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

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Chapter 13

Arterial wave reflection decreases gradually from supine to upright

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Blood pressure 2011; 20: 370-375
ABSTRACT

Background An increase in total peripheral resistance (TPR) usually increases arterial wave reflection. During passive head up tilt (HUT), however, arterial wave reflection decreases with increasing TPR. This study addressed whether arterial wave reflection gradually decreases during head up tilt.

Methods In 10 healthy volunteers (22-39 years, 9 males) we recorded finger arterial pressures in supine position (0°), and 30 and 70 degrees HUT (30° and 70°) and active standing (90°). Aortic pressure was constructed from the finger pressure signal and hemodynamics were calculated. Arterial wave reflection was quantified as the augmentation index (AIx) and the reflection magnitude (RM).

Results During head up tilt, heart rate increased \((p<0.001)\), stroke volume and cardiac output decreased \((p<0.001\) and \(p<0.01)\), diastolic blood pressure increased \((p<0.001)\), whereas systolic blood pressure did not change. TPR increased from 0.9 dyn s/cm\(^5\) at 0° to 1.2, 1.4 and 1.4 dyn s/cm\(^5\) at 30°, 70° and 90° \((p<0.001)\). AIx fell gradually from 25 % at 0° to 16, -1 and -10 % at 30°, 70° and 90° \((p<0.001)\). The RM decreased from 0.572 at 0° to 0.456 at 90° \((p<0.001)\).

Conclusion From supine to upright arterial wave reflection represented as AIx and RM gradually decreases in the presence of increasing TPR.
INTRODUCTION

The augmentation index (AIx) is used as a marker of arterial stiffness and arterial wave reflection and has been shown to predict the survival of end stage renal disease patients and cardiovascular events in coronary patients. There is, however, discussion whether the AIx primarily reflects arterial stiffness. Pulse wave velocity (PWV) is a more direct measure of arterial stiffness and is considered the gold standard of non-invasive arterial stiffness measurements. Both PWV and AIx increase with age, but the AIx seems to reach a plateau around 60 years. So, the AIx is only partially determined by arterial stiffness. The other two factors that influence the AIx are heart rate and the time of return of the reflected wave. The AIx has a negative linear relation with heart rate and is therefore usually presented after correction for a heart rate of 75 beats per minute.

The location and the contribution of the site of reflection to the AIx have been more difficult to establish. Besides major bifurcations, the main reflection sites are thought to be high resistance small arteries and arterioles. Indeed, angiotensin II or noradrenalin induced vasoconstriction cause an increase in AIx and total peripheral resistance (TPR), whereas vasodilators, such as nitroprusside and calcium channel blockers lower AIx and TPR. These pharmacologically induced changes in arterial wave reflection are independent of arterial stiffness.

Thus an increase in TPR usually causes an increase in arterial wave reflection as quantified by the AIx. AIx and TPR, however, do not always react in parallel. It has been shown that passive head up tilt (HUT) of 60º decreased the AIx compared to supine position while increasing TPR. Humans usually are not in supine position for the majority of the day and arterial wave reflection decreases during HUT of 60º but it is unknown at which HUT angle arterial wave reflection is minimal. We therefore studied AIx and TPR during different angles of passive tilt and active standing. A second aim of the study was to disentangle the contribution of forward and backward waves during head-up tilt and standing.

METHODS

Study subjects and design

We studied 10 healthy volunteers, aged 22-39 years, 9 were male. The participants were non-smokers, used no medication and had no history of orthostatic fainting. Informed consent was obtained from all participants and the study was approved by the ethics committee of Copenhagen (KF01-120/96) and performed in accordance with the Declaration of Helsinki. The study protocol has been described previously. In short, after instrumentation the subjects rested in supine (0º) position for 30 min. Participants were subjected to a passive tilt (with foot support) protocol which included 30 and 70 degrees head-up tilt (30º and 70º) and an active standing (90º) period, all preceded and followed by a period of supine rest (0º) to minimize crossover
effect of tilt. We used the first supine period as a baseline measurement and compared the
different tilt angles to this baseline measurement.

Hemodynamics
Noninvasive finger arterial pressure was recorded with a TNO Finapres Model 5, sampled at
100 Hz and analyzed off-line. We selected 20 consecutive beats before and 1 minute after each
change body position for analysis. From the beat selection an aortic pressure was constructed
with a generalized pressure transfer filter\(^1^4\) to obtain beat-to-beat systolic blood pressure
(SBP), diastolic blood pressure (DBP), pulse pressure (PP) and mean arterial pressure (MAP).
Subsequently aortic stroke volume (SV) was calculated with a pulse contour method using
the 3-element Windkessel model.\(^1^5, 1^6\) Heart rate (HR) was the inverse of the interbeat interval.
Cardiac output (CO) was the product of SV and HR, and TPR is MAP divided by CO.

Arterial wave reflection
Arterial wave reflection was quantified from the pressure signal as the AIx, defined as the ratio
of augmented pressure and the pulse pressure. Also, the constructed aortic pressure was separated
into forward (Pf) and backward (Pb) waves by waveform analysis as described by Westerhof and
colleagues.\(^1^7\) For wave separation the flow wave from the Windkessel was used. This allows the
calculation of the reflection magnitude (RM) as the ratio of Pb and Pf . Calculations were per-
formed in Mathematica (Wolfram Research Inc., Mathematica, Version 4, Champaign, IL, USA).

Statistical analysis
Differences in hemodynamics and arterial wave reflection between supine and standing posi-
tion and the different angles of tilt were calculated using Friedman's ANOVA. The outcomes of
different angles of tilt and standing were post-hoc compared to supine with Wilcoxon signed
rank test. Data are expressed as median. A p-value < 0.05 was considered significant. Data were

RESULTS
Hemodynamic and arterial wave reflection data are shown in table 1 and in figures 1 and 2. Compared
to supine position, aortic DBP and HR increased, whereas SV and CO decreased during stepwise
increased angles of passive head up tilt and active standing. Aortic SBP did not significantly change.
TPR increased from 0.9 dyn s/cm\(^5\) at 0º to 1.2, 1.4 and 1.4 dyn s/cm\(^5\) at 30º, 70º and 90º (p<0.001).
AIx fell from 25 % at 0º to 16, -1 and -10 % at 30º, 70º and 90º (p<0.001). The RM also decreased from
0.572 at 0º to 0.551, 0.469 and 0.456 at 30º, 70º and 90º (p<0.001). In multivariate analyses heart rate
was an important contributor of AIx or RM (beta for heart rate - 0.66, p<0.001 and - 0.65, p<0.001
Wave reflection during head up tilt

respectively), but the tilt angle remained a significant and independent predictor of Alx or RM after correction for heart rate (beta for tilt angle - 0.27, \( p = 0.02 \) and - 0.31, \( p < 0.01 \)).

Figure 3 shows the average measured aortic pressures and the derived forward and backward pressure. The amplitude of the forward pressure waves increased from supine to vertical postural position, while the backward waves decrease. The measured pressure wave, which is the sum of Pf and Pb, does not significantly change in amplitude, but due to the decrease in arterial wave reflection the shape of the pressure wave does change from a Murgo type A to a type C.18

**DISCUSSION**

In this study we show in a group of healthy subjects that from supine to upright the Alx and RM decrease gradually and from the onset on, while TPR increases in response to increasing angles of passive head up tilt and active standing. The arterial wave reflection was lowest and TPR highest in the standing position.

Tahvanainen and colleagues have shown that the Alx compared to supine position reproducibly decreases upon 60° HUT independent of age.11 12 Our study extends these findings by showing that there is a stepwise decrease in Alx during tilting and that this response is also present with active standing.

The Alx response upon tilting and standing seems counterintuitive, since usually an increase in TPR coincides with an increase in arterial wave reflection.8, 19, 20 We will briefly discuss the

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Data shown are medians for aortic SBP=systolic blood pressure, DBP=diastolic blood pressure, MAP=mean arterial pressure, HR=heart rate, SV=stroke volume, CO=cardiac output, TPR=total peripheral resistance, Alx=augmentation index, RM=reflection magnitude, Pf=forward pressure wave (Pf) and Pb=backward pressure wave. Differences between the different angles of tilt were calculated using Friedman’s ANOVA with post-hoc comparison to supine (0°) with Wilcoxon signed rank test. * \( p < 0.05 \) vs 0°, ** \( p < 0.01 \) vs 0°.
current concept of arterial wave reflection as used to describe the behaviour of forward and backward waves in supine position and we will propose an explanation for our contrasting results after postural change. At any place in the arterial system the arterial pressure wave is the resultant of a forward and a backward pressure wave. The forward pressure wave is formed by contraction of the left ventricle against the arterial load in the proximal aorta. The forward wave travels down the elastic large arteries, the aorta and its main branches, where at places of impedance mismatch the wave reflects and travels back to the heart. The backward wave that arrives in the proximal aorta is the resultant of all individual reflecting waves and augments.

Figure 1 Hemodynamics during different angles of tilt and standing
Data shown are mean±SE for aortic SBP=systolic blood pressure, DBP=diastolic blood pressure, MAP=mean arterial pressure, HR=heart rate, SV=stroke volume, CO=cardiac output, TPR=total peripheral resistance.
Figure 2 Arterial wave reflection during different angles of tilt and standing
Data shown are mean±SE for augmentation index (Alx) and reflection magnitude (RM).

Figure 3 Wave separation
Measured (solid lines), forward (interrupted lines) and backward (dotted lines) pressure waves during different angles of tilt and standing.
the forward pressure wave to form the pressure wave as ‘seen’ by the heart. The main sites of reflection are thought to be high resistance arteries and arterioles. Indeed, pharmacologically induced vasoconstriction increases TPR and arterial wave reflection, whereas vasodilation decreases TPR and arterial wave reflection. In response to passive head up tilt or active standing the postural change causes a gravitational shift of blood to the lower body. This pooling of blood causes a decrease in cardiac preload which in turn reduces cardiac output. To counteract the initial drop in blood pressure, the baroreflex increases vasomotor tone by an increase in sympathetic output, which accelerates HR and increases TPR. Since small resistance arteries and arterioles are thought to be the major reflection site of arterial pressure waves, the higher vasomotor tone is thought to increase arterial wave reflection. Sympathetic nervous system induced increases in vascular resistance by cold pressure test or isometric fatiguing hand-grip have shown to increase arterial wave reflection. Clearly other factors influence arterial wave reflection as well, since a decrease in arterial wave reflection and a concomitant increase in TPR during head up tilt has previously been shown. It is difficult to disentangle all the anatomical, functional and hemodynamic changes upon postural change and its relation to arterial wave reflection. The change in body position per se could have an effect on arterial diameter and function and could thereby influence arterial wave reflection. Lower body negative pressure (LBNP) mimics the hemodynamic response to head up tilt, but does this without changing body position. Comparable to the response to tilting, LBNP causes a decrease in SV, an increase in HR and TPR and also causes a decrease in arterial wave reflection. So, changes in body position alone cannot fully explain the decrease in arterial wave reflection. Instead, the baroreflex mediated increase in sympathetic outflow upon postural change, leads to vasoconstriction of resistance arteries but this might not be the case for all arterial beds. As part of the fright and flight response, catecholamines cause beta2 receptor dependent dilation of arterioles of the skeletal musculature. It could be that arterial wave reflection during passive tilting and active standing is partially dependent on these beta2 receptor dependent arterioles. In line with this is the observation that stimulation of the beta2 receptor with salbutamol in supine position causes an endothelium-dependent vasodilation and subsequently a decrease in arterial wave reflection. Alternatively, the shift of blood volume to the lower body upon tilting or standing might cause the aorta and lower arteries to expand leading to alterations in impedance mismatch and decreased arterial wave reflection. Finally, the decrease in SV might influence the forward pressure wave and thereby influence arterial wave reflection. However, the principal differences in the pressure wave were observed in the backward wave. Furthermore, we found no relation between SV and AIx (data not shown). Therefore it is unlikely that the observed decrease in SV could explain the decrease in arterial wave reflection.

A limitation of our study is that we did not correct the AIx for the increase in HR with an earlier proposed method. We did, however, correct for heart rate in a multivariate analysis and found that changes in arterial wave reflection during tilting remain significant after correction for changes in HR. We are therefore convinced that the decrease in arterial wave reflection is
not solely caused by the increase in HR. Also, we studied young healthy volunteers making it difficult to extrapolate our findings to older subjects or patients with cardiovascular risk factors or previous cardiovascular disease. Nevertheless, the AIx response to head up tilt does not significantly differ between younger and older persons. Finally, we used a model to derive aortic flow to be able to perform wave separation, and not directly measure aortic flow, which will have introduced errors.

In conclusion, we have shown that from supine to upright arterial wave reflection decreases gradually with a lowest value in the standing position.

**Perspectives** Whether this response is different in specific patient groups and whether this differentially effects central blood regulation needs further study. The reaction of arterial wave reflection and thereby central blood pressure upon standing might be different for patients with a disturbed baroreflex, with increased arterial stiffness or with an activated sympathetic system, such as heart failure patients. Arterial wave reflection is normally assessed in supine position and it is thought that increased arterial wave reflection augments central systolic pressure thereby increasing left ventricular load, which might cause an increase in left ventricular mass. Since humans usually spend most of their time in an upright position it is relevant to know whether organ damage such as left ventricular mass is associated with the AIx during tilting or standing and whether this relation is different from supine measured AIx.
REFERENCES


