Research Paper

Clinical Autonomic Research 1999, **9**:185–192

Estimation of beat-to-beat changes in stroke volume from arterial pressure: a comparison of two pressure wave analysis techniques during head-up tilt testing in young, healthy men

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Received 10 March 1999; accepted 24 May 1999

Objective: The aim of this study was to compare beat-to-beat changes in stroke volume (SV) estimated by two different pressure wave analysis techniques during orthostatic stress testing: pulse contour analysis and Modelflow, *ie,* simulation of a three-element model of aortic input impedance.

Methods: A reduction in SV was introduced in eight healthy young men (mean age, 25; range, 19–32 y) by a 30-minute head-up tilt maneuver. Intrabrachial and noninvasive finger pressure were monitored simultaneously. Beat-to-beat changes in SV were estimated from intrabrachial pressure by pulse contour analysis and Modelflow. In addition, the relative differences in Modelflow SV obtained from intrabrachial pressure and noninvasive finger pressure were assessed.

Results: Beat-to-beat changes in Modelflow SV from intrabrachial pressure were comparable with pulse contour measures. The relative difference between the two methods amounted to 0.1 ± 1% (mean ± SEM) and was not dependent on the duration of tilt. The difference between Modelflow applied to intrabrachial pressure and finger pressure amounted to −2.7 ± 1.3% (p = 0.04). This difference was not dependent on the duration of tilt or level of arterial pressure.

Conclusions: Based on different mathematical models of the human arterial system, pulse contour and Modelflow compute similar changes in SV from intrabrachial pressure during orthostatic stress testing in young healthy men. The magnitude of the difference in SV derived from intrabrachial and finger pressure may vary among subjects; Modelflow SV from noninvasive finger pressure tracks fast and brisk changes in SV derived from intrabrachial pressure.

Keywords: aortic impedance, blood pressure, Finapres, head-up tilt, pulse contour, simulation, stroke volume.

For several years prolonged head-up tilt testing has been used as a tool in the clinical evaluation of patients presenting with postural dizziness or recurrent neurocardiogenic syncope [1]. The induction of venous pooling with sudden arterial hypotension and consequent syncope for diagnostic purposes has created a need for continuous monitoring of blood pressure and left ventricular stroke volume (SV) [2]. Invasive blood pressure monitoring predisposes subjects to fainting during orthostatic stress [3,4], and therefore noninvasive monitoring is recommended [1].

The noninvasive Finapres device (Netherlands Organization for Applied Scientific Research, Biomedical Instrumentation, TND-BMI, Amsterdam) has been shown to provide a reliable alternative for continuous intra-arterial measurements in a variety of situations [5], including sudden changes in blood pressure induced by prolonged head-up tilt testing [6,7]. For the noninvasive estimation of beat-to-beat changes in SV during orthostatic stress, impedance cardiography [8] and pulse contour [9] are the techniques clinically feasible. However, SV from impedance cardiography correlates moderately with thermodilution [10], and multiple assumptions about chest dimensions and composition have to be made. In addition, pulse contour methods assume aortic dimensions are constant, although these properties alter with changing distending pressures [11].

Recently, a pressure wave analysis technique has been introduced that estimates continuous SV from arterial pressure by simulating a nonlinear, three-element model of aortic input impedance: the Modelflow technique [12]. This technique, in contrast to pulse contour methods, takes into account the variation in aortic properties with changes in distending pressures [12].

The aim of this study was to compare beat-to-beat changes in SV as introduced by orthostatic stress in healthy young men estimated by pulse contour analysis and Modelflow. Earlier, changes were reported in SV obtained by pulse contour analysis of the intrabrachial and finger pressure waveform during prolonged head-up tilt testing [6]. In the present study arterial pressure recordings were reanalyzed to compare continuous SV obtained with the Modelflow technique with pulse contour measures. Furthermore, the relative differences in Modelflow SV obtained from intrabrachial and non-invasive finger pressure were quantified.

Materials and methods

Subjects

Eight normotensive, healthy male volunteers were investigated. Subject characteristics are summarized in Table 1.

Table 1. Subject characteristics and average values and range of heart rate (HR) and mean arterial pressure (MAP) during head-up tilt

Subject no.	Age (yr)	Height (cm)	Weight (kg)	HR (bpm) (range)	MAP (mm Hg) (range)
1	32	182	77	80 (67–93)	80 (61–97)
2	22	181	72	70 (55–95)	81 (62–99)
3	30	197	86	80 (63–102)	80 (62–93)
4	22	183	72	74 (47–89)	74 (40–97)
5	26	186	80	82 (59–104)	83 (56–100)
6	24	187	76	75 (47–97)	78 (60–94)
7	19	185	73	83 (55–98)	83 (59–99)
8	22	185	75	83 (63–102)	80 (62–93)
Mean	25	186	76	78	80
SD	±4	±5	±5		

Mean, average difference; SD, standard deviation; bpm, beats per minute.

Written informed consent was obtained before enrollment. The protocol was approved by the medical ethical committee of the Academic Medical Center and conforms to the principles outlined in the Declaration of Helsinki of the World Medical Association.

Protocol

The experimental procedure was started at 9.00 A.M. in a room with a constant ambient temperature of 22° C. Finger and intrabrachial pressures were measured simultaneously. After a 30-minute supine rest period the subjects were tilted up to 70° in 2 to 3 seconds using a manually driven tilt table with foot support. Blood pressure and heart rate were continuously monitored before and during the subsequent period of head-up tilt. The test was terminated by returning the subject to the horizontal position at the completion of the 30-minute head-up tilt, at the request of the subject, or when systolic blood pressure decreased more than 20 mm Hg.

Measurements

Intra-arterial blood pressure was measured through a Teflon (DuPont, Wilmington, DE) cannula with a length of 11 centimeters. After local anesthesia with 1% lidocaine, the cannula was inserted into the brachial artery of the nondominant arm by the Seldinger technique. Via a 70-centimeter long polyethylene tube the cannula was connected to the transducer of a commercially available Oxford Medilog Mark II system (Romulus Technology Ltd., Uxbridge, United Kingdom) and positioned on the anterior axillary border at the second intercostal space, at heart level. The dynamic performance of the invasive system was measured by applying 100 mm Hg pressure steps with 10 millisecond rise time while recording the responses on a high speed electronic strip chart recorder (Model TA 4000; Gould Inc., Cleveland, OH). The resonance frequency of the catheter-manometer system ranged from 14 to 30 hertz.

Finger pressure was measured with a Finapres model 5 (Netherlands Organisation for Applied Scientific Research, Biomedical Instrumentation). Finapres is based on the arterial volume-clamp method of Peňáz [13] and the Physiocal [7] (physiological calibration) criteria of Wesseling *et al.* [14]. The cuff was applied to the mid-phalanx of the middle finger of the dominant arm. The pressure transducer and the finger cuff were positioned at heart level. In the first minute of head-up tilt the positions of the finger cuff and intra-arterial pressure transducer were checked for possible hydrostatic level errors and, if necessary, readjusted. In the Finapres device, a built-in expert system (Physiocal [7]) was in operation to establish and maintain a proper volume clamp setpoint [14]. Intrabrachial and finger pressure signals and an event marker were recorded simultaneously on a Sanborn thermopaper writer for direct inspection and on a four channel FM tape recorder (Bell and Howell, model TI) for off-line evaluation.

Stroke volume computation

Pulse contour analysis: this method computes changes in left ventricular stroke volume from the pulsatile systolic area. SV is computed as: $SV = A_{sys} / Z_{ao}$, where SV is the pulse contour stroke volume of the heart, A_{sys} the area under the systolic portion of the pressure wave, and Z_{ao} the characteristic impedance of the aorta. However, the characteristic properties of the aorta are pressure dependent and vary with age [11]. In addition, the pulse wave velocity increases with age, causing peripheral reflections to return to the heart during systolic ejection, disturbing the model. We, therefore, used the improved method of Wesseling *et al.* [15], who developed a correction formula using mean arterial pressure to correct for pressure-dependent properties of the arterial impedance, and heart rate to correct for early reflections coming from the periphery, the degree of correction depending on the age of the subject [15]. Mathematically: $Z_{ao} = a / [b + (c \times \text{MAP}) + (d \times \text{HR})]$ where MAP is mean arterial pressure,

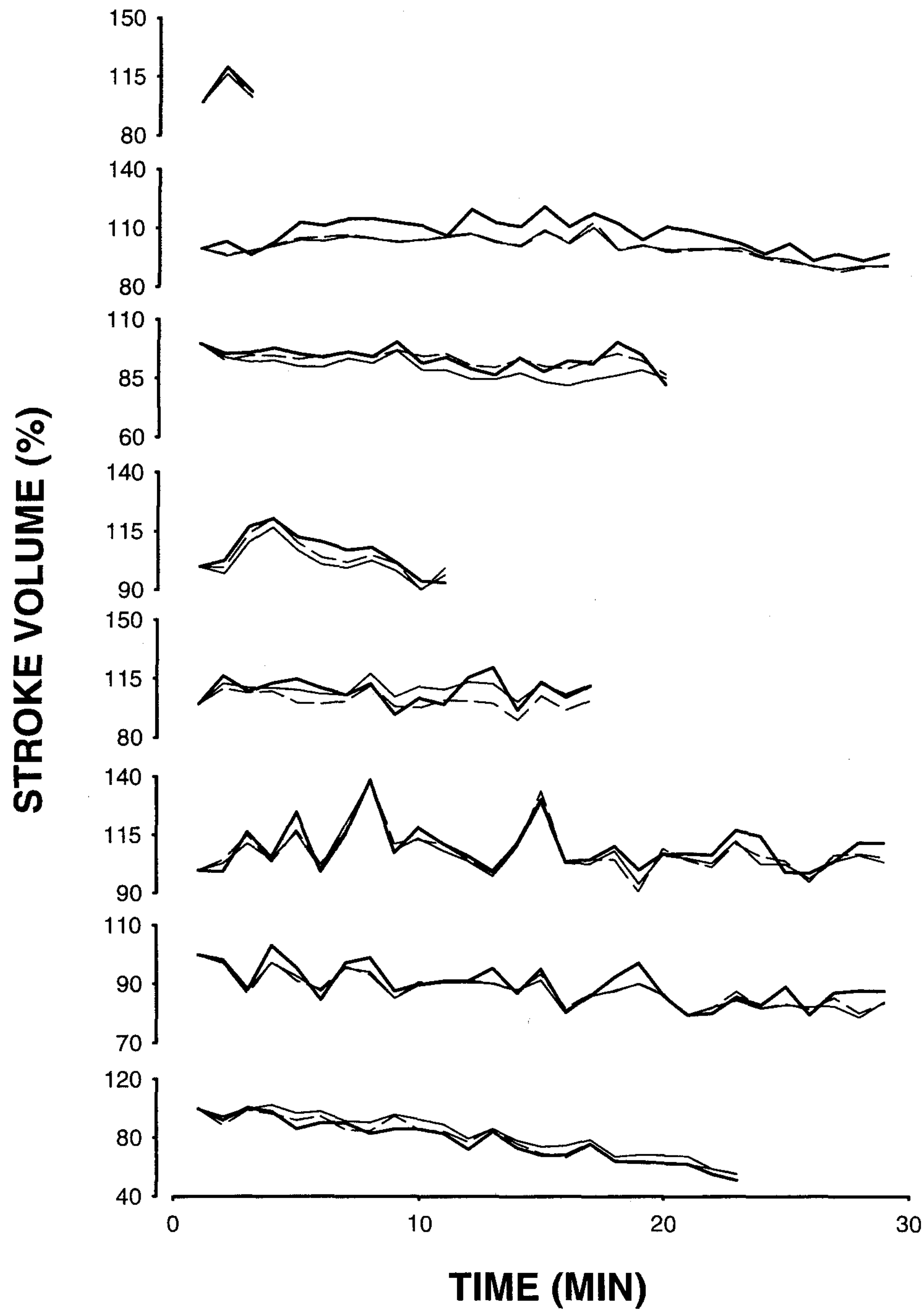

Figure 1. Relative changes in stroke volume (SV) during a 30-minute head-up tilt in eight subjects. Values reflect the averages of a 10-second period around each minute of tilt. The first subject tolerated tilt testing for less then 4 minutes. *Bold lines*, Modelflow SV derived from the finger pressure curve; *thin lines*, Modelflow SV derived from intrabrachial pressure curve; *dashed lines*, pulse contour SV derived from the intrabrachial pressure curve.

HR is heart rate, and *a*, *b*, *c*, and *d* age-dependent parameters, respectively.

Pulse contour SV from radial artery pressure correlated to thermodilution cardiac output (CO) with a regression slope close to 1 ($r = 0.94$) [16]. The standard deviation for the difference between the two methods was 11% (0.5 L/min) under the adverse conditions of open-heart surgery. Furthermore, pulse contour SV from noninvasive finger pressure compared to inert gas rebreathing CO in healthy subjects produced a scatter of comparable magnitude [17].

Modelflow: This method computes an aortic flow waveform from an arterial pressure signal using a nonlinear, three-element model of the human aortic input impedance [12]. Integrating the aortic flow waveform per beat provides SV. CO is computed by multiplying SV and heart rate.

The model of human aortic input impedance [18] describes the behavior of the aorta in opposing ejection of blood by the left ventricle and thereby the relation between aortic pressure and aortic inflow [19]. The three elements of the model represent the major properties of the aorta

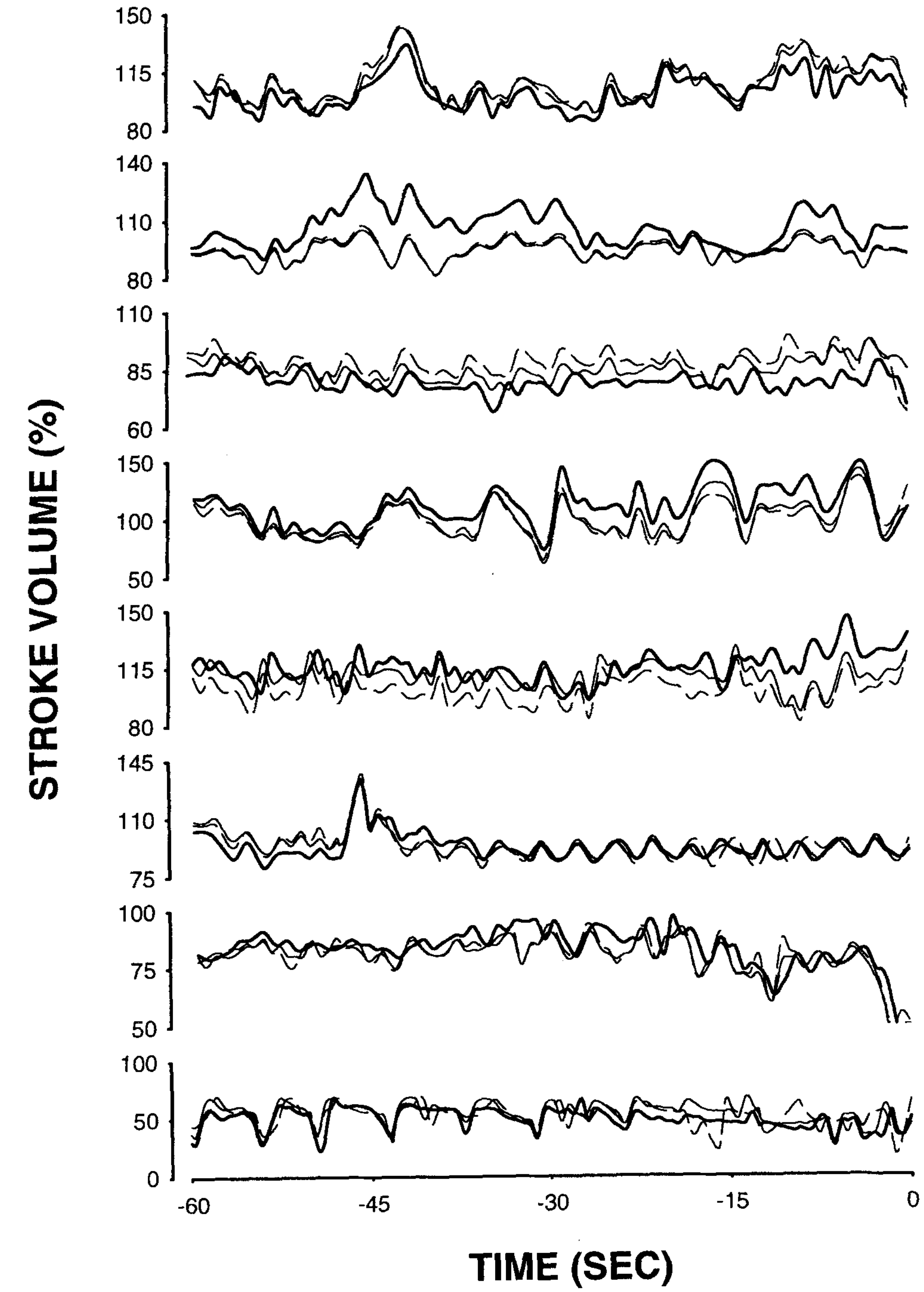

Figure 2. Individual beat-to-beat changes in SV during the last minute before tilt back. *Bold lines*, Modelflow SV derived from the finger pressure curve; *thin lines*, Modelflow SV derived from intrabrachial pressure curve; *dashed lines*, pulse contour SV derived from the intrabrachial pressure curve.

and arterial system: aortic characteristic impedance, arterial compliance, and peripheral vascular resistance [18]. The major determinants of the systolic inflow are the aortic characteristic impedance and arterial compliance; these elements are dependent on the elastic properties of the aorta. The third element, peripheral vascular resistance, is not a major determinant of systolic inflow [12], is time-varying, and is calculated for each heartbeat as the quotient of measured arterial pressure and computed Modelflow CO.

The elastic properties of thoracic human aorta were studied by Langewouters *et al.* [11]. They found that the elastic behavior of the aorta varied nonlinearly with changing distending pressures; the cross-sectional area of the aorta (A) increases with aortic pressure in a nonlinear manner: at lower pressures the area increases quickly, at higher pressures the area increases slowly. They described the relation of cross-sectional area to pressure (P) by an arctangent equation, mathematically expressed as:

$$A\,(P) = A_{max}\,0.5 + 1 \arctan P - P_0\,P_1$$

A (*P*), aortic cross-sectional area for any pressure *P*; A_{max}, P_0, and P_1, age and gender dependent parameters, respectively.

Values of two of the major model elements (aortic characteristic impedance and arterial compliance) can be derived from the pressure-area equation by algebraic manipulation: the dimension of compliance is defined as a change in volume (dV) divided by a change in pressure (dP). Assuming that aortic length (l) is constant, changes in volume ($V = \pi.r^2.l$ or $\pi.A.l$) are proportional to changes in cross-sectional area (dA). Consequently, compliance (C) is computed by $C = dA/dP$ and aortic characteristic impedance (Z_0) can be derived from the standard formula: $Z_0 = \sqrt{\rho/A.C}$, with ρ, density of blood.

With the arterial pressure waveform, subject gender, and age as input, the Modelflow software computes values of the model elements C_w and Z_0 for each new pressure sample taken at 100 hertz. Modelflow applies the values for A_{max}, P_0, and P_1 from a built-in database. Instantaneous values of C_w and Z_0 are used in the model simulation resulting in the computation of an aortic flow waveform.

In cardiac surgery patients, Modelflow CO (radial artery pressure) showed adequate tracking of bolus thermodilution CO over a range of 3.1 to 6.9 L/min for several hours [12]. In mechanically ventilated patients with septic shock, Modelflow cardiac output reflects thermodilution cardiac output over a range of 4.1 to 18.2 L/min [20]. Under these circumstances, Modelflow applied to the noninvasive finger pressure accurately tracks changes in thermodilution cardiac index for several hours; the overall discrepancy between both measurements was 0.14 $L.min^{-1}.m^{-2}$ [21]. Modelflow SV as obtained from finger pressure in healthy subjects subjected to orthostatic stress tracks thermodilution-based estimate of SV with a small (3 ± 8 ml) offset during 70° passive head-up tilt [22].

Data analysis

The intrabrachial and finger pressure signals as recorded on magnetic tape were A/D converted off-line at a sampling rate of 100 hertz. Beat-by-beat systolic, mean, and diastolic blood pressures were recorded. Mean arterial pressure was obtained as the integral of pressure over one beat divided by the corresponding beat interval. Instantaneous heart rate in beats/min was computed as the inverse of the interbeat interval.

A pulse wave reconstruction technique was applied to the finger pressure signal to reconstruct a brachial artery blood pressure curve. This technique corrects for the physiologic pulse shape and pressure level differences between the brachial artery and finger [23]. Application of pulse wave reconstruction has been demonstrated to increase the comparability of Modelflow SV from intrabrachial and finger pressure in patients with a varying degree of vascular disease [24].

A change in finger cuff position can alter the shape of the arterial waveform used for the SV computation. Therefore, only data obtained after the finger cuff readjustment were used in the comparison and the SV baseline value was defined as the 10-second period around the first minute of tilt-up (55 to 65 s). In absence of a reference SV measurement, changes in SV are expressed as percentage changes from baseline.

Stroke volume measurements during head-up tilt were analyzed in two ways. First, to compare the long-term (30 min) applicability and to permit for statistical analysis, values were averaged over 10-second periods around each minute of tilt-up (115 to 125 s, 175 to 185 s, etc.) and expressed as percentage changes from baseline. Second, to enable inspection of the sudden and fast changes in SV as observed in the latest stages of tilt, percentage changes during the last minute prior to tilt-back are presented on a beat-to-beat basis.

Statistical analysis

Individual data are presented as mean difference ± standard deviation (SD). Group results are expressed as mean difference ± standard error of the mean (SEM). In order to assess the random differences between subjects and to correct for the unequal number of data points between subjects, a general mixed model of analysis of variance was used (Biomedical Programs, BMDP, University of California, Los Angeles, California). Sequential analysis (Wald test [25]) was applied to assess systematic differences in SV and to identify a possible time dependency. A p value less than 0.05 was considered significant.

Results

Subject characteristics and heart rate (HR) and mean arterial pressure (MAP) range during the head-up tilt maneuver are presented in Table 1. In six of the eight subjects head-up tilt had to be terminated within 30 minutes: two subjects experienced presyncopal symptoms (weakness and abdominal discomfort) without a fall in blood pressure after 4 and 21 minutes and were tilted back on request; after 12, 18, 23, and 29 minutes a fall in systolic blood pressure greater than 20 mm Hg developed in the other four subjects with prompt recovery upon tilt back [6].

Stroke volume from intrabrachial pressure: pulse contour and Modelflow

During a 30-minute head-up tilt, percentage changes in pulse contour SV from intrabrachial pressure were closely followed by Modelflow SV in almost all subjects (Figs. 1 and 2, Table 2). The mean SV difference between the two techniques amounted to 0.1 ± 1.0% (mean ± SEM). This difference was not dependent on the duration of tilt.

Modelflow stroke volume from intrabrachial and finger pressure

Before application of the pulse wave reconstruction the difference between Modelflow SV from intrabrachial and finger pressure amounted to −0.8 ± 2.8% (mean ± SEM). With pulse wave reconstruction the difference was −2.7 ± 1.3% (intrabrachial vs finger pressure $p = 0.04$). The difference in SV was independent of the duration of tilt and level

Table 2. Individual differences between pulse contour analysis and model simulation applied to the intrabrachial pressure wave

Subject no.	Data points (10 s avg) when tilt-up	Mean ± SD (%) during HUT	Data points (beats) during last min. tilt-up	AVG ± SD (%) during last min. of tilt-up
1	2	2.1 ± 1.8	85	0.4 ± 3.1
2	28	0.2 ± 1.0	72	1.0 ± 0.6
3	19	4.5 ± 2.7	86	3.3 ± 4.3
4	10	2.7 ± 1.2	68	−1.6 ± 4.9
5	16	−7.3 ± 3.2	86	−9.0 ± 3.0
6	28	0.7 ± 2.1	82	0.2 ± 4.2
7	28	0.3 ± 1.1	90	1.1 ± 3.5
8	22	−2.4 ± 2.0	102	−1.3 ± 9.1

Mean, average difference for each subject; SD, standard deviation; HUT, head-up tilt.

of arterial pressure (range MAP: 40–100 mm Hg). The magnitude of the difference in SV varied among subjects up to 7% (subject 2 in Table 3). Still, Modelflow SV from non-invasive finger pressure tracked fast and brisk changes in SV derived from intrabrachial pressure in all subjects (Fig. 2).

Discussion

Pressure wave analysis applied to a peripheral arterial pressure signal

Theoretically, aortic pressure is the preferred waveform for the computation of SV in both pressure wave analysis techniques. However, aortic pressure is not routinely available in clinical practice, and peripheral arterial pressure resembles aortic pressure sufficiently to compute SV [12]. With pulse contour analysis, the percentage changes in pulsatile systolic area of the aortic waveform were similar to changes in the peripherally derived pulsatile systolic area, even though absolute values were different [26]. In addition, the computed flow waveform in Modelflow was distorted because the peripheral pressure wave was distorted; however, the area under the computed flow waveform (*ie*, stroke volume) was affected only minimally [12].

Pressure wave analysis: pulse contour versus Modelflow

A study comparing both techniques applied to radial artery pressure in cardiac surgery patients (mean age, 58 y) demonstrated a reduction in the SD of the difference in CO from 12% with pulse contour to 8% with Modelflow, in reference to thermodilution CO [12]. This is in contrast to the finding of the present study in young, healthy volunteers reporting similar changes in SV with both techniques from intrabrachial pressure recordings (Figs. 1 and 2). This comparability of SV tracking can be attributed to the young age of the subjects investigated: in the three-element model of aortic input impedance, the principal element that determines flow in young adults is aortic characteristic impedance. With increasing age, arterial compliance diminishes [27] and becomes the dominant element in the model. Langewouters *et al.* [11] found that the human arterial compliance decreases nonlinearly when arterial pressure rises. Therefore, consideration of the nonlinear decrease in compliance becomes more important with increasing age. The Modelflow technique accounts for this physiological decrease with more precision than pulse contour analysis [12]. In the present investigation, the performance of Modelflow was equivalent to pulse contour analysis. This may be attributed to the fact that changes in compliance are not a major contribution to Modelflow SV computation in young adults.

Modelflow applied to intrabrachial and finger pressure

Modelflow SV estimation from the noninvasive finger pressure signal is a technique that can easily be performed during prolonged head-up tilt testing, allowing beat-to-beat SV monitoring throughout the investigation. However, finger arteries are affected by contraction and dilatation in relation to psychological and physical (heat, cold, blood loss, orthostasis) stress [28]. Thus, finger arterial pressure depends on several factors affecting peripheral blood flow. Effects

Table 3. Individual differences in Modelflow SV derived from intrabrachial and finger pressure

Subject no.	Data points (10 s avg) when tilt-up	Mean ± SD (%) during HUT	Data points (beats) during last min. tilt-up	AVG ± SD (%) during last min. of tilt-up
1	2	−3.8 ± 0.2	85	6.3 ± 4.2
2	28	−7.1 ± 3.7	72	−12.4 ± 7.3
3	19	−5.2 ± 3.0	86	5.4 ± 4.9
4	10	−5.5 ± 1.9	68	−11.7 ± 15
5	16	0.5 ± 5.4	86	−5.2 ± 12
6	28	−3.1 ± 4.6	82	0.7 ± 4.7
7	28	−2.1 ± 3.1	90	−3.1 ± 6.5
8	22	4.6 ± 2.0	102	4.9 ± 6.3

Mean, average difference for each subject; SD, standard deviation; HUT, head-up tilt.

of these phenomena are, however, reduced by the built-in Physiocal algorithm in Finapres and reliable tracking of intra-arterial measurements by noninvasive finger pressure has been demonstrated under circumstances of low arterial pressure [6] and in patients with both hypertension and vascular disease [26]. This study clearly demonstrates that Modelflow SV from noninvasive finger pressure can track fast and brisk changes in simultaneous intrabrachial recordings in healthy young male subjects, although the magnitude of the difference in SV may vary among subjects.

Recently Voogel *et al.* [24] demonstrated that pulse wave reconstruction with age and pressure level correction significantly increased the comparability of Modelflow SV from intrabrachial and finger pressure in patients with a varying degree of vascular disease ($-7.5 \pm 17\%$ to $4.1 \pm 12\%$, $p < 0.05$). It is well-known that pulse shape and pressure levels obtained from the finger differ from those of the brachial artery. Owing to pulse wave reflections and the gradual decline of MAP from the heart toward the periphery, the finger pressure wave becomes distorted [30]. These physiologic phenomena [27] and their correction become more important with increasing age and degree of atherosclerosis [24]. In the present study we found a small difference between SV from intrabrachial pressure and finger pressure regardless of pulse wave reconstruction. However, our study indicates that in healthy young men the tracking of intrabrachial-derived Modelflow SV by finger pressure—derived Modelflow SV may be improved by pulse wave reconstruction (SEM decreased from 2.8% to 1.3%) at the cost of a slightly increased average difference (difference from -0.8% to -2.7% with reconstruction).

Conclusions

A limitation of this study is the absence of a reference technique to determine beat-to-beat SV, and we are therefore unable to comment on the absolute changes in SV with both techniques during head-up tilt testing. In healthy subjects, validation of a new technique to monitor SV is troublesome because a reference measurement requires a pulmonary artery catheter (thermodilution) or is difficult to obtain with changes in posture over longer periods of time (Doppler ultrasound echocardiography) [31,32]. In addition, standard CO techniques are discontinuous and deliver values for SV averaged over many heartbeats. These methods do not reflect the considerable beat-to-beat fluctuations in SV, present even in the recumbent position [32], as found with the techniques discussed in this article.

Beat-to-beat pulse contour and impedance cardiography SV have been compared during head-up tilt by Schondorf *et al.* [33]. They concluded that both pulse contour and impedance SV cannot be used interchangeably during head-up tilt but can be regarded as equivalent descriptors of a population response to head-up tilt. In addition, a comparison of Modelflow and Doppler ultrasound SV [34] during orthostatic stress in healthy young men showed equal assessment of beat-to-beat changes in SV during supine rest.

In conclusion, we compared beat-to-beat changes in SV estimated by two different pressure wave analysis techniques—pulse contour analysis and Modelflow—in healthy young men during orthostatic stress. Both techniques applied to intrabrachial pressure tracked percentage changes in SV with comparable performance. Furthermore, finger pressure—derived Modelflow SV can be used to track beat-to-beat SV changes from baseline compared to simultaneous intrabrachial recordings. However, prudence is called for when interchanging finger pressure—derived Modelflow values for intrabrachial-derived values in the individual subject.

Acknowledgments

This work was supported in part by a grant from the Dutch Heart Foundation (NR 94.140) and the Ruitinga-van Swieten Foundation (W.T. Jellema).

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