup and COrebr values did not differ in the 30° HDT position. Changes in the COrebr-to-COpc ratio are highly variable among subjects in response to a change in posture. Therefore, COpc must be recalibrated for each subject in each posture.

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There is a growing interest in monitoring physiological parameters noninvasively, both in research and in clinical situations. Blood pressure can now be measured noninvasively and continuously in the finger by using Finapres, which is based on the volume-clamp method of Penáz (15, 22). One of the attractive derivatives of this method is the calculation of stroke volume (SV) on a beat-to-beat basis, a technique originally developed for use with the intra-arterial blood pressure wave (aorta or brachial artery). Several models (1, 7, 17, 19, 23) can be used to calculate SV from pulse contour analysis. We have many years of experience with the method of Wesseling and co-workers (23), which is based on a transmission line model of the circulation. In this model, corrections are used for age-dependent, dynamic changes in the aortic impedance due to changes in arterial pressure and heart rate (HR), and also for reflections of the pressure waveform from the periphery. Any pulse contour method will give only relative changes in SV. Calibration against an absolute method is necessary when absolute values are required.

In an earlier study (18), in which cardiac output (CO) was influenced by changes in volume status of the test subjects (by intravenous saline loading and lower body negative pressure), we demonstrated that the method of Wesseling et al. (23) can be successfully applied to the noninvasively measured pressure wave of the fin-

gar in a close-to-supine [6° head-down tilt (HDT)] position. Acetylene (C2H2) rebreathing (COrebr) was used as the absolute reference method for CO measurement. The study showed the calibration factor (COrebr-to-COpc ratio), where COpc is CO measurement by pulse contour analysis, to be stable over a period of weeks.

A major drawback of earlier validation studies (10, 18, 23) is that comparisons are made in only one, mostly supine, body position. Finapres is used in the upright and supine positions during the same session, e.g., to track beat-to-beat blood pressure changes during orthostatic tolerance testing (9, 20). Because body position tends to alter CO and the pulse wave at the same time, an evaluation explicitly testing the reliability of pulse contour analysis at different body positions seemed indicated. We therefore tested the pulse contour method applied to the Finapres waveform during orthostasis, using COrebr as a reference.

We used two different protocols: 1) standing vs. a close-to-supine (6° HDT) position and 2) four different tilt angles on a tilt table.

Methods

Subjects

The standing vs. 6° HDT protocol was performed in six healthy male volunteers (subjects S1-S6, age 21–34 yr) during a 27-day HDT experiment (10 days in 6° HDT position) at the Deutsche Forschungsanstalt für Luft und Raumfahrt (DLR; Cologne, Germany). Written informed consent was obtained from all subjects after approval of the study by the DLR Institutional Research Review Committee.

Six healthy male volunteers (age 23–30 yr) participated in the tilt-table study (subjects T1–T6). Written informed consent was obtained from all subjects. The study was approved by the Medical Ethics Committee of the Academic Medical Center of the University of Amsterdam.

Study Protocols

Standing vs. 6° HDT. Data were collected from subjects in the standing position and during a brief (20-min) episode of 6° HDT before the actual 10-day, extended HDT period, and on the first and fifth day of recovery. Rebreathing measurements were performed, using a bag-in-box system with a 3-liter rubber anesthesia bag. A gas mixture of 1.5 liters [0.3% C18O-0.5% C2H2-1.0% He-98.2% air (78.1% N2-21% O2-0% CO2-0.9% inert gases)] was used. The protocols for the experiments performed at DLR have been described elsewhere (18) in detail. In all subjects a rebreathing frequency of 24 breaths/min was used. Rebreathing measurements were performed in duplicate both in the standing and in the 6° HDT position. The washout period between duplicates was at least 2.5 min.

Tilt table. Rebreathing measurements were performed, using a bag-in-box system with a 2.3-liter rubber anesthesia...
time 0 expiratory partial pressures against time of rebreathing. The C2H2, the pulmonary capillary blood flow can be derived concentration. Knowing the alveolar-to-blood conductance of k
and k
are derived from a semilogarithmic plot of the end-
expiratory partial pressures (N2, O2, CO2, He, and C2H2) were monitored at the mouth by means of a mass spectrometer (Centronic 200 MGA). Gas partial pressures were corrected to a sum of 99.2%. Argon (not measured) was assumed to account for 0.8%. Respiratory flow was measured by using an Alveo Test (Erich Jaeger, Würzburg, Germany) flowmeter. In subject T1, a rebreathing frequency of 24 breaths/min was used, which was lowered in subjects T2-T6 to 15 breaths/min.

Body positions were changed by using a computer-controlled tilt table. Four different tilt angles were used, −30, 0, 30, and 70°, with the subject supported by a shoulder support or footboard, respectively. A total of 12 measurements was performed in each subject, each angle in triplicate. The 12 measurements were made in random order. Between measurements, subjects were in the supine position for 5 min. After a new tilt angle was imposed, an adaptation period of 2 min was allowed before the COrer measurement was started. In this protocol, the available washout period for C2H2 be-
tween measurements was at least 7 min. During both the standing vs. 6° HDT and the tilt-table experiments, the noninvasive finger arterial pressure wave was measured by a Finapres (TNO-BMI, model 5). The finger was held at heart level, both in the frontal and transverse plane to avoid hydrostatic level errors during the maneuvers. All analog data were stored on tape for later off-line analysis. Before the start of all measurement series, subjects were familiarized with the equipment and the protocol.

Data Analysis
All analog data on tape were analog-to-digital converted at a sample rate of 100 Hz for computer analysis. Rebreathing. Data were evaluated by using the continu-
ously ventilated two-compartment lung model of Hook and Meyer (8). In this model, the equilibration of partial pressures of a soluble perfusion-limited gas (C2H2) in two compart-
ments (rebreathing bag and alveolar space) is described by a biexponential process with a fast (k1) and a slower (k2) rate constant, where k1 represents the bag-alveolar gas mixing and k2 the alveolar-lung capillary blood-gas transfer. Both k1 and k2 are derived from a semilogarithmic plot of the end-
expiratory partial pressures against time of rebreathing. The time 0 intercept of k2 is used for calculating the initial C2H2 concentration. Knowing the alveolar-to-blood conductance of C2H2, the pulmonary capillary blood flow can be derived according to

\[ Qc = \frac{\beta_2 \cdot V_R \cdot k_1 \cdot k_2}{\beta_0 \cdot S_A \cdot k_1 - k_2} \]

where \( Qc \) is pulmonary capillary blood flow, \( \beta_0 \) and \( \beta_2 \) are the capacitance coefficients of C2H2 for gas and blood respectively, \( V_R \) is the rebreathing bag volume, \( S_A \) is the zero intercept of the slower alveolar exponential component, and \( k_1 \) and \( k_2 \) are rate constants of the fast and slow alveolar compartments, respectively. Model calculations showed the model to be relatively insensitive to changes in respiration rate, dead space, alveolar volume, tidal volume, and the ratio of tidal volume to bag volume.

Pulse contour analysis. Beat-to-beat values for systolic, diastolic, and mean pressure and HR were derived from the pressure wave. To calculate SV from the pressure wave (SVpc), the method of Wesseling et al. (23) was used, which relates the pulsatile systolic area (PSA; area under the pressure curve from the start of the upstroke to the incisura) and SVpc by the effective characteristic impedance of the aorta (Zao). In this method, corrections are used for age-
dependent, dynamic changes in Zao because of changes in arterial pressure and HR, which are due to changes in aortic cross section and compliance (both pressure and age depen-
dent) and to reflections of the pressure waveform from the periphery (which is influenced by HR). SV for each beat was calculated from the PSA with the correction formula

\[ SV_{pc} = \left(\frac{PSA}{Zao_{sys}}\right) \times [1,320 + HR \times 10 - \text{age} \times (0.28 \times MAP - 16)]/2,000 \]

where HR is the momentary HR (in beats/min), MAP is mean arterial pressure (in mmHg) of the same beat, and Zao_{sys} is a first approximation of Zao and is given the value (90 + age)/1,000. As Zao is not actually known, only uncalibrated SV is derived. Beat-by-beat COpc was then calculated by multiplying SVpc by the HR belonging to the same beat. A more comprehensive description of the method is given in the literature (18, 23).

Beat-by-beat Finapres SVpc and COpc data were collected continuously for the duration of the measurement protocol. For comparison with rebreathing, COpc data were averaged over the time interval in which rebreathing data indicated completed bag-alveolar mixing and before the start of recirculation, which was, on average, the period between 6 and 20 s after the start of rebreathing. For all measurements the ratio between the methods (R_{rebr/pc} = CO_{rebr}/CO_{pc}) was calculated. R_{rebr/pc} values for the supine or 6° HDT position for each subject were averaged, and this value was used as the reference calibration factor for the pulse contour data. Calibrated SVpc and COpc will be referred to as SV_{cal-sup} and CO_{cal-sup}, respectively.

One-minute prerebreathing Finapres data were evaluated by averaging beat-by-beat data in the resting period starting 80 s before rebreathing. This was compared with the measurements during rebreathing (over the same time interval used for the comparison with rebreathing) to check for possible effects of the rebreathing maneuver itself on blood pressure and HR and derived data (SV_{cal-sup}, CO_{cal-sup}).

Statistics
We estimated the separate roles of body position and measurement methods by two-way ANOVA (model with inter-
action). If different, Student’s t-test was applied to compare the categories within a group (with Bonferroni correction).

RESULTS
Standing Vs. 6° HDT
Changes in CO_{rebr} in response to the change in body position were dependent on the moment in the HDT study. When the 6° HDT is taken as the reference position, the decrease in CO_{rebr} during standing was largest just after the extended (10-day) HDT period and smallest before the extended HDT period (−1.4 l/min (−23%) and −1.0 l/min (−16%), respectively (Table 1). This is most likely caused by the change in cardiovascular filling state. Standing CO_{rebr} was significantly differ-
Table 1. CO values at 2 body positions on 3 different days during the HDT study, measured with the C2H2-rebreathing and the pulse contour method, during rebreathing and 1 min before rebreathing

<table>
<thead>
<tr>
<th>Position</th>
<th>COrebr</th>
<th>% (range)</th>
<th>Pulse Contour COcalsup</th>
<th>% (range)</th>
<th>Before rebreathing,</th>
<th>During rebreathing,</th>
<th>Before rebreathing,</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>liters/min</td>
<td></td>
<td>liters/min</td>
<td></td>
<td>liters/min</td>
<td></td>
<td>liters/min</td>
</tr>
<tr>
<td>6° HDT</td>
<td>6.5 ± 1.0</td>
<td>100 (97–103)</td>
<td>6.5 ± 1.0</td>
<td>100 (96–104)</td>
<td>5.9 ± 0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing</td>
<td>5.5 ± 1.0*</td>
<td>84 (68–94)</td>
<td>6.0 ± 1.2†</td>
<td>92 (75–106)</td>
<td>5.3 ± 0.8*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovery day 1</td>
<td>6.0 ± 1.1</td>
<td>100 (95–105)</td>
<td>6.0 ± 1.1</td>
<td>100 (98–102)</td>
<td>5.3 ± 0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6° HDT</td>
<td>4.6 ± 0.7*</td>
<td>77 (70–87)</td>
<td>5.3 ± 1.2‡</td>
<td>88 (72–102)</td>
<td>4.6 ± 1.1*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing</td>
<td>4.5 ± 0.6*</td>
<td>80 (69–91)</td>
<td>5.4 ± 1.3§</td>
<td>94 (75–111)</td>
<td>4.8 ± 1.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 6 subjects. Measurements of 6° head-down tilt (HDT) were used for calibration of pulse contour. CO, cardiac output; COcalsup, calibrated CO pulse contour data; COrebr, CO measured by C2H2-rebreathing method. Significant difference from 6° HDT position, *P < 0.01. For COcalsup: Significant difference from COrebr: †P < 0.05, ‡P < 0.01.

ent from the 6° HDT position for each measurement period.

We calculated COcalsup in both standing and 6° HDT positions, before and during rebreathing. On average, the decrease in COcalsup in response to standing was one-half that of COrebr. Standing COcalsup was significantly different from the 6° HDT position before and on the first day after the HDT period, both during and just before the rebreathing measurement.

As shown in Fig. 1A, when we took 6° HDT as the reference position, we found a large range in the individual change of Rrebr/pc (the ratio between the methods) during standing.

Subjects S1 and S6 showed almost no change (<6%), and in subject S4 there was only a small decrease (8%) in Rrebr/pc between HDT and standing. In contrast, in subjects S2 and S5 there was a moderate-to-large decrease (14–34%) in Rrebr/pc. In subject S3 there were large changes (20%) due to standing, but the direction of the change was inconsistent among the three measurement periods.

In the 6° HDT reference position, Rrebr/pc was constant within 9% in subjects S1–S5 and within 12% in subject S6 over the total of six measurements in each subject (3 days, duplicate measurements). In the standing position, differences were larger and ranged from 8 to 15%, with one outlier of 34% in subject S3.

When body position was changed from 6° HDT to standing, average Rrebr/pc for six subjects changed from 1.04 ± 0.09 to 0.96 ± 0.13 (P < 0.05) before HDT, from 1.03 ± 0.10 to 0.90 ± 0.10 (P < 0.01) on the first day of recovery, and from 1.01 ± 0.10 to 0.97 ± 0.16 (P < 0.01) on the fifth day of recovery. Proportional changes in Rrebr/pc when standing were −7 (range ± 13 to −27%), −12 (range 0 to −28%), and −14 (range ± 4 to −33%), respectively.

The difference between COrebr and COcalsup for the 6° HDT and standing postures are shown in the Bland-Altman (4) scattergrams of Fig. 2A. The overall differences (all subjects, all measurement days) are 0.0 ± 0.2 l/min in 6° HDT and 0.7 ± 0.8 l/min in the standing position.

The MAP difference between the 6° HDT and standing position was smallest before the HDT period (14%) and largest on the first day of recovery (31%) (Table 2). The average response in HR was somewhat larger after the HDT period. HR increase during rebreathing compared with prerebreathing was only marginally different and independent of the measurement day.

Tilt-Table Maneuvers

In four of six subjects (T1-T4), COrebr declined with increasing positive [head-up tilt (HUT)] tilt angle, whereas in two subjects (T5 and T6) COrebr decreased when the tilt angle was changed from 0 to 30° but did not decrease further when the tilt angle was changed to 70°. Results at 30 and 70° HUT were significantly different from the supine position. When tilted down to −30°, five of six subjects reacted with a small-to-moderate (3–15%) decrease in COrebr, whereas in subject T3 COrebr increased by 0.8 l/min (15%). Results at −30° were not significantly different from the supine position. Average values for six subjects are presented in Table 3.

We calculated COcalsup in all four positions, both before and during rebreathing. During rebreathing, three of six subjects showed decreases in COcalsup after being tilted to angles of 30 and 70°. In these subjects the decreases in COcalsup were, on average, one-half those of COrebr. In two subjects COcalsup did not change, and in one subject it even increased. Also during tilt, we found a large range in the individual change in Rrebr/pc when using supine as the reference position (Fig. 1B). Average Rrebr/pc for six subjects changed from 1.27 ± 0.34 in the supine position to 1.06 ± 0.34 (P < 0.01) at 30° and to 0.96 ± 0.39 (P < 0.01) at 70°. Proportional changes in Rrebr/pc during tilt were −17% (range −13
to –29%) and –27% (range –11 to –44%), respectively. Thus in all subjects there was an overestimation of CO_cal,sup in the HUT positions compared with supine, but of different magnitude in each subject.

Bland-Altman scattergrams (4) of differences between CO_rebr and CO_cal,sup are shown in Fig. 2B for each tilt position. The overall differences (all subjects, triplicate measurements) are 0.0 ± 0.6, 0.3 ± 0.5, 0.9 ± 0.6, and 1.5 ± 0.8 l/min for supine, 30° HDT, 30° HUT, and 70° HUT, respectively.

In all subjects MAP increased significantly during tilt from supine to 30 and 70° HUT. During tilt from supine to –30°, MAP increased slightly, but this increase was not significant (Table 4).

In five of six subjects HR increased with tilt angle (–30 to 70°). Only in subject T3 did HR decrease with tilt angles from –30 to 30° and increase at 70° but did not reach the value at –30°. Averaged values are presented in Table 4. The HR increase during rebreathing compared with prererebreathing was affected only slightly by the tilt angle: 7, 6, 10, and 7 beats/min, respectively, for the four tilt angles.

Prerebreathing Pulse Contour Measurements

On the basis of analysis of the pulse contour before and during the rebreathing maneuver, we estimate that the rebreathing maneuver itself tends to increase CO.

In the standing vs. 6° HDT experiments, CO_cal,sup increased between 0.6 and 0.7 l/min (10–15%) due to the rebreathing maneuver. Results were similar for both the 6° HDT and standing postures (Table 1). In the 6° HDT position this increase was primarily caused by the increase in HR, whereas in the standing position both HR and SV_cal,sup increased; however, again, differences among subjects were large.

In the tilt experiments, the increase in CO_cal,sup during the rebreathing period was largest in subject T1, whose rebreathing was performed at a higher respira-
tion rate than in the other five subjects. On average, CO_{cal sup} increased by 0.5 l/min (9.4%), 0.4 l/min (7.8%), and 0.4 l/min (9.1%) at tilt angles of 30° HDT, 0°, and 30° HUT, respectively, and by 0.9 l/min (19.0%) at 70° HUT (Table 3). This increase was primarily due to an increase in HR compared with prererebreathing, but it also occurred at 70° HUT in subjects T1 and T2 partly by an increase in SV_{cal sup}.

Fig. 2. Bland-Altman scattergrams of all data points. A: measurements during standing and 6° HDT. B: measurements in 4 body positions during tilt experiments. CO_{cal sup} and CO_{rebr}, calibrated CO measurement by pulse contour analysis at a (near-)supine position and CO measured by acetylene rebreathing, respectively. Horizontal lines, means ± 1.96 SD.
In the present study we made a direct comparison of CO measurements by using pulse contour analysis at different body positions with an absolute, and noninvasive, reference method.

To investigate the rebreathing maneuver itself, we searched the literature for studies that compared C2H2 rebreathing to other CO measurement methods in different body postures. We found none. One might reason that in the HUT compared with supine position a change in distribution of the ventilation-perfusion ratio (VA/Q) is to be expected (24). In a study using C2H2 rebreathing in dogs, Friedman et al. (6) did not find a significant difference in estimation of pulmonary blood flow when VA/Q was changed over a large range by occlusion of either one pulmonary artery or one main bronchus. Using a three-compartment computer model, Burma and Saidel (5) found a small overestimation (<10%) of pulmonary blood flow in the upright position compared with supine, when the VA/Q distribution in the upright position as described by West (24) was used. A small underestimation was found by Petrini et al. (16), who used a two-compartment model with changing VA/Q. Verbanck and Paiva (21), in a model study, found only a very small influence of VA/Q on CO estimation. From these studies we concluded that the rebreathing method can be used very well as a reference CO measurement method even under conditions where VA/Q is changing.

In the standing vs. 6° HDT experiments, we used the 6° HDT position as a reference. This position was part of the HDT study measurement protocol in which the supine position was not planned. As our later tilt experiments indicate only a small but not significant difference between supine and 30° HDT, we consider it admissible to use the 6° HDT position as a substitute reference position. In three of six subjects (S1, S4, S6), differences between the pulse contour and rebreathing methods were small or absent, but in the other three subjects we found a substantial overestimation of COcalc sup compared with COrebr in the standing position. Differences between the duplicate measurements within each subject were small.

In the tilt experiments, we found COpc in the HUT position to overestimate CO in all six subjects. Among subjects, variability in responses to tilt was high using the pulse contour method, but within each subject the ratio between pulse contour and rebreathing was consistent within the triplicate measurements. In contrast to the first part of the study, in which duplicate measurements were made shortly after the initial measurement and without an in-between change of body position, triplicate measurements during the tilt experiments were made during a random sequence of 12 measurements in 4 positions. This, and the lower rebreathing frequency used, may explain the larger SDs found within the triplicate measurements in the tilt experiments (Fig. 1B).

### Table 2. MAP and heart rate during rebreathing at 3 different days during the HDT study

<table>
<thead>
<tr>
<th>Position</th>
<th>MAP During Rebreathing</th>
<th>Heart Rate Before HDT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>%</td>
</tr>
<tr>
<td>6° HDT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing</td>
<td>77 ± 7</td>
<td>100 ± 2</td>
</tr>
<tr>
<td></td>
<td>88 ± 9*</td>
<td>114 ± 10</td>
</tr>
<tr>
<td>Recovery day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing</td>
<td>67 ± 5</td>
<td>100 ± 2</td>
</tr>
<tr>
<td></td>
<td>88 ± 8*</td>
<td>131 ± 10</td>
</tr>
<tr>
<td>Recovery day 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing</td>
<td>72 ± 7</td>
<td>100 ± 1</td>
</tr>
<tr>
<td></td>
<td>88 ± 5*</td>
<td>123 ± 8</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 6 subjects. MAP, mean arterial pressure. Significant difference from the 6° HDT position, *P < 0.01.

### Table 3. CO values at 4 tilt angles, measured with the C2H2 rebreathing and the pulse contour method during rebreathing and 1 min before rebreathing

<table>
<thead>
<tr>
<th>Tilt Angle, °</th>
<th>COrebr</th>
<th>Pulse Contour COcalc sup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>liters/min</td>
<td>% (range)</td>
</tr>
<tr>
<td>-30</td>
<td>5.3 ± 0.8</td>
<td>96 (137–82)</td>
</tr>
<tr>
<td>0</td>
<td>5.6 ± 1.0</td>
<td>100 (114–92)</td>
</tr>
<tr>
<td>30</td>
<td>4.3 ± 0.8*</td>
<td>78 (115–78)</td>
</tr>
<tr>
<td>70</td>
<td>3.9 ± 0.7*</td>
<td>71 (123–81)</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 6 subjects. Supine measurements were used for calibration of pulse contour. Significant difference from the supine position, *P < 0.01. For COcalc sup: significant difference from COrebr, †P < 0.01.
In the supine position, the calibration factors in four of six subjects (T1-T4) were within the range found in our earlier study: 0.91–1.24 (18). In the other two subjects the calibration factors were 1.58 and 1.77 (Fig. 2B). CO_rebr values in the supine position for these four subjects were not different from those for the other four subjects, but the variance in R_rebr/pc was larger at all tilt angles. This was due to a larger variance in the rebreathing measurements. Pulse contour measurements were consistent within each triplicate measurement. Also, in these two subjects there was no further decrease in R_rebr/pc from 30 to 70° HUT.

As already found in our earlier study (18), the rebreathing procedure itself changes the cardiovascular status of the subject: both HR and CO_cal_sup increased compared with prerebreathing values. In the standing vs. 6° HDT study, which followed the same protocol, all measurements were made by using a rebreathing frequency of 24 breaths/min. The increase in CO_cal_sup due to the rebreathing maneuver was ~0.7 l/min in both positions, but, especially in the standing position, differences among subjects were large. During the tilt experiments, CO_cal_sup increased less during rebreathing in the supine reference position compared with the 6° HDT reference position (0.4 vs. 0.7 l/min) but slightly more (0.9 vs. 0.7 l/min) at 70° HUT compared with standing.

Tilt experiments were started in subject T1 by using a rebreathing frequency of 24 breaths/min. We decreased the rebreathing frequency to 15 breaths/min in the other five subjects to minimize the effect of rebreathing on CO_cal_sup although a less accurate estimation of the k2 rate constant can then be expected, because of less available data points for the curve fit. Despite the different breathing frequency and the consequently larger increase in CO_cal_sup due to the rebreathing maneuver, subject T1 produced differences between CO_cal_sup and CO_rebr similar to those in subjects T2-T6. Therefore, we included the results from this subject in this study. When subject T1 is excluded, the average increase in CO_cal_sup during rebreathing is reduced to 0.3, 0.2, 0.2, and 0.7 l/min for the tilt angles of 30° HDT, 0°, 30° HUT, and 70° HUT, respectively.

In the 6° HDT and standing positions the differences between CO_cal_sup prerebreathing and during rebreathing were approximately equal (0.6–0.7 l/min, Table 1). Therefore, the difference between pulse contour and rebreathing of 0.5–0.9 l/min in the standing position cannot be attributable to the rebreathing maneuver itself. The same is true for the supine, 30° HDT, and 30° HUT positions during the tilt experiments, where the difference between CO_cal_sup prerebreathing and during rebreathing was 0.4 l/min in all three cases (Table 2). At 70° HUT, however, the increase in CO_cal_sup due to rebreathing was approximately twice as much (0.9 l/min) as in the supine position. Part of the 1.5-l/min difference between the methods at 70° HUT may therefore be attributable to the larger influence of the rebreathing maneuver on the parameter to be measured (SV) in some of the subjects (T1 and T2). This does not fully explain the large interindividual range of change in R_rebr/pc (~11 to ~44%) at this tilt angle, as both extreme values were found in subjects in which SV_cal_sup was not influenced by the rebreathing maneuver.

Why does R_rebr/pc change when the position of subjects is changed from the (near) supine to the upright position? First, this is likely not to be caused by using Finapres as an arterial pressure measurement device. Jellema et al. (11) found no difference between noninvasive finger arterial and intrabrachial CO_rebr responses during tilt experiments. However, in both cases the method has been applied to a pressure wave more peripheral than aortic pressure, for which the method was originally developed.

Overestimation of CO in the upright position by pulse contour can be caused by a too-large systolic area (PSA) and/or a too-small estimated characteristic Zao. In the original model study of Wesseling et al. (23), hydrostatic pressure gradients as a result of the upright position are not taken into account. MAP is used in the model corrections to adapt the estimation of Zao for changes in compliance. A possible consequence is that an increasing pressure in the thoracic and abdominal aorta could mean a change toward the properties of a more rigid system with an increase in pulse-wave velocity (2) and/or a change in mismatch of characteristic impedance at the primary reflection sites (12, 13). Consequently, reflections may play a more dominant role in the systolic part of the pulse wave, also at higher HRs when ejection time is shorter. A change in the location of the primary reflection site will have the same effect. When a larger part of the PSA is due to reflections (14, 25), this has to be corrected in the model by assuming a less compliant arterial system, which results in an increase in the estimated Zao, leading to a lower estimated SV.

In our earlier validation study (18), in which saline infusion was used to enlarge SV, only a small increase in HR (+4.1%) and no change in MAP (+1.3%) was seen. During lower body negative pressure, which was
used to reduce SV, HR increased at most by +24% (at −40 mmHg lower body negative pressure), whereas MAP decreased by 2.2–4.1%. Furthermore, all measurements were performed in the same body position (6° HDT). In the present study, responses in HR and MAP due to HUT and standing were much larger, and both parameters increased. Maximal responses during standing were +62% for HR and +31% for MAP; at 70° HUT they were +35% for HR and +17% for MAP. By using Wesseling’s correction formula (23), these changes in HR and MAP will result in a decrease in the estimated Zao (and hence in a larger SVpc), which in this situation is probably a correction in the wrong direction.

In conclusion, the present model used to adapt the estimation of Zao to different hemodynamic parameters, i.e., HR, blood pressure, and the influence of age, does not account for situations in which a hydrostatic pressure gradient exists. Responses of COcal-sup in body position are widely different in our subjects and are sometimes nonphysiological. In our earlier study (18), the reproducibility of the pulse contour measurements in one body position was good over a long time period and over a large range of COs. Also, in the present study, pulse contour measurements in any one body position were well reproducible. However, pulse contour analysis using the Finapres waveform needs additional calibrations when changes in body position are involved.

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Address for reprint requests and other correspondence: W. J. Stok, Academic Medical Center, Department of Physiology, University of Amsterdam, Meibergdreef 9, 1105AZ Amsterdam, The Netherlands (E-mail: w.stok@amc.uva.nl).

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REFERENCES


