Carotid artery pulse wave time characteristics
to quantify ventriculo-arterial responses
to orthostatic challenge

Koen D. Reesink¹, Evelien Hermeling¹, M. Christianne Hoeberigs²,
Robert S. Reneman³, Arnold P.G. Hoeks¹
Departments of Biophysics¹, Radiology², Physiology³
Cardiovascular Research Institute Maastricht (CARIM)
Maastricht University, Maastricht
The Netherlands

Running head: Ventriculo-arterial interaction by pulse wave analysis

Corresponding author:
Koen D. Reesink, PhD
Department of Biophysics,
CARIM, Maastricht University
P.O. Box 616
6200 MD Maastricht
The Netherlands
Phone: +31-(0)43-3881664
E-mail: k.reesink@bf.unimaas.nl
Central blood pressure waveforms contain specific features related to cardiac and arterial function. We investigated posture-related changes in ventriculo-arterial hemodynamics by means of carotid artery (CA) pulse wave analysis. ECG, brachial-cuff pressure and common CA diameter waveforms (by M-mode ultrasound) were obtained in 21 healthy volunteers in supine and sitting position (age 19-30; male/female: 10/11). Pulse wave analysis was based on a timing extraction algorithm which automatically detects acceleration maxima in the second derivative of the CA pulse waveform. The algorithm enabled determination of isovolumic contraction and ejection periods (supine; ICP: 43 ± 8 ms, 4 ms precision; EP: 302 ± 16 ms, 5 ms precision; mean ± SD). Compared to supine, in sitting position diastolic blood pressure (DBP) increased by 7 ± 4 mmHg (p<0.001) and R-R interval decreased by 49 ± 82 ms (p=0.013) reflecting normal baroreflex response, while EP decreased to 267 ± 19 ms (p<0.001). Shortening of EP was significantly correlated to earlier arrival of the lower body peripheral reflection wave (r²=0.46, p<0.001). ICP increased by 7 ± 7 ms (p<0.001), ICP/EP increased from 14 ± 3% (supine) to 19 ± 3% (p<0.001) and DBP/ICP decreased by 7% (p=0.023). These results suggest that orthostasis causes a decrease in left ventricular output due to arterial wave reflections and presumably reduced cardiac preload. We conclude that CA ultrasound and pulse wave analysis enable non-invasive quantification of ventriculo-arterial responses to changes in posture.
Keywords: hemodynamics, orthostasis, systolic time intervals, vascular ultrasound
INTRODUCTION

Carotid artery ultrasonography is an established source of clinical and experimental information. Measurement of the structural and functional properties of the carotid arterial segment yields a host of indices for the assessment of cardiovascular risk, vascular adaptation, and therapeutic efficacy [3,17,22,25,37]. Due to its non-invasiveness, carotid artery ultrasound is particularly suited to study large populations, but could be equally valuable in monitoring cardiovascular remodeling and therapeutic progress in individual patients. Although the close relationship between arterial and cardiac function has been well-recognized and has been investigated extensively in experimental and clinical studies [3,9,15], to the best of our knowledge, hardly any attempts have been made to quantify left ventricular function by means of carotid artery ultrasound.

The majority of approaches to non-invasive evaluation of left ventricular function utilize temporal characteristics of the central or peripheral arterial pulse wave [12,26,35] or cardiac Doppler signal analysis [32,33,38]. In general, reduced ejection duration and concomitant lengthening of the isovolumic contraction and relaxation periods are considered indicative of ventricular dysfunction. The ratio of pre-ejection period and ejection period (PEP/EP) is widely used to quantify left ventricular function, because it can easily be obtained from simultaneous continuous ECG and blood pressure recordings [12,26,35] or accelerometry in pacemaker recipients [24]. However, PEP as obtained by these
and related methods comprises electro-mechanical delay, isovolumic contraction period, and arterial transit time depending on the site of measurement. Hence, PEP/EP is a complex function of electrophysiological and contractile cardiac properties and arterial stiffness. To exclude the spurious components in PEP and related indices, cardiac Doppler and tissue Doppler techniques have been employed to discriminate systolic time intervals. Tei et al discriminated the isovolumic contraction (ICP), isovolumic relaxation (IRP) and ejection periods by timing analysis of mitral and aortic flow velocity patterns [32,33]. In a comparative study in normals and dilated cardiomyopathy patients, the myocardial performance index (MPI = (ICP+IRP)/EP) and the ICP/EP ratio had greater discriminatory power in identifying left ventricular dysfunction than mitral deceleration time, early to atrial peak velocity ratio (E/A), PEP/EP, stroke index and cardiac index [32]. Rhodes et al introduced a non-invasive estimate of left ventricular isovolumic dP/dt based on approximation of isovolumic pressure development and measurement of ICP using echophonocardiography [26]. This method, however, may be particularly sensitive to error due to the approximation of ventricular end-diastolic pressure.

Because the temporal characteristics of the carotid artery diameter match those of the local transmural pressure waveform [2,12], pulse wave analysis applied to the pulsatile carotid artery diameter (distension waveform) obtained by ultrasound may provide an interesting alternative. Recently, our group has shown that the onset and duration (ICP) of isovolumic contraction can be determined automatically from the late diastolic phase of the carotid artery distension.
waveform [34]. This offers the possibility to monitor both central arterial and left ventricular hemodynamics by a single non-invasive measurement technique. To test the feasibility of extracting systolic time intervals (specifically ICP and EP) from the distension waveform, we obtained M-mode recordings of the common carotid artery diameter in a group of young healthy volunteers. In addition to extraction of systolic time intervals, analysis included arterial transit time by identifying the lower body peripheral reflection wave in early diastole [19]. Normal orthostatic stress, i.e., a change in position from supine to sitting, was induced in these subjects to alter arterial and cardiac loading conditions in order to establish the precision and the discriminatory properties of carotid artery pulse wave analysis. In normals, orthostatic stress induces reduced cardiac preload, increased peripheral resistance, increased arterial blood pressure, and heart rate, but has little effect on intrinsic ventricular contractility [6,8,10,11,16].
METHODS

Subjects

Carotid artery distension waveforms were obtained from 21 presumed healthy volunteers (age: range 19-30, mean 21 years; sex: 10 male, 11 female). None of the subjects had a history of cardiovascular disease, diabetes, hypercholesterolemia, or established hypertension and none of them was receiving medication affecting cardiovascular function. The study was approved by the medical ethical committee of Maastricht University and the Academic Hospital Maastricht, the Netherlands. All volunteers gave written informed consent prior to enrollment.

Protocol

Measurement sessions were held in the afternoon in a quiet and temperature-controlled room (20-22°C). Before starting any measurement, the subjects were allowed to acclimatize for 10 minutes in supine position [27]. Subjects were studied successively in supine (baseline) and in sitting position. After changing position, 15 minutes were allowed for hemodynamic stabilization. All measurements were obtained by one person.

After localizing the right common carotid artery with an ultrasound scanner in B-mode (7.5 MHz linear array, ATL HDI-9, Advanced Technology Laboratories, Bothell, WA), multiple M-mode recordings were obtained. The ultrasound probe was positioned such that the M-line intersected the common
carotid artery 2-3 cm proximal to the carotid bifurcation. In each position a minimum of three (range 3-5) repeated measurements were obtained per subject. Recording length was 5 seconds and thus each measurement contained 4-7 consecutive heart beats. Single lead ECG (II) was acquired simultaneously for triggering purposes. During each recording the subjects were performing end-expiratory breath-hold to minimize hemodynamic fluctuation due to respiration. In each position arterial blood pressure was measured by means of a brachial cuff positioned at heart level (Omron 705CP, Omron, Matsusaka, Japan). Six repeated blood pressure measurements were taken per position: three prior to M-mode measurement and one after each of the first three M-mode recordings.

**Signal processing**

The M-mode and R-wave trigger sample rate was 1 kHz (pulse repetition frequency). The ultrasound radio frequency (RF) data were acquired at a sampling rate of 20 MHz and stored on hard disk for off-line analysis. The RF data were preprocessed in the depth direction by applying a fourth order bandpass filter matching the frequency range of the ultrasound probe (effective center frequency 5-6 MHz, 4 MHz bandwidth). Arterial wall velocity was extracted by means of in-house echo-tracking software [5]. Markers were placed on the first acquired RF signals of the anterior and posterior artery wall facilitating wall-tracking by the complex cross-correlation method [4]. A 10-millisecond temporal correlation window was used with an overlap of 50%, resulting in an effective sample rate of 200 Hz for the wall velocity. The distension waveform, i.e. the
change in diameter over time, was obtained by integrating wall velocity over time (yielding wall displacement) and calculating the difference between the displacement signals of both walls [5]. The distension waveforms were filtered using a 3-point (15 ms) rectangular moving average filter without phase delay. The filtered distension signal was then interpolated by a cubic spline method (Matlab, The Mathworks, Natick, MA) to reestablish a sample interval of 1 ms. The second derivative of the distension waveform, i.e. diameter acceleration, was calculated by passing the interpolated signal through a cascade of two first order recursive high-pass filters with a cut-off frequency of about 40 Hz. The second filter in the cascade was applied in reverse order to cancel out the phase shift of the first filter yielding zero phase delay [34]. To suppress residual respiratory interference and spurious intra-recording baseline excursions, the acceleration signal was post-processed by an additional second order zero-phase delay recursive high-pass filter with a cut-off frequency of 20 Hz.

Timing analysis

Utilizing the acceleration waveform, a proprietary algorithm implemented in Matlab (The Mathworks, Natick, MA) determined the intra-beat positions (referenced to the R-wave) of the following time points (Figure 1) [34]: start of left ventricular isovolumic contraction (SIC, local acceleration maximum preceding aortic valve opening) [7,34], aortic valve opening (AVO, maximum of the second derivative within 150 ms after the R-wave peak), and aortic valve closure (AVC, maximum acceleration following peak distension). The intra-beat position of the
lower body peripheral reflection wave (PR) was determined by identifying peak distension in early diastole (following AVC) [19].

Calculations

From the primary intra-beat positions the isovolumic contraction period (ICP = AVO – SIC) and the ejection period (EP = AVC – AVO) were derived (Figure 1).

End-diastolic carotid artery diameter directly followed from the distension waveform in combination with the initial identification of the anterior and posterior wall positions. Carotid artery distension, i.e., the peak-to-peak change in diameter, was defined as the difference between the maximum and the preceding minimum distension. Maximum distension velocity (dD/dt,max) was determined by calculating the incremental slope at the peak distension velocity position (first zero-crossing of the second derivative of the distension following AVO).

We calculated ICP/EP (in %) as a measure of left ventricular function [1,32]. Similar to the approach of Rhodes et al, the ratio of diastolic blood pressure over ICP was calculated [26]. To explore the applicability of the diameter acceleration as an alternative measure of systolic left ventricular function, we calculated (dD/dt)/ICP (in mm/s²).

Arterial pulse pressure (PP) was calculated from systolic (SBP) and diastolic blood pressure (DBP): PP = SBP – DBP. Mean arterial pressure (MAP) was estimated by MAP = DBP + PP/3.
**Statistical analysis**

For each primary hemodynamic variable group mean and standard deviation, average difference between supine and sitting conditions, and intra-subject standard deviation (precision) were calculated [34]. Statistical difference between supine and sitting was tested by Student’s two-tailed paired t-test. Sex differences in response to posture were analysed by Student’s two-tailed two-sample t-test assuming equal variance (Excel, Microsoft Corporation, Redmond, WA). Associations between pairs of variables were judged by scatter plots (Excel, Microsoft Corporation, Redmond, WA) and linearity was evaluated by the Pearson correlation coefficient. P-values <0.05 were considered statistically significant. Values are given as mean ± SD, unless stated otherwise.
RESULTS

An example of a distension waveform and the acceleration waveform derived from it is given in Figure 1. Table 1 shows the values of all variables as obtained in supine (baseline) and sitting conditions. Extraction of the various characteristic time points and systolic time intervals showed good reproducibility. For each time point, the intra-subject standard deviation (precision) was smaller than the observed difference and inter-subject standard deviation with postural intervention (Table 1).

Baseline

In supine position, average heart rate was 60 beats per minute, mean arterial blood pressure was 81 ± 9 mmHg, and pulse pressure was 46 ± 7 mmHg (Table 1). On average, intra-subject R-R variability was 5%. Relative distension was 11.8% and maximum distension velocity (dD/dt,max) 10.8 ± 2.0 mm/s. At the level of the carotid arteries, start of isovolumic contraction and aortic valve opening were observed 68 ± 8 ms and 111 ± 9 ms after the R-wave, respectively, yielding an ICP of 43 ± 8 ms. Aortic valve closure was detected after 412 ± 21 ms, yielding a mean EP of 302 ± 16 ms. Arrival of the lower body peripheral reflection wave was timed at 522 ± 31 ms. Baseline ICP/EP was 14 ± 3%. Average isovolumic pressure development (DBP/ICP) was 1572 ± 369 mmHg/s and average systolic diameter acceleration ((dD/dt)/ICP) was 263 ± 67 mm/s².
Postural intervention

Changing posture from supine to sitting position induced a decrease in R-R interval of 49 ± 82 ms (p=0.013), whereas mean and diastolic central arterial pressures increased (p<0.001, Table 1). Systolic pressure remained unaffected (p=0.09) and consequently pulse pressure significantly decreased during sitting (p<0.001). A decrease in pulsatility was also seen at carotid artery level: distension decreased from 0.74 ± 0.15 mm to 0.69 ± 0.14 mm (p=0.012). However, posture-induced changes in carotid artery distension and pulse pressure were not correlated ($r^2 = 0.003$). Carotid artery diameter did not change (p=0.449), thus relative distension decreased from 11.8% to 11.1%. In sitting position, dD/dt,max was reduced to 9.4 ± 1.7 mm/s (p<0.001).

Figure 2 illustrates the time-related changes in the carotid artery pulse wave with postural intervention (beats obtained from a single subject). In sitting position, the systolic upstroke of the pulse wave (SIC, AVO) reached the carotid artery later than in supine position (p<0.001, Table 1), reflecting decreased pulse wave velocity in cranial direction. Changes in start of isovolumic contraction (SIC) and aortic valve opening (AVO) were significantly correlated ($r^2 = 0.42$, p<0.01, Table 2). ICP significantly increased by 7 ± 7 ms (+16%, p<0.001). Changes in isovolumic contraction period (ICP) were neither correlated to changes in AVO, diastolic blood pressure, R-R interval, nor to changes in ejection period (Table 2). In upright position, timing of aortic valve closure (AVC) was earlier and consequently ejection period (EP) decreased to 267 ± 19 ms (supine: 302 ± 16 ms, p<0.001, Table 1). Advanced arrival of the lower body peripheral reflection
and earlier aortic valve closure were significantly correlated ($r^2 = 0.40$, p<0.01). Shortening of EP was significantly correlated to arrival of the lower body reflection wave (Figure 3, Table 2). Changes in EP were correlated to changes in R-R interval (p<0.05) but not to changes in diastolic blood pressure or ICP (Table 2).

In response to the postural intervention, ICP/EP increased by $5 \pm 3\%$ (p<0.001) and both (dD/dt)/ICP and DBP/ICP decreased (p<0.05). Changes in ICP/EP, DBP/ICP, and (dD/dt)/ICP were neither correlated to changes in R-R interval nor to changes in blood pressure (Table 2).

Except for EP and ICP/EP, no significant differences related to postural change were found between men (n=10) and women (n=11). The average increase in ICP/EP was $6.2 \pm 2.5\%$ in men, but only $3.2 \pm 2.5\%$ in women (p=0.011). Similarly, EP decreased more in men than in women (male: $42 \pm 12$ ms, female: $29 \pm 15$ ms, p=0.039). The advance in arrival of the peripheral reflection wave (PR) was similar in men and women (p=0.12).
DISCUSSION

In the present study, we were able to determine the isovolumic contraction period and ejection period from carotid artery distension waveforms with good precision. Our results demonstrate the feasibility of quantifying systolic left ventricular function and ventriculo-arterial interaction by means of carotid artery ultrasonography and pulse wave analysis.

Ventricular function indices

The isovolumic contraction and ejection periods as measured at baseline were similar to those found using cardiac Doppler techniques and phonographic methods (Table 3) [20]. The obtained ICP/EP values correspond to previously reported values in normals as well [32,33]. Compared to the dP/dt estimates reported by Rhodes et al, our DBP/ICP index value is closest to the dP/dt,max value as derived from invasive left ventricular pressure [26]. Interestingly, when left ventricular pressure development is offset by 10 mmHg, accounting for end-diastolic pressure, we arrive at similar values as Rhodes et al (Table 3). These investigators studied a heterogenic group of patients that were either younger or older than our healthy individuals, which is reflected by the respective standard deviations. Average systolic diameter acceleration, reflected by (dD/dt)/ICP, is a factor of 10-20 smaller than left ventricular myocardial isovolumic acceleration (IVA) as obtained by tissue Doppler imaging. Both indices are related to systolic ventricular function by characterizing local tissue velocity as a function of time.
However, the measured (dD/dt)/ICP may be influenced by central arterial stiffness and blood pressure, whereas IVA has been shown to be load-independent [36].

*Changes in ventricular function indices with orthostatic challenge*

By decreasing carotid artery transmural pressure, orthostatic stress elicits a baroreflex response which temporarily increases heart rate and arterial blood pressure [6,11,16,28,30]. These basic effects were reproduced in our study. Additionally, orthostatic challenge is associated with reductions in venous return, and hence cardiac preload and left ventricular output [6,10,11,28].

In our subjects, ICP, EP and all derived function indices consistently suggested a significant reduction in pump function. Comparable observations were made by Ovadia et al measuring accelerometer derived systolic time intervals in young patients suffering from upright syncope [24]. In their study, PEP increased, EP decreased and PEP/EP increased in upright position. Vijayalakshmi et al reported a similar response of these systolic time intervals in healthy subjects using head-up tilting [35]. While ICP/EP has been shown to be a valid measure of systolic left ventricular function in patients [1,32], the implied reduction in output due to orthostatic stress in healthy subjects is likely to result from changes in loading conditions. As orthostatic challenge affects preload by passive (blood pooling) effects [11,28] and afterload by active(reflex) mechanisms [6,14], it is difficult to discriminate the various factors that modulate ICP, EP and the derived function indices. Tolerance of orthostatic stress in
normals is primarily related to intact autonomic chronotropic response and reflex constriction of peripheral resistance vessels [6,11,14,31] and not to inotropic effects [6,8,11,16]. ICP is correlated to dP/dt,max [38] and is as such preload and afterload dependent [36]. Both the preload reduction and afterload increase, as induced by orthostatic challenge, increase the duration of isovolumic contraction. Similarly, the reduction in EP may be indicative of reduced ventricular filling and hence diminished stroke volume [6,10,11]. Moreover, an increase in peripheral resistance, as is expected with orthostatic challenge [6,16], would allow a decrease in left ventricular output while maintaining or even enhancing DBP (Table 1). Both ICP and EP are rate-dependent (Table 2) [32], but in our subjects heart rate increase was only modest. The changes in ICP/EP were independent from R-R and DBP (Table 2). The rate-independence of the ICP/EP has previously been demonstrated [32].

Theoretically, a DBP increase (Table 1) with constant ICP would suggest a contractility increase reflected by the DBP/ICP ratio. Apparently, the rise in ICP with postural intervention dominated over the DBP increase in our subjects, because DBP/ICP decreased significantly, independently of R-R and DBP. Compared to the other indices the change in DBP/ICP was borderline significant (p<0.023). The accuracy of DBP/ICP may be limited due to the errors made in approximating left ventricular isovolumic pressure development [26]. Furthermore, the precision of the DBP/ICP index will be dependent on both reproducible timing extraction [34] and precise manometer leveling. In the present study, depending on chest size, the upper arm cuff might have been
below heart level in supine position, leading to overestimation of mean and
diastolic blood pressure and subsequent underestimation of the change in blood
pressures upon sitting. Because the observed changes are moderate and similar
to published values in normals [6,11,28], it appears unlikely that the outcome of
our study is influenced by manometer level errors.

The (dD/dt)/ICP index changed significantly and was independent of
changes in R-R and DBP as well. The variability in response among subjects,
however, was considerable. Moreover, the reproducibility of dD/dt,max and
(dD/dt)/ICP was acceptable but not convincing (Table 1). The validity of diameter
acceleration in characterizing ventricular contraction or ejection remains to be
determined, while the index is potentially confounded by changes in blood
pressure and arterial stiffness.

The significant difference in the ICP/EP and EP responses between men
and women might reflect greater muscle exercise capacity and related vascular
capacity in our male subjects. If this assumption is valid, then reflex peripheral
vasoconstriction may have been more potent in our male subjects, because the
change in DBP was not significantly different between men and women.

The borderline significance of the decrease in DBP/ICP might suggest that
intrinsic contractility changed barely in our study, which is in accordance with
related studies [6,8,10,11,16]. In our subjects, increased ICP and ICP/EP and
decreased DBP/ICP and (dD/dt)/ICP should be considered indicative of changes
in ventricular loading due to passive and active peripheral responses to
orthostasis.
**Ventriculo-arterial interaction**

Orthostasis induces increased hydrostatic pressure in the arteries of the lower body. Because the stiffness of conductance arteries increases with increasing distending pressure [2,23,25], orthostasis is likely to affect pulse wave propagation velocity such that waves reflected in the lower body periphery tend to return earlier at heart level. Our results confirm earlier arrival of PR in sitting position. Moreover, PR was significantly correlated to aortic valve closure and ejection period shortening (Figure 3). This intra-beat ventriculo-arterial interaction appears to dominate over heart rate and blood pressure related effects on ejection time (Table 2). In our subjects we identified PR by detecting the maximum diameter in diastole following the dicrotic notch (Figure 1). With age, the peripheral reflections may gradually shift into the systolic phase of the cardiac cycle [21,25]. Therefore, in older subjects or in cardiovascular patients this detection method may not be feasible or valid.

**Accuracy and precision of timing extraction**

The prerequisite for applying timing analysis to the carotid distension waveform successfully is that the pulse wave contour is maintained during its propagation from the aortic root to the site of measurement in the common carotid artery. Studinger et al, observed similar distensibility coefficients in both proximal aortic and carotid arterial segments in normal subjects [29], which implies continuous pulse wave propagation velocity. Impedance mismatch between aorta and
carotid artery due to the difference in diameter [20] is unlikely to affect the timing characteristics of the transmitted wave from aorta to the common carotid artery: reflected waves travel in opposite direction, away from the site of measurement. Distortion of the pulse wave timing patterns due to the viscoelastic properties of normal large arteries appears negligible when measured by the appropriate technique [2,13]. The similarity of our ICP, EP, and ICP/EP values and those obtained in related studies in healthy subjects suggests that time-related features of the pulse wave are preserved in transit [12,26,32,34,35].

Intra-subject variability due to low frequency interference (unstable probe position, unstable breath-hold) was effectively suppressed by the employed acceleration post-processing filter. Therefore, in the present study the precision of ICP (4 ms; supine position) is slightly better than in our previous study (5 ms) [34]. More important to note is the fact that there reproducibility is on the same order of magnitude for both postures (Table 1). For all timing parameters and indices as obtained by pulse wave analysis, precision was such that individual differences could be discriminated. Tekten et al reported a reproducibility of less than 3 ms for ICP and of about 20 ms for EP using tissue Doppler echocardiography. Because their analysis was performed manually, it remains difficult to discriminate measurement- and analysis-based variability. Phonographic determination of systolic time intervals is similarly dependent either on manual or dedicated signal processing [12,26,38].
Study limitations

The postural intervention used in our healthy young subjects is probably limited in terms of hemodynamic challenge. In hypertensive and diabetic subjects, or in the elderly, normal orthostatic challenge may have more pronounced and likely more differentiating effects [9,14,15,18,21]. Evaluation of the ventriculo-arterial interaction as a function of posture in these populations could enable further discrimination of the various (patho-) physiological mechanisms in regard to baroreflex function and orthostatic intolerance [6,16,18,24,28].

In the present study, no gold-standard measurement of systolic time intervals was obtained. Because the non-invasive alternatives (Doppler echocardiography, phonocardiography) are subject to similar reproducibility errors [33], they were considered to be unsuitable to serve as gold standard. Furthermore, invasive pressure measurements are non-ethical in the population studied. The validity of extracting ICP from the arterial pulse waveform was previously demonstrated on a data set containing simultaneously recorded intraventricular and aortic pressures [34].

The present study was not intended to establish any of the indices as being conclusive in quantifying true ventricular or arterial function, but to determine the feasibility (precision) of the measurements. The use of carotid artery ultrasound as a means to quantify ventricular systolic time intervals and its validity in characterizing ventriculo-arterial interaction in patients requires further investigation.
In conclusion, ultrasound-based carotid artery pulse wave analysis enables non-invasive quantification of the hemodynamic ventriculo-arterial responses to postural changes.
Acknowledgments

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Disclosures

No conflicts of interest or disclosure information to declare.
REFERENCES


6 Chandler MP, Mathias CJ. Haemodynamic responses during head-up tilt and tilt reversal in two groups with chronic autonomic failure: pure


FIGURE LEGENDS

**Figure 1** Characteristics of the distension waveform and the derived acceleration signal. R, ECG R-wave peak; SIC, start of isovolumic contraction; AVO, aortic valve opening; AVC, aortic valve closure; PR, lower body peripheral reflection; dD/dt,max, maximum distension velocity; a.u., arbitrary units.

**Figure 2** Changes in distension waveform timing with postural intervention. SIC, start of isovolumic contraction; AVO, aortic valve opening; AVC, aortic valve closure; PR, lower body peripheral reflection; ICP, isovolumic contraction period; EP, ejection period; a.u., arbitrary units. Time zero corresponds to the peak of the R-wave. Bars at the bottom pertain to the systolic time intervals.

**Figure 3** Correlation between the change in arrival of the lower body peripheral reflection wave (PR) and the change in ejection period (EP).
Table 1 Effect of posture on central hemodynamics

<table>
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<th>Supine</th>
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<th>Sitting – Supine</th>
<th>Precision</th>
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<td>mean±SD</td>
<td>mean±SD</td>
<td>p-value</td>
</tr>
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<td>SBP mmHg</td>
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<td>MAP mmHg</td>
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<td>86±8 *</td>
<td>5±4</td>
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<td>PP mmHg</td>
<td>47±7</td>
<td>42±7 *</td>
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<td>&lt;0.001</td>
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<td>Diameter mm</td>
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<td>6.24±0.39</td>
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<td>Distension mm</td>
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<td>dD/dt,max mm/s</td>
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<td>SIC ms</td>
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<td>AVO ms</td>
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<td>EP ms</td>
<td>302±16</td>
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<td>ICP/EP %</td>
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<td>(dD/dt)/ICP mm/s²</td>
<td>263±67</td>
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<td>DBP/ICP mmHg/s</td>
<td>1572±369</td>
<td>1457±241 *</td>
<td>-114±213</td>
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</tbody>
</table>

Values are means ± SD. *p<0.05, paired Student t-test, n=21. Prec., precision; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, arterial pulse pressure; SIC, start of isovolumic contraction; AVO, aortic valve opening; AVC, aortic valve closure; PR, lower body peripheral reflection; ICP, isovolumic contraction period; EP, ejection period. SIC, AVO, AVC, and PR values express delay time with respect to the R-wave.
Table 2 Associations between posture-induced changes in hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>ΔEP</th>
<th>ΔAVO</th>
<th>ΔPR</th>
<th>ΔDBP</th>
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</thead>
<tbody>
<tr>
<td>ΔSIC</td>
<td>-</td>
<td>0.42*</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ΔICP</td>
<td>0.08</td>
<td>0.17</td>
<td>-</td>
<td>0.18</td>
<td>0.10</td>
</tr>
<tr>
<td>ΔAVC</td>
<td>-</td>
<td>-</td>
<td>0.40*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ΔEP</td>
<td>-</td>
<td>-</td>
<td>0.46*</td>
<td>0.02</td>
<td>0.25*</td>
</tr>
<tr>
<td>ΔICP/EP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ΔDBP/ICP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&lt;0.01</td>
<td>0.16</td>
</tr>
<tr>
<td>Δ(dD/dt)/ICP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.09</td>
<td>0.02</td>
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</tbody>
</table>

Pearson correlation expressed as $r^2$-values; Δ denotes change with posture (sitting – supine). Two-tailed p-values, n=21: *p<0.05; #p<0.01; §p<0.001. SIC, start of isovolumic contraction; ICP, isovolumic contraction period; AVC, aortic valve closure; AVO, aortic valve opening; EP, ejection period; PR, lower body peripheral reflection; DBP, diastolic blood pressure.
Table 3 Non-invasive systolic time intervals and related indices in literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>AVO  (ms)</th>
<th>ICP  (ms)</th>
<th>EP   (ms)</th>
<th>ICP/EP (%)</th>
<th>dP/dt (mmHg/s)</th>
<th>IVA (mm/s²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>CA US</td>
<td>111±9</td>
<td>43±8</td>
<td>302±16</td>
<td>14±3</td>
<td>1572±369</td>
<td>263±67</td>
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<tr>
<td>Hasegawa et al. 1991</td>
<td>CA Phono</td>
<td>131±15</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>Hasegawa et al. 1991</td>
<td>CA Pleth</td>
<td>127±16</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Tei et al. 1995</td>
<td>DEC</td>
<td>-</td>
<td>40±11</td>
<td>310±43</td>
<td>13±3</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Tekten et al. 2003</td>
<td>Tissue DEC</td>
<td>-</td>
<td>38±5</td>
<td>310±13</td>
<td>12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yumoto et al. 2005</td>
<td>Phono</td>
<td>-</td>
<td>22±3</td>
<td>-</td>
<td>-</td>
<td>1390±450</td>
<td>-</td>
</tr>
<tr>
<td>Present study</td>
<td>CA US+BCP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1331±331</td>
<td>-</td>
</tr>
<tr>
<td>Rhodes et al. 1993</td>
<td>DEC+Phono+BCP</td>
<td>-</td>
<td>41±11</td>
<td>-</td>
<td>-</td>
<td>1381±403</td>
<td>-</td>
</tr>
<tr>
<td>Rhodes et al. 1993</td>
<td>LVP catheter</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1540±480</td>
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<tr>
<td>Vogel et al. 2003</td>
<td>Tissue DEC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1150±113</td>
<td>3800</td>
</tr>
</tbody>
</table>

Values are means ± SD. CA, carotid artery; US, ultrasonography; Phono, phonography; Pleth, plethysmography; DEC, Doppler echocardiography; BCP, brachial cuff pressure; LVP, left ventricular pressure; AVO, aortic valve opening; ICP, isovolumic contraction period; EP, ejection period. aIsovolumic dP/dt estimated by DBP/ICP. bFetal sheep, LVP catheter. cIsovolumic dP/dt estimated by (DBP – 10)/ICP. dPigs, LVP catheter. eIVA (isovolumic acceleration) estimated by (dD/dt)/ICP. Data were obtained in recumbent/supine subjects.
Figure 1 Characteristics of the distension waveform and the derived acceleration signal. 
R, ECG R-wave peak; SIC, start of isovolumic contraction; AVO, aortic valve opening; AVC, 
aortic valve closure; PR, lower body peripheral reflection; dD/dt,max, maximum 
distension velocity; a.u., arbitrary units.
Figure 2 Changes in distension waveform timing with postural intervention. SIC, start of isovolumic contraction; AVO, aortic valve opening; AVC, aortic valve closure; PR, lower body peripheral reflection; ICP, isovolumic contraction period; EP, ejection period; a.u., arbitrary units. Time zero corresponds to the peak of the R-wave. Bars at the bottom pertain to the systolic time intervals.
Figure 3 Correlation between the change in arrival of the lower body peripheral reflection wave (PR) and the change in ejection period (EP).

$r^2 = 0.46$
$p<0.001$