Central hemodynamics and arterial function
van den Bogaard, B.

Citation for published version (APA):
van den Bogaard, B. (2012). Central hemodynamics and arterial function

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Active standing reduces wave reflection in the presence of increased peripheral resistance in young and old healthy subjects

Shyrin CAT Davis
Berend E Westerhof
Bas van den Bogaard
Lysander WJ Bogert
Jasper Truijen
Yu-Sok Kim
Nico Westerhof
Johannes J van Lieshout

Journal of Hypertension 2011; 29: 682-9
ABSTRACT

Objective Pressure wave reflections are age dependent and generally assumed to increase with increasing peripheral resistance. We sought to determine the effect of standing on wave reflection in healthy older and younger individuals and the influence of increased peripheral resistance.

Methods During supine rest and active standing, continuous finger arterial blood pressure was measured. Data obtained in the supine period and after 1 and 5 minutes standing were analyzed. Aortic pressure and flow, calculated from finger pressure, were used to derive forward and backward pressure waves, reflection magnitude (ratio of backward and forward pressure waves), augmentation index, and peripheral resistance.

Results Fifteen healthy older (aged 53±7 years) and fifteen healthy younger (aged 29±5 years) subjects were included. In both groups, upon standing, stroke volume, cardiac output and pulse pressure decreased with an increase in heart rate and in diastolic pressure. In the older group peripheral resistance increased from 1.3±0.4 to 1.5±0.4 and 1.5±0.4 for supine, 1 minute and 5 minute standing, whereas reflection magnitude decreased from 0.67±0.1 to 0.61±0.1 and 0.61±0.1 and augmentation index from 33±11 to 23±12 and 25±11. In the younger group peripheral resistance increased from 0.9±0.2 to 1.1±0.2 and 1.1±0.2 while reflection magnitude decreased from 0.55±0.05 to 0.48±0.05 and 0.49±0.05 and augmentation index from 18±11 to 1±18 and 4±19.

Conclusion With standing, hemodynamic variables change similarly in older and younger subjects. The opposite changes in reflection magnitude and peripheral resistance suggest that reflection and pressure augmentation are not solely dependent on peripheral resistance.
INTRODUCTION

Elevated central aortic systolic and pulse pressure predict adverse cardiovascular events.\(^1\)\(^-\)\(^3\) Since central arterial pressure is related to the elastic properties of arteries, attention has been directed towards arterial stiffness, pulse wave velocity (PWV) and wave reflections as independent cardiovascular risk factors.\(^4\) The central arterial pressure wave is composed of a forward and a backward travelling wave.\(^5\)\(^-\)\(^7\) The amplitude of the forward travelling wave is determined by left ventricular ejection and the proximal arterial load represented by the characteristic impedance\(^5\) whereas the amplitude of the backward travelling wave is determined by the amplitude of the forward travelling wave and the distal reflection coefficient. High-resistance arterioles are considered to be the major sites of wave reflection in the circulatory system.\(^8\)

An increase in total peripheral resistance (TPR) is assumed to enhance wave reflection\(^9\),\(^10\) although opposite changes in TPR and reflection during a Valsalva manoeuvre\(^11\) and during head-up tilt have been reported.\(^12\) In response to postural stress, the gravitational displacement of blood to the lower regions of the body reduces cardiac preload accompanied by a fall in cardiac output. It is assumed that there is a rapid translocation of about 500 to 700 ml thoracic blood to the lower extremity.\(^13\),\(^14\) Blood pressure is maintained by a baroreflex mediated increase in vasomotor tone with enhancement of the TPR. The reflex increase in TPR and hydrostatic changes in pressure distribution along the vasculature are likely to modify arterial properties resulting in changing reflection coefficients, thus pressure wave reflection and pressure wave shape, including augmentation index, reflection magnitude and timing of the pulse wave reflections.\(^4\),\(^15\),\(^16\)

Throughout the normal human lifespan, aortic wall stiffness increases with age leading to higher PWV and modification in both time of return and magnitude of the backward wave. In contrast to the aorta, the peripheral muscular arterial wall undergoes relatively modest change with age. However, microvascular structure and function and thus TPR are altered in the presence of increased aortic stiffness as previous studies have demonstrated in large, community based samples.\(^17\)-\(^19\) We aimed to study the effect of standing on wave reflection in healthy older and younger individuals and the influence of increased peripheral resistance during this postural stress.

METHODS

Subjects
Thirty healthy subjects participated in this study. Fifteen subjects younger than 40 years of age were assigned to the younger (YOUNG) group and fifteen subjects older than 50 years were classified as older individuals (OLD). All participants were free of medication. Exclusion criteria were a history of cardiovascular disease and orthostatic hypotension. The Medical
Ethical Committee of the Academic Medical Center of the University of Amsterdam approved the study and participants gave their written informed consent. Experiments were performed in accordance with the Declaration of Helsinki.

**Measurements**

The subjects were requested to abstain from caffeinated beverages for 12 h prior to reporting to the laboratory (~ 22 ºC) at 8:00 AM after an overnight fast. After instrumentation they rested 30 min and a baseline recording of cardiovascular variables was obtained with the subject in supine position. After another 5 minutes the subject assumed the free standing position and remained so for 5 minutes.

Continuous blood pressure (BP) was measured noninvasively by finger photoplethysmograph (Nexfin20,21 BMEYE, Amsterdam, the Netherlands) with the cuff placed on the middle phalanx of the left middle finger kept at heart level and the signal was A/D converted at 200 Hz for off-line analysis. Changes in BP measured by photoplethysmography track those in intra-arterial BP both at rest and during orthostatic stress.22,23

**Calculations**

Arterial pressure was analyzed off-line providing for aortic pressure constructed with a generalized pressure transfer filter24,25 delivering beat-to-beat systolic (SBP), diastolic (DBP), and mean (MAP) aortic pressure and Pulse Pressure (PP). End of left ventricular ejection (EJT) was determined from the pressure incisura. Stroke volume (SV) was obtained from aortic flow as calculated with the 3-element Windkessel model as reported earlier.26,27 Heart Rate (HR) was the inverse of the inter beat interval (IBI). Cardiac Output (CO) was HR times SV, and total peripheral resistance (TPR) was the ratio of MAP and CO.

For each participant, the corresponding pressure and flow curves of 20 consecutive beats were selected in the supine, and respectively 1 and 5 minutes standing positions and ensemble averaged (see Figure 1). Wave form separation by dedicated software programmed in Mathematica (Wolfram Research, Inc., Mathematica, Version 4.0, Champaign, IL) was applied to derive forward (Pf) and backward pressure (Pb) waves.6,7,28 The Reflection Magnitude was the ratio of the amplitudes of Pb and Pf. The Augmentation Index (AIx) was calculated as reported10,28,29 and additionally corrected for HR.30 The return time of reflected wave was derived by cross-correlation (cross-correlation time, CCT), i.e. the time shift giving the highest coefficient of correlation was taken as the time difference between Pf and Pb.

**Statistics**

Data are given as mean±SD for each group in the supine, and the two standing positions. Differences between supine and standing for 1 and 5 minutes were established with repeated measures ANOVA and Holm-Sidak. The YOUNG and OLD were compared with a t-test. Differences were considered statistically significant at p<0.05.
Group characteristics

Thirty healthy Caucasian subjects (18 males and 12 females) were included and assigned to the YOUNG (29±5 years; n=15) respectively OLD (53±7 years; n=15) group ($p<0.05$). Gender ratio was not different. Examples of measured and derived variables during supine and standing procedure in the older and younger are shown on Figures 1 and 2, respectively.

**RESULTS**

**Figure 1** Representative example of hemodynamic response in an individual of the older group
The top panel shows the entire series of aortic pressure with the selected 20 beats used for analysis during supine, and respectively 1 and 5 minutes of standing. The second and third panel from the top shows 20 separate beats of aortic pressure and flow plotted over each other with mean pressures set equal. The fourth panel shows the forward and backward waves obtained by waveform separation.
Supine and Standing

The two age groups differed in that PP, SBP, TPR, Pb, RM and AI were lower and SV, CO and CCT higher in the YOUNG (Table 1). These differences were consistent throughout supine and standing. MAP, EJT and Pf were comparable for both groups in the supine position, but lower in YOUNG when standing. In response to standing, PP, SV, CO, EJT, Pb, CCT and AI decreased, while DBP, HR and TPR increased in both groups. In YOUNG but not in OLD, Pf declined in response to postural stress. Conversely, MAP increased in OLD but not in the YOUNG. Supine and standing pressures are given in Figure 3, and SV, CO and HR in Figure 4. Pb and Pf both decreased in the younger group upon standing, whereas in the older only Pb declined (Figure 5). During standing, the increase in TPR respectively the decrease in RM and AI were similar among groups.

Figure 2 Response in an individual of the younger group
For explanation see Figure 1.
### Table 1 The Young versus the Old during postural change challenging

<table>
<thead>
<tr>
<th></th>
<th>OLD</th>
<th>YOUNG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Stand 60 s</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>53 ± 12</td>
<td>48 ± 12*</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>124 ± 20</td>
<td>127 ± 19</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>71 ± 11</td>
<td>79 ± 13*</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>94 ± 14</td>
<td>100 ± 15*</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>65 ± 11</td>
<td>75 ± 14*</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>69 ± 11</td>
<td>55 ± 11*</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>4.5 ± 0.9</td>
<td>4.0 ± 0.8*</td>
</tr>
<tr>
<td>EJT (s)</td>
<td>0.34 ± 0.02</td>
<td>0.31 ± 0.04*</td>
</tr>
<tr>
<td>TPR (dyn·s·cm⁻⁵)</td>
<td>1.3 ± 0.4</td>
<td>1.5 ± 0.4*</td>
</tr>
<tr>
<td>Pb (mmHg)</td>
<td>26 ± 6</td>
<td>23 ± 6*</td>
</tr>
<tr>
<td>Pf (mmHg)</td>
<td>39 ± 6</td>
<td>37 ± 6</td>
</tr>
<tr>
<td>RM</td>
<td>0.67 ± 0.1</td>
<td>0.61 ± 0.1*</td>
</tr>
<tr>
<td>CCT (ms)</td>
<td>0.114 ± 0.01</td>
<td>0.107 ± 0.01*</td>
</tr>
<tr>
<td>Alx</td>
<td>33 ± 11</td>
<td>23 ± 12*</td>
</tr>
</tbody>
</table>

All blood pressures are aortic pressures. SBP=systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial pressure; EJT=ejection time; TPR=total peripheral resistance; Pb=amplitude backward pressure; Pf=amplitude forward pressure; RM=reflection magnitude; CCT=cross-correlation time i.e., time of return of the reflected wave; Alx=augmentation index. Supine vs Standing: * $p<0.05$; older vs younger: # $p<0.05$. 
Figure 3 Averaged blood pressures of the 15 individuals per group
Triangles, circles and inverted triangles represent systolic, mean and diastolic blood pressure, respectively. Supine vs Standing: * p<0.05; older vs younger: # p<0.05.

Figure 4 Averaged values of stroke volume, cardiac output, and heart rate
The circles represent OLD and the squares represent YOUNG. Supine vs Standing: * p<0.05; OLD vs YOUNG: # p<0.05.
When AI corrected for HR, it was still lower at 1 minute standing but became similar to the supine value for 5 minutes standing for both groups (Friedman test).

**DISCUSSION**

The new finding of this study is that the reflection parameters (RM and AI) decrease from supine to standing while the peripheral resistance increases, in both older and younger subjects. These findings extend previous observations that showed decreased wave reflection during 60° head up tilt. Also in line with our study, Tahvanainen and colleagues found no age-related differences in the AIx response to head up tilt.

From supine to standing, the altered pressure distribution along the aorta and leg arteries affects arterial diameters and local compliances, thereby modifying the reflection magnitude and augmentation index. Sitting versus supine AIs were reported to be comparable. This may implicate that the reduced wave reflection during standing can in part be attributed to changes in leg vasculature, perhaps being less affected in the sitting position. At present, there is insufficient data on distal aortic and leg arterial diameter and compliance changes from supine to standing to make a quantitative estimate. Nevertheless our data indicate that both reflection magnitude and augmentation index decline from supine to standing (Figure 6). A related result is the return time of the reflected wave, here expressed in cross correlation time (CCT), which decreases in both groups by standing. With comparable mean arterial pressure in the YOUNG group, pulse wave velocity remains similar thus CCT is expected to be similar. Therefore, the earlier return of the reflected wave in the YOUNG must have resulted from a difference in reflection phase angle between supine and standing. However, individual reflected waves collectively
behave like a single backward wave arising from one functional reflection site, which appears from the distal aorta, near the termination of the abdominal aorta in the abdomen. The implication of opposite changes in TPR and reflection indices in response to orthostatic stress is that major reflections do not originate in the periphery but rather find their origin in the conduit arteries, most likely the distal abdominal aorta where they combine as one. Consequently the current assumption that in healthy subjects an increase in total peripheral resistance is accompanied by an age-dependent enhanced wave reflection with TPR as the strongest determinant and predictor of reflection, does not hold during passive tilt and active standing. In supine position sympathetic nervous system induced increases in vascular resistance by cold pressure test or isometric-fatiguing handgrip have shown to increase wave reflection.

In a model study, peripheral resistance had little effect on a local reflection coefficient. The frequency dependent reflection coefficient at the distal end of a brachial artery increased by 15% at the first harmonic (at heart rate) when peripheral resistance was increased with 400%.

**Figure 6** Averaged total peripheral resistance, reflection magnitude and augmentation index
The circles represent older and the squares represent younger. Supine vs Standing: * p<0.05; OLD vs YOUNG: # p<0.05.
The data obtained in this study during supine position demonstrate the previously expected higher TPR together with a higher RM and AI in the older subjects. Ageing of the vessels results in increased stiffness of the elastic arteries and may increase reflection magnitude. TPR, however, is predominantly determined by de microcirculation and increases due to vessel remodelling and rarefaction. In other words different processes take place in conduit arteries and microcirculation. Apparently, processes different from ageing take place in-between supine to standing, involving predominantly changes in pressure distribution over large arteries and vasoconstriction of the microcirculation. The rise in TPR and the opposite decrease in reflection indices in the present study have also been reported during a Valsalva manoeuvre and were probably also induced by pressure redistribution over the aorta but have drawn little attention.39

Changes in most variables were similar in direction in YOUNG and in OLD, although different in magnitude. In OLD, Pf did not decrease with standing while it did in YOUNG. In part this can be explained by a smaller decrease in stroke volume. Despite differences due to age-related vascular remodelling similar pattern in wave reflection is observed in YOUNG as in OLD during postural stress.

**Limitations** The present study is limited to the magnitude and the effect of TPR on wave reflection, future studies should focus on changes arterial stiffness (PWV) with standing. Particularly since it has recently been shown that sympathetic nerve activity is related to PWV.40 Aortic pressure and flow were not measured but were determined from distal, non-invasive pressure measurement. A previous study demonstrated that from the supine to standing position the bias for systolic finger pressure did not change significantly.22 The reconstruction of aortic pressure from radial pressure using a generalized transfer function is well-accepted to study wave reflection.41, 42 We used a finger to aortic transfer function that gave results similar to those of Sharman and colleagues during exercise.25, 43 Radial to aortic44 and finger to brachial45 transfer functions have previously been validated suggesting that finger to aorta transfer functions should perform adequately.

The use of model-derived flow is a new approach and can be seen as an incremental improvement over the triangulation method. Stroke volume has been validated in supine and standing position46. The model is adapted as a function of mean pressure and of patient parameters (age, gender, height and weight). It also holds that calibration of flow does not affect the RM.6 When using a triangle as flow wave shape the same response in RM to standing was found (data not shown), although RMs tended to be somewhat smaller as was the case when comparing triangulated RMs to measured RMs in the original publication.6 The three element Windkessel model that delivers flow has been extensively validated. Particularly the tracking of changes in SV is a strong point of this method.46, 47 An advantage of using model derived flow is that the shape is smoother than a triangle, which is not a perfect description of flow.48 Of note, both methods automatically follow changes in heart rate and ejection period.
The effect of HR on augmentation index was accounted for by using a relation that was determined in supine subjects.\textsuperscript{30} It is not known whether postural stress modifies that relationship. Nevertheless assuming that the relation holds, corrected AI was still lower at 1 minute standing in both groups. Corrected AI became similar to the supine value after 5 minutes standing. The RM is less sensitive to HR changes, since the separation of Pf and Pb disentangles the timing effects such as the shift into systole of Pb.

**Perspectives** Most studies are performed with the subject in supine position, whereas humans spend two-thirds of the day in either the seated or standing postures which influences wave reflection. Moreover, a direct relation between vascular resistance and wave reflection does not exist from the supine position to active standing therefore new studies should be designed to investigate the role of vascular resistance in systolic hypertension.
REFERENCES


