Original Article

Individual changes of central blood pressure in response to upright posture: different hemodynamic phenotypes

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Objectives: Most studies about upright regulation of blood pressure have focused on orthostatic hypotension despite the diverse hemodynamic changes induced by orthostatic challenge. We investigated the effect of passive head-up tilt on aortic blood pressure.

Methods: Noninvasive peripheral and central hemodynamics in 613 volunteers without cardiovascular morbidities or medications were examined using pulse wave analysis, whole-body impedance cardiography and heart rate variability analysis.

Results: In all participants, mean aortic SBP decreased by −4 (−5 to −3) mmHg [mean (95% confidence intervals)] and DBP increased by 6 (5–6) mmHg in response to upright posture. When divided into tertiles according to the supine-to-upright change in aortic SBP, two tertiles presented with a decrease [−15 (−14 to 16) and −4 (−3 to −4) mmHg, respectively] whereas one tertile presented with an increase [+7 (7– 8) mmHg] in aortic SBP. There were no major differences in demographic characteristics between the tertiles. In regression analysis, the strongest explanatory factors for upright changes in aortic SBP were the supine values of, and upright changes in systemic vascular resistance and cardiac output, and supine aortic SBP.

Conclusion: In participants without cardiovascular disease, the changes in central SBP during orthostatic challenge are not uniform. One-third presented with higher upright than supine aortic SBP with underlying differences in the regulation of systemic vascular resistance and cardiac output. These findings emphasize that resting blood pressure measurements give only limited information about the blood pressure status.

Keywords: central blood pressure, head-up tilt, hemodynamics, hypertension, orthostatic, phenotype

Abbreviations: AIx, augmentation index; ANOVA, analysis of variance; BP, blood pressure; CRP, C-reactive protein; GFR, glomerular filtration rate; HRV, heart rate variability analysis; PWV, pulse wave velocity; SVR, systemic vascular resistance

INTRODUCTION

Hypertension [office blood pressure (BP) ≥140/90 mmHg] affects more than one billion people globally and is the leading risk factor for cardiovascular morbidity and mortality [1]. Lowering of BP with antihypertensive medication substantially reduces this risk [2,3]. However, uncertainty about BP treatment targets exists. Recent studies and meta-analyses suggest a benefit with intensive BP lowering even to under 120 mmHg SBP [2,4], while guidelines recommend a more conservative first-line treatment target to less than 130/80 mmHg with an emphasis on avoiding excessive BP reduction and related adverse events [5]. For diagnosing and treating hypertension, BP is classically measured from the upper extremity with a brachial cuff using a manual or semi-automated sphygmomanometer in a seated position. However, brachial BP measurement does not accurately represent BP on the aortic level because of the phenomenon of pulse pressure amplification [6]. Although antihypertensive agents are effective in lowering brachial BP, their effect on central BP varies [7,8], and evidence is accumulating that central BP is a stronger predictor of cardiovascular events than peripheral BP [9,10].

When assuming the upright position, blood pools to the lower extremities, resulting in decreased cardiac output. As compensatory mechanisms, heart rate and systemic vascular resistance (SVR) increase, and this usually results in higher diastolic and lower SBP both in the peripheral and central circulation [11]. The central hemodynamics usually differ in the upright versus supine position, and the changes in response to upright posture are affected, for example, by sex [12], hypertension [11], and antihypertensive medication [8]. In addition, upright hemodynamic regulation can be divided into different phenotypes according to the magnitude of the parallel changes in SVR and cardiac index [13]. Hence, supine or seated brachial BP may not give all relevant information about central hemodynamics whenever assessing cardiovascular risk or monitoring the effect of antihypertensive therapy.

Studies regarding orthostatic effects on BP have mostly concentrated on orthostatic hypotension using consecutive brachial or continuous finger BP measurements [14–16]. A constant finding in these studies has been that the SBP response to upright posture is variable, ranging from orthostatic hypotension to overt orthostatic hypertension [14–18]. In this context, central BP, or detailed hemodynamic measurements (cardiac output, SVR) have rarely been examined. Moreover, BP-lowering medications [8], cardiovascular disease [19], and aging [20] can have significant influences on the response to orthostatic challenge.

In this study, we examined the response of aortic SBP to passive head-up tilt in 613 volunteers without cardiovascular disorders and medications with direct cardiovascular influences. For comparison, posture-related changes of BP in the third finger were also recorded. Our aim was to assess the underlying hemodynamic mechanisms behind the variations of the changes in central BP during supine and upright postures.

METHODS

Study population

The volunteers were taking part in an ongoing study on hemodynamics (clinical trials registration number NCT01742702). Recruitment was done via announcements in local newspapers, occupational healthcare providers, Tampere University, Tampere University Hospital and Varala Sports Institute [11–13,20]. A total of 613 participants were included in the present study. None were on cardiovascular medication and participants with diagnosis of diabetes mellitus, coronary artery disease, cerebrovascular disease, chronic kidney or liver disease, heart rhythm other than sinus, heart failure, psychiatric illness other than mild depression or anxiety, and alcohol or substance abuse were excluded. Recordings were not performed during any acute illness. The participants were interviewed and examined by a physician and information about lifestyle and medical and family history were recorded.

Altogether 91 women used female hormones for contraception or as replacement therapy (13 estrogen, 33 progesterone, 45 combined estrogen and progesterone, 26 progesterone via an intrauterine device), 22 participants were on levothyroxine for hypothyroidism (all in euthyroid state), 37 on antidepressants (selective serotonin or serotonin-noradrenalin reuptake inhibitors or mirtazapine), and 12 on proton-pump inhibitors for gastro-esophageal reflux. Antihistamines were used by 16, vitamin D supplementation by 35, calcium supplementation by eight, and inhaled glucocorticoids for asthma by 15 participants. Six patients were on self-prescribed low-dose acetylic salicylic acid but none had a diagnosis of cardiovascular disease. In total, 60 participants presented with impaired fasting plasma glucose (6.2–6.9 mmol/l), and in seven participants the value was within the diabetic range (7.0–10.3 mmol/l) but none had medication for diabetes or glucosuria.

All participants gave written informed consent. The study was approved by the ethics committee of Tampere University Hospital District (study code R06086M) and executed according to the principles of the Declaration of Helsinki.

Laboratory analyses

Urine and blood samples were taken after ~12 h of fasting. Measurements of plasma sodium, potassium, calcium, C-reactive protein (CRP), cystatin C, glucose, creatinine, uric acid, triglycerides, and total, high-density and low-density lipoprotein cholesterol concentrations were determined using Cobas Integra 700/800 (F. Hoffmann-La Roche Ltd, Basel; Switzerland) or Cobas6000, module c501, and plasma insulin with an electrochemiluminescence immunoassay on Cobas e411 analyzer (F. Hoffmann-La Roche Ltd). Blood cell count was calculated by ADVIA 120 or 2120 (Bayer Healthcare, Tarrytown, New York, USA). Radioimmunoassays were used for the analyses of plasma renin activity (GammaCoat Plasma Renin Activity 125-I RIA Kit; DiaSorin, Saluggia, Italy) and aldosterone concentration (Active Aldosterone RIA, Beckman Coulter, Fullerton, California, USA). Glomerular filtration rate was evaluated using CKD-EPI-creatinine-cystatin-C formula [21], and insulin sensitivity using the quantitative insulin sensitivity check index (QUICKI) [22].

Hemodynamic measurements during passive head-up tilt

Simultaneous continuous recordings using pulse wave analysis and impedance cardiography were executed in a temperature-controlled laboratory by trained research nurses. Prior to the measurements, the participants were instructed to refrain from caffeine-containing products, smoking and heavy meals for 4 h, and from alcohol for 24 h. Electrodes for impedance cardiography were placed on body surface, plethysmographic sensor to the left third finger (Finometer model 1, Finapres Medical Systems, Amsterdam, the Netherlands; the unprocessed BP signal was captured), automatic tonometric sensor for pulse wave analysis on the left wrist over the radial artery (Colin BP-508T; Colin Medical Instruments Corp., San Antonio, Texas, USA), and a brachial BP cuff was attached to the right upper arm for BP calibration while the participants were subjected to about ~10 min of supine rest. The plethysmographic and tonometric sensors were held at the level of the heart during the recordings: the left arm was abducted in a support to 90° during the measurements. Before the capture of data, the research nurses measured supine brachial BP twice according to the guidelines [5] using an auscultatory sphygmomanometer (Heine Gamma G7). Hemodynamics were then recorded continuously in a beat-to-beat fashion for 10 min: 5 min supine, followed by 5 min of passive head-up tilt [11–13]. Mean tonometric BP values during the last 3 min in supine position were also compared with the manually measured brachial BP values using scatter plots.

Pulse wave analysis

Radial BP and pulse wave were recorded in a beat-to-beat fashion providing a continuous pulse wave form. BP was calibrated approximately every 2.5 min by a contralateral brachial cuff measurement [11]. A validated general transfer function was used to derive aortic pulse wave form from the radial pulse wave with the SphygmoCor device (PWMx system, AtCor Medical, Australia) [23]. The SphygmoCor software was used to calculate augmentation index (AIx,

augmented pressure/pulse pressure × 100%) and augmentation index adjusted to heart rate 75 beats/min (AIx@75) from the aortic pulse wave.

Impedance cardiography

Heart rate, stroke volume and cardiac output were determined beat-to-beat using a whole-body impedance cardiography system (CircMon, JR Medical Ltd, Tallinn, Estonia). SVR was calculated using the cardiac output measurement provided by CircMon and radial BP measurement from SphygmoCor. Cardiac output and SVR were normalized to the body surface area (cardiac index and systemic vascular resistance index, SVRI). Previous studies with CircMon have shown good correlation of stroke volume measurement with three-dimensional echocardiography [24] and cardiac output measurement with the thermodilution method [25]. Total arterial compliance was evaluated by dividing stroke volume by aortic pulse pressure [26]. The CircMon calculates pulse wave velocity (PWV), a marker of arterial stiffness, by measuring the time difference between the onset of the decrease in impedance in the whole-body impedance signal and the popliteal artery signal, hence determining aortic-to-popliteal PWV [27]. PWV obtained with impedance cardiography correlates well with PWV measurements using ultrasound [27] or the tonometric SphygmoCor device [28].

Heart rate variability

Cardiac autonomic tone was evaluated by heart rate variability (HRV) analysis. Electrocardiograms were recorded with the CircMon device at a 200 Hz sampling rate. Data analyses were carried out using Matlab software (MathWorks Inc.) For recognizing normal R-R intervals, a beat was considered ectopic if the interval differed greater than 20% from the previous interval. Cubic spline interpolation method was used to process the artifacts [29]. As measurements were carried out in a relatively short period of time (5 min supine, 5 min upright) only frequency-domain analyses were applied. Variables calculated were power in the low-frequency range (0.04–0.15 Hz), power in the high-frequency range (0.15–0.40 Hz) and the LF : HF ratio [30].

Statistical analyses

The study population was divided into tertiles according to the magnitude of the supine to upright change in aortic SBP (tertiles 1–3). The differences between the tertiles were analyzed using analysis of variances (ANOVA) for normally distributed variables and the Kruskal–Wallis test for non-normally distributed variables. Mean values of the last 3 min in the supine and upright positions were used for comparisons as the hemodynamic signal was most steady during these periods (Fig. 1). The hemodynamic variables between the tertiles were further compared using ANOVA for repeated measures. Differences between tertile frequencies were analyzed with the chi-square test, and Pearson's correlations was calculated as appropriate. Because of skewed distributions, the HRV variables low-frequency power, high-frequency power and low-frequency/high-frequency ratio were logarithmically transformed for the statistical analyses. The Bonferroni correction was applied in all post hoc analyses. The demographic and laboratory data are provided as means (standard errors of mean) or medians (with 25th to 75th percentile) in Table 1.

Linear regression analysis with stepwise elimination was applied for the analysis of the putative explanatory variables for the supine to upright change in aortic SBP. Data processing was done using IBM SPSS Statistics software 26.0 (Armonk, New York, USA), and P less than 0.05 was considered significant.
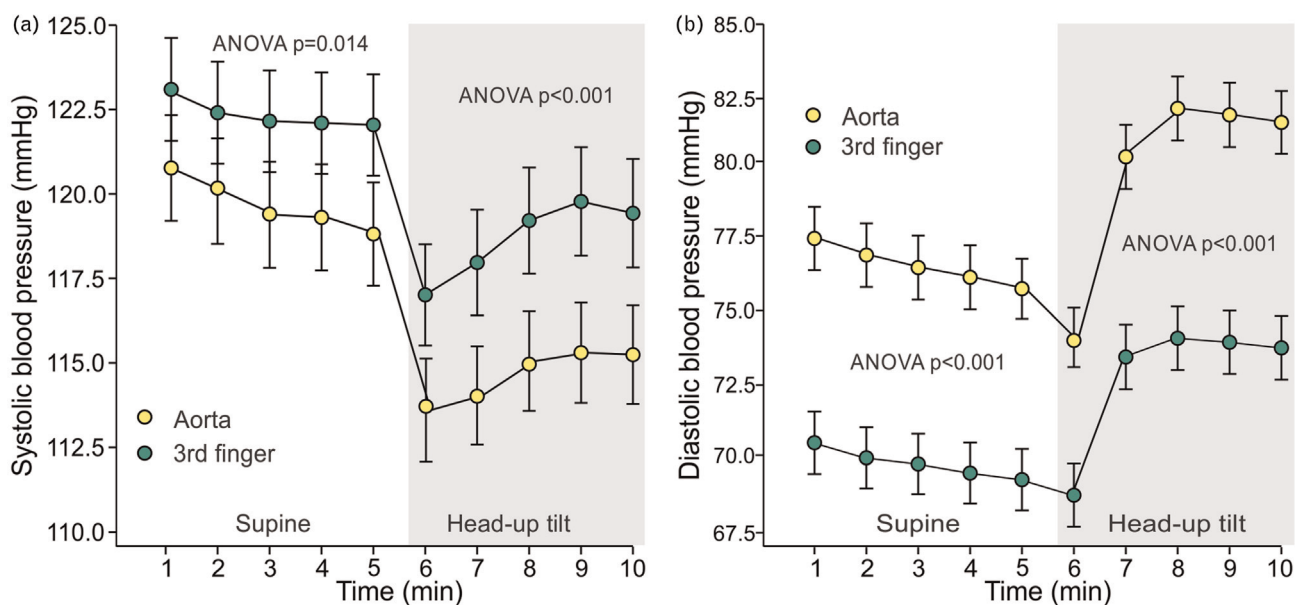
FIGURE 1 SBP (a) and DBP (b) in the aorta and third finger during passive head-up tilt ($n = 613$); means and 95% confidence intervals of the mean; P values represent ANOVA for repeated measures analyses for the difference in blood pressure between the aorta and the third finger.

TABLE 1. Clinical characteristics and laboratory results in tertiles of supine-to-upright change in aortic SBP

	Tertile 1 ($n = 203$)	Tertile 2 ($n = 207$)	Tertile 3 ($n = 203$)
Aortic SBP change in tilt	−15.4 (0.5)	−3.7 (0.2)*	7.4 (0.4)*,†
Male/female	100/103	95/112	106/97
Age (years)	47.3 (0.8)	44.2 (0.8)*	43.2 (0.9)*
Estimated GFR (ml/min per 1.73 m^2)	95.0 (1.0)	99.0 (1.0)*	101.1 (1.0)*
Height (cm)	173.8 (0.7)	172.4 (0.6)	173.2 (0.7)
BMI (kg/m^2)	26.6 (0.3)	26.7 (0.3)	27 (0.3)
Office SBP (mmHg)	143.9 (1.6)	139.1 (1.6)	138.5 (1.4)*
Office DBP (mmHg)	90 (1)	88 (1)	89 (1)
Never smoker	143	148	137
Present smoker	26	25	25
Previous smoker	60	59	66
Alcohol (standard drinks/week)	2 (0−6)	3 (1−5)	3 (1−6)
Extracellular water balance	1.00 (0.01)	1.00 (0.01)	1.02 (0.01)
Sokolow–Lyon m. (mm)	26 (1)	25 (0)	24 (1)
Hemoglobin (g/l)	145 (1)	143 (1)	144 (1)
Fasting plasma			
Sodium (mmol/l)	140.5 (0.1)	140.3 (0.1)	140.3 (0.1)
Potassium (mmol/l)	3.8 (0)	3.8 (0)	3.8 (0)
Creatinine (μmol/l)	74.9 (0.9)	73.2 (0.9)	73.0 (1.0)
Cystatin C (mg/l)	0.87 (0.01)	0.84 (0.01)*	0.83 (0.01)*
Calcium (mmol/l)	2.3 (0.1)	2.3 (0.1)	2.3 (0.1)
C-reactive protein (mg/l)	0.6 (0.5−1.7)	1.0 (0.5−2.2)	0.8 (0.5−1.9)
Triglycerides (mmol/l)	0.98 (0.72−1.47)	0.99 (0.71−1.33)	1.13 (0.78−1.70)†
High-density lipoprotein (HDL) cholesterol (mmol/l)	1.61 (0.03)	1.60 (0.03)	1.54 (0.03)
Low-density lipoprotein (LDL) cholesterol (mmol/l)	3.14 (0.1)	3.0 (0.1)	3.0 (0.1)
Uric acid (μmol/l)	295 (5)	302 (5)	312 (6)
Glucose (mmol/l)	5.5 (0.1)	5.4 (0.1)	5.5 (0.1)
Insulin (mU/l)	10.2 (2.0)	8.0 (0.4)	8.5 (0.4)
QUICKI	0.358 (0.003)	0.358 (0.002)	0.360 (0.003)
Renin activity (ng Ang I/ml/h)	0.67 (0.41−1.12)	0.75 (0.41−1.21)	0.76 (0.41−1.29)
Aldosterone (pmol/l)	434 (324−565)	431 (314−602)	447 (326−617)

Results shown as mean (standard error of mean) or median (25th to 75th percentile). GFR, glomerular filtration rate (CKD-EPI cystatin-C creatinine formula); Sokolow–Lyon measurement, see text; QUICKI, quantitative insulin sensitivity check index.
*P less than 0.05 versus tertile 1.
†P less than 0.05 versus tertile 2.

RESULTS

Study population

Demographic and laboratory data in tertiles of the mean supine-to-upright change in aortic SBP, ranging from −15.4 to +7.4 mmHg, are presented in Table 1. In the whole study population, the change in upright aortic SBP ranged from −39 to +33 mmHg. Participant age was slightly lower, and estimated GFR slightly higher, in tertiles 2 and 3 than in tertile 1, whereas office SBP was lower in tertile 3 than in tertile 1. There were no differences in sex distribution, BMI, office DBP, smoking status, alcohol use, extracellular water balance, and Sokolow–Lyon voltage between the tertiles. Cystatin C was slightly higher in tertile 1 than in tertiles 2 and 3, and triglycerides were higher in tertile 3 than in tertile 2 but no differences in hemoglobin concentration, plasma chemistry, cholesterol values, uric acid, glucose, insulin sensitivity, renin activity, and aldosterone concentration were observed between the tertiles. None of the participants were taking medications with direct cardiovascular influences. The use of other medications did not differ between tertiles.

Hemodynamic measurements

In the whole group ($n = 613$), upright aortic SBP was −3.9 (−4.7 to −3.0) mmHg lower [mean (95% confidence intervals)], and aortic DBP was +5.5 (4.8−6.2) mmHg higher, than the supine values (Fig. 1). Subsequently, mean aortic BP was 2.4 (1.7−3.0) mmHg higher in the upright than supine position. The parallel BP changes in the third finger were very similar, but SBP was higher, and DBP was lower, than in the aorta (Fig. 1). The correlations between mean laboratory BP values during the 3 min recording period and manually measured brachial BP values were good (Figure S1, Supplementary file, http://links.lww.com/HJH/B735, which shows scatter plots and Pearson's correlations between laboratory BP measurements versus manually obtained brachial BP).

On the basis of previous work [10], aortic SBP is ~10 mmHg lower than brachial SBP, in the absence of differences in DBP. Thus, aortic BP 130/90 mmHg corresponds approximately to brachial 140/90 mmHg. If the 130/90 mmHg cut-off point was applied to classify the present participants to hypertensive and normotensive groups, 133 (21.7%) were hypertensive both supine and upright, 52 (8.5%) were hypertensive only upright, 35 (5.7%) were hypertensive only supine, whilst 393 (64.1%) were normotensive. When applying the cut-off limits +20 mmHg for orthostatic hypertension and −20 mmHg for orthostatic hypotension [31], these phenomena were found in 5 (0.8%) and 45 (7.3%) of participants on the aortic level, respectively.
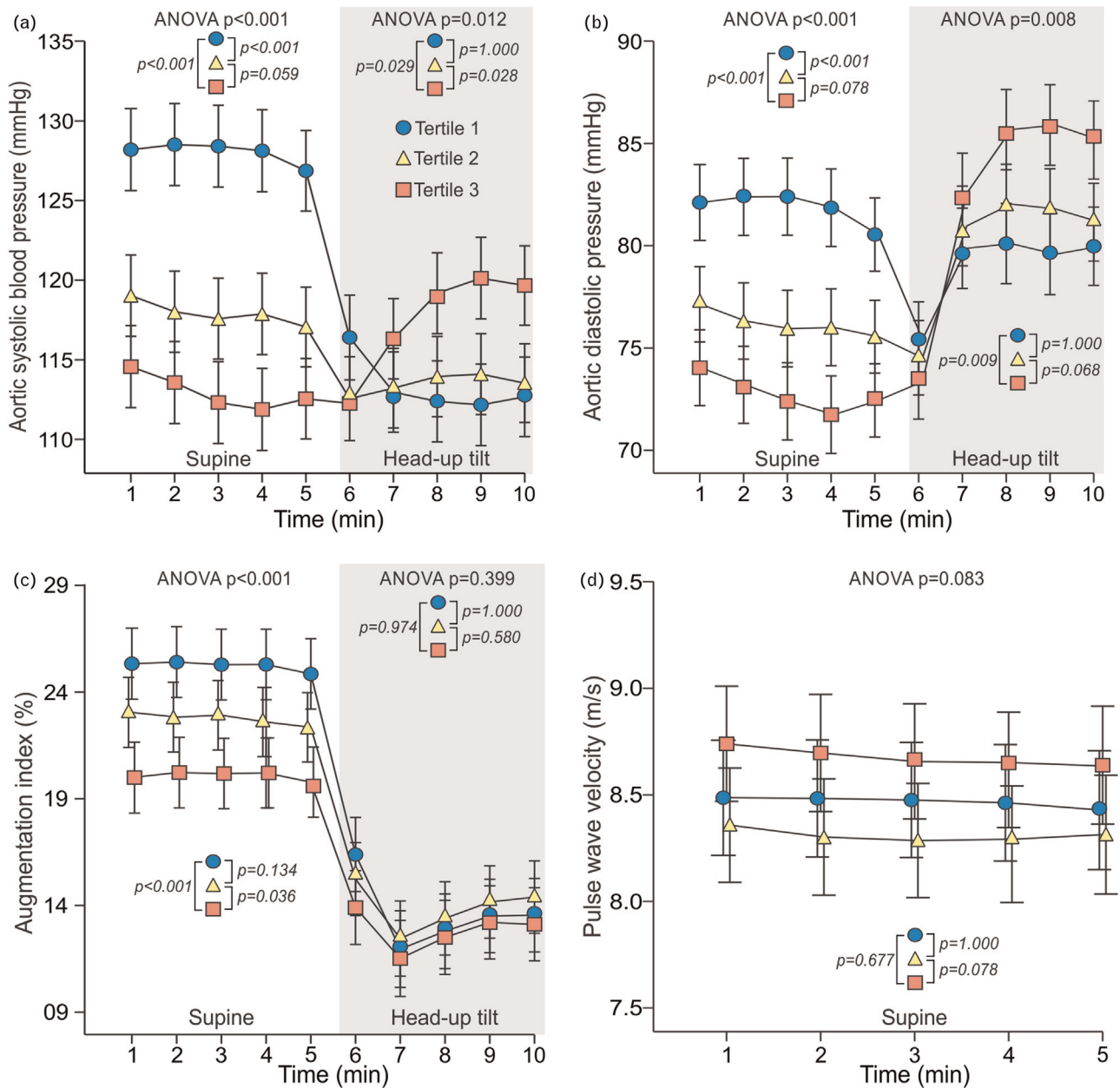
FIGURE 2 Aortic SBP (a) and DBP (b), augmentation index (c), and pulse wave velocity adjusted for mean supine aortic blood pressure (d) shown in tertiles according to the change in aortic SBP during head-up tilt; means and 95% confidence intervals of the mean; *P* values represent ANOVA for repeated measures analyses between the tertiles.

When divided into tertiles according to the change in aortic SBP during head-up tilt (Table 1), supine aortic SBP was highest in tertile 1, whereas upright aortic SBP was highest in tertile 3 (Fig. 2a). Supine aortic DBP was also highest in tertile 1, while upright aortic DBP was higher in tertile 3 than in tertile 1 (Fig. 2b). Supine aortic pulse pressure was highest in tertile 1 with no differences in upright values (Fig. S2C, Supplementary file, http://links.lww.com/HJH/B735, data presented similarly as in Figs. 2 and 3). Supine AIx was lowest in tertile 3. In response to upright posture, AIx decreased so that no differences between the tertiles were observed (Fig. 2c). The upright decrease in AIx was highest in tertile 1 (*P* < 0.001). The results remained unchanged when AIx was adjusted to heart rate 75 beats/min (AIx@75, Fig. S2A, Supplementary

file, http://links.lww.com/HJH/B735, data presented similarly as in Figs. 2 and 3). According to the expert consensus instructions [32], PWV was measured in the supine position and adjusted to mean aortic BP, and no differences between the tertiles were found (Fig. 2d). When evaluated using the ratio of stroke volume to aortic pulse pressure, total arterial compliance was highest in tertile 3 in the supine posture but no differences between tertiles were observed in the upright posture (Fig. S2B, Supplementary file, http://links.lww.com/HJH/B735, data presented similarly as in Figs. 2 and 3).

In response to upright posture, heart rate increased by ~13 beats/min (Fig. 3a), and stroke index decreased by ~12 ml/m² (Fig. 3b), with no differences between tertiles. Supine cardiac index was higher in tertile 3 than tertile 1,
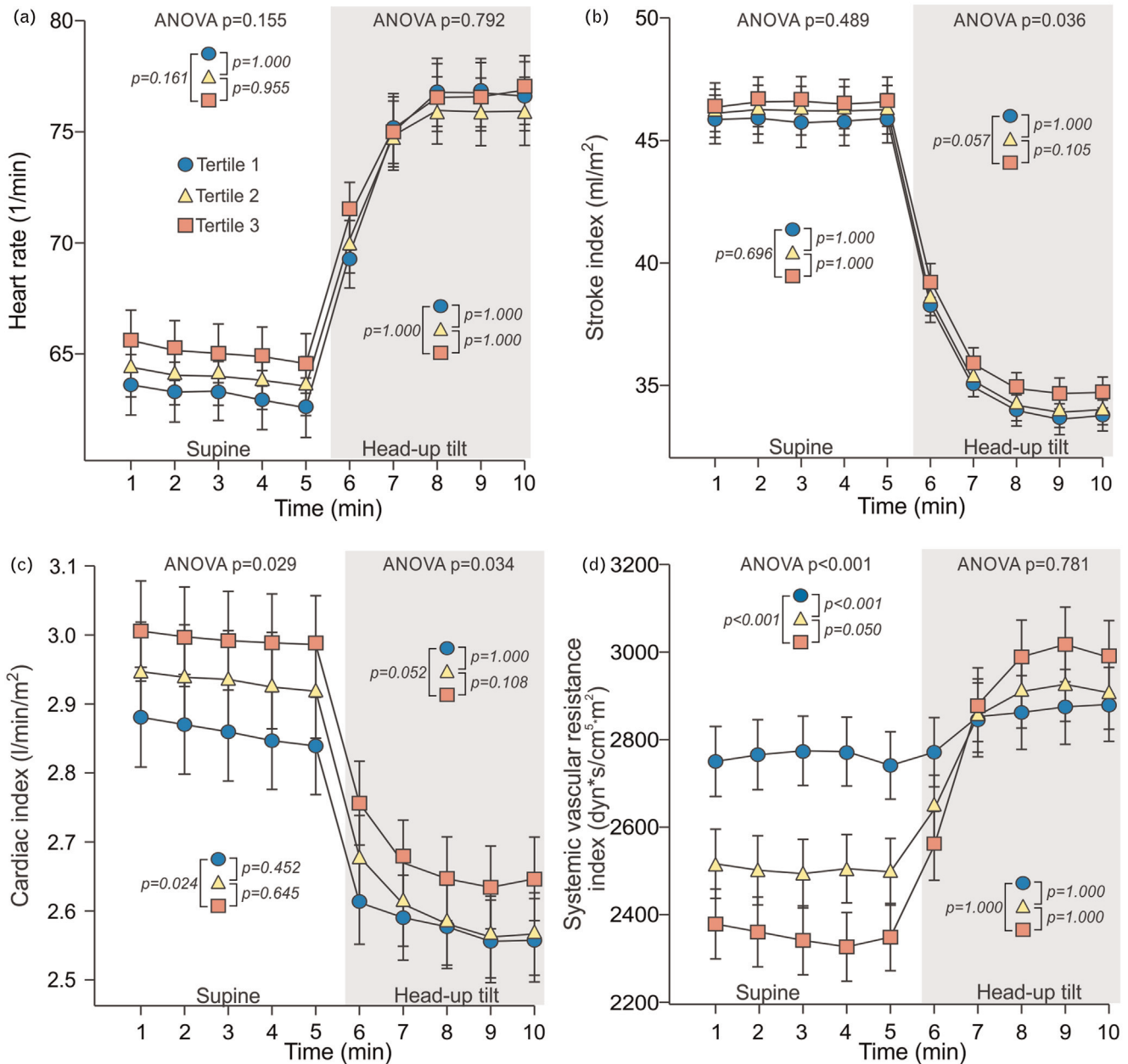
FIGURE 3 Heart rate (a), stroke index (b), cardiac index (c), and systemic vascular resistance index (d) shown in tertiles according to the change in aortic SBP during head-up tilt; means and 95% confidence intervals of the mean; *P* values represent ANOVA for repeated measures analyses between the tertiles.

whilst in the upright posture cardiac index decreased in all tertiles without differences in the magnitude of the change or actual upright values (Fig. 3c). SVRI was highest during supine measurements in tertile 1, but upright SVRI was corresponding in all tertiles (Fig. 3d). In response to head-up tilt, the average increase in SVRI in tertile 3 was six-fold when compared with tertile 1 (659 versus 110 $dyn\, s/cm^5\, m^2$, respectively) (Fig. 3d). The magnitude of the upright change in SVRI was different in all tertiles ($P < 0.001$ for all comparisons).

The HRV analyses did not reveal any differences between the tertiles in low-frequency power either supine or upright (Fig. 4a). Supine high-frequency power was corresponding in all tertiles but upright high-frequency power was higher in tertile 3 than in tertile 1 (Fig. 4b). The low frequency : high frequency ratio of HRV, a variable reflecting cardiac sympathovagal balance [30], clearly increased in response to upright posture ($P < 0.001$) but no differences between the tertiles were observed in supine or upright positions (Fig. 4c).

Explanatory factors for supine to upright change in aortic SBP in linear regression analysis

When analyzed using a stepwise linear regression model, both the changes and the initial values of SVR and cardiac output, in addition to initial aortic SBP, were the strongest
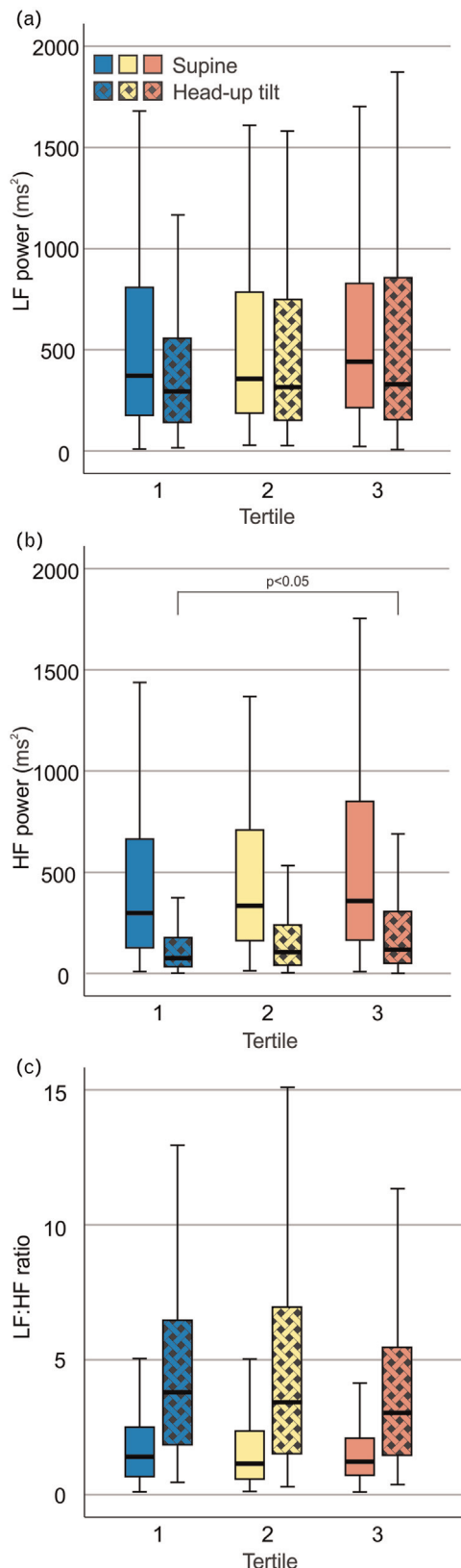
FIGURE 4 Heart rate variability in supine (uniform color) and upright (basket-weave) positions: low-frequency power (a), high-frequency power (b), and low-frequency : high-frequency ratio (c) in tertiles according to the change in aortic SBP during head-up tilt; median (thick line inside box), 25th to 75th percentile (box), and range (whiskers, outliers omitted form figure but included in statistics).

explanatory variables for the supine-to-upright change in aortic SBP (Table 2). The change in AIx, and the level of PWV, weight, age, and high alcohol intake influenced the change in aortic SBP (Table 2).

DISCUSSION

In this study, we examined the hemodynamic determinants of the supine-to-upright change in aortic SBP in 613 participants without cardiovascular disease or medications. The results showed that while in the whole group both peripheral (finger) and central average SBP decreased during passive head-up tilt, one-third of the participants exhibited an increase in upright aortic SBP.

In the upright position, blood pools to the lower extremities, which decreases venous return to the heart, leading to reduced stroke volume and cardiac output. Noninvasive finger recordings indicate that during the very first seconds of upright posture, SBP decreases rapidly, then recovers and stabilizes during the following 30–180 s [15]. This is mainly because activation of the sympathetic nervous system and the subsequent increases heart rate and SVR [33]. The magnitude of the change in SBP induced by upright posture is age-dependent: the difference in the upright versus supine SBP is smallest in young participants, while the difference progressively increases with advancing age, so that when compared with supine values the upright SBP is lowest in the highest age groups [15,20]. The regression analysis in the present study population also showed that higher age was related with a larger upright reduction in central SBP.

Previous studies have mainly focused on the change in brachial SBP in the upright position. In the present study, we performed noninvasive assessments to study the hemodynamics of the different phenotypic supine-to-upright changes in aortic SBP. In the supine position, tertile 3 that presented an increase in upright SBP, expressed lower SVRI and higher cardiac index than tertile 1 but in the upright position, SVRI was corresponding in all tertiles. Subsequently, the related increase in SVRI during upright tilt was six-fold in tertile 3 versus tertile 1, in the absence of statistically significant differences in the changes in cardiac index. This indicates that substantial variations in the regulation of peripheral arterial resistance result in different upright changes of aortic SBP. Accordingly, the change in SVR was the strongest explanatory factor for the supine to upright change in aortic SBP in the regression analysis, followed by the initial values and the change in cardiac index, and initial level of SVR.

Most of the studies regarding the effect of upright position on BP have focused on orthostatic hypotension but orthostatic hypertension is also a recognized but underappreciated disorder [17,18,34]. A widely accepted definition for orthostatic hypotension is an at least 20 mmHg decrease of upright SBP but no widely accepted consensus applies to the definition of orthostatic hypertension. In previous studies, the cut-off limits from 10 to 20 mmHg increase in upright brachial SBP have been applied to determine this condition [17,34]. The prevalence of orthostatic hypertension is highest among individuals with autonomic nervous

TABLE 2. Linear regression analysis with stepwise elimination: explanatory variables for supine to upright change in aortic SBP

Change in aortic SBP	B	Beta	P value
$R^2 = 0.760$, $P < 0.001$			
Constant	−24.82		<0.001
Change in systemic vascular resistance	0.050	1.162	<0.001
Change in cardiac output	13.097	0.904	<0.001
Initial cardiac output	6.336	0.705	<0.001
Initial aortic systolic pressure	−0.347	−0.641	<0.001
Initial systemic vascular resistance	0.015	0.456	<0.001
Change in augmentation index	0.294	0.186	<0.001
Pulse wave velocity	0.542	0.103	0.001
Weight	0.053	0.081	0.006
Age	−0.052	−0.058	0.033
High alcohol consumption	3.048	0.041	0.046

Variables used ($n = 603$ participants): age, sex, height, weight, smoking status (never, present, previous), alcohol intake (none, low, moderate, high), blood leukocyte count, plasma high-density lipoprotein (HDL) cholesterol, plasma phosphate, pulse wave velocity, initial aortic SBP, initial aortic DBP, augmentation index, cardiac output, systemic vascular resistance, extracellular fluid balance; and changes in cardiac output, augmentation index, systemic vascular resistance.

system disorders, in elderly hypertensive individuals, and in association with extreme night-time BP dipping [17]. The present HRV analyses indicate that disorders of the autonomic nervous system were unlikely to affect the results or our study population. Higher upright HF power in tertile 3 versus tertile 1 reflected stronger parasympathetic activation in tertile 3 but no differences in heart rate were found. Furthermore, arterial stiffness did not account for the differences in upright responses in our study as PWV was similar in all tertiles. When arterial compliance was evaluated by calculating the stroke volume to aortic pulse pressure ratio, the supine values were highest in tertile 3 but no upright differences were observed. This suggests that the supine differences in stroke volume/aortic pulse pressure ratio more reflected deviations in BP and pulse pressure than differences in arterial compliance.

Augmentation index is a measure of wave reflection, which is directly related to arterial stiffness, SVRI, and stroke volume and inversely related to heart rate [28]. The relationship between AIx and SVRI can explain the difference in AIx between tertile 1 and tertile 3 in the supine position. However, in the absence of differences in arterial stiffness, and upright heart rate, stroke volume, and SVRI, the upright AIx values were also similar in the tertiles. Adjusting AIx to heart rate of 75 beats/min did not change the results.

In addition to the measurement of changes in BP, hemodynamic phenotypes in response to upright posture can be determined using additional approaches [13]. Independent of the BP level, the response to upright posture can be divided to constrictor and sustainer phenotypes, the former presenting with highest and the latter with lowest changes in SVRI and cardiac output during head-up tilt [13]. The sustainer phenotype was also characterized by increased large arterial stiffness [13], an acknowledged marker of cardiovascular risk [32]. The tertile 1 in our study presented with similarities to the sustainer phenotype: a small increase in SVRI, numerically lowest decrease in cardiac index, and low upright HF power. Furthermore, systematic differences in the upright regulation of SVRI and cardiac output have been discovered between men and women [12,35]. Altogether, differences in the regulation of SVR seem to be a crucial explanation for various hemodynamic phenotypes during orthostatic challenge. A pivotal

role for SVR in orthostatic hypertension was also suggested in a study constituting 186 medicated hypertensive individuals, as those with orthostatic hypertension exhibited exaggerated posture-related rises in SVR [36].

Previously, the cause of the variation in upright BP has been addressed from an evolutionary viewpoint, and the authors proposed that human adaptation to bipedalism is not yet perfected [33]. Subsequently, an overly active response to upright position can lead to abnormally high BP in some individuals. This could also be one of the mechanisms leading to the development of established hypertension [33]. Indeed, orthostatic hypertension has been proposed as one of the forms of prehypertension [17]. Both genetic and environmental familial factors are known to affect the reaction to upright position: 40% of the variation in upright SBP was reported to be familial, and 25% of the variation was attributable to genes and 15% to shared environmental factors [37].

The measurement of upright BP is not clinical routine with the exceptions of the evaluation of orthostatic hypotension or syncope, and upright BP has even been somewhat neglected in the clinical guidelines [5]. Nevertheless, both orthostatic hypotension and hypertension are associated with adverse cardiovascular outcomes [34,38,39]. A U-shaped curve exists between orthostatic BP reactions, increased arterial stiffness, and clinical endpoints like cerebral infarcts [39,40], highlighting the importance of the measurement of upright BP. Although diagnostic cut-offs for BP are artificial, it is noteworthy that using the above 130/90 mmHg cut-off of aortic BP [10] for hypertension, almost 10% of individuals in this study were hypertensive solely in the upright position. No recommendations are available for antihypertensive treatment among these individuals. Of note, some small studies have shown beneficial effects of alpha-blockers and clonidine in the treatment of orthostatic hypertension [17].

In addition to the various responses to orthostasis, other differing hemodynamic phenotypes have also been reported. Picone *et al.* [41] found different aortic-to-brachial-to-radial BP amplification phenotypes with indistinguishable brachial-cuff BP values. In addition, hypertensive patients have also exhibited different hemodynamic phenotypes with regard to alterations in peripheral arterial resistance and cardiac output [42,43].

The study populations in several studies concerning the hemodynamic responses to orthostatic challenge have been quite heterogenous regarding age, ethnicity, comorbidities, and medications [14,16,31]. In the present study, the population characteristics were rather homogenous, which emphasizes that the hemodynamic phenotypes of upright aortic SBP were not attributed to cardiovascular diseases or medications. The difference in age between tertiles 1 and 3 (47 versus 43 years) was statistically significant but probably clinically of minor impact. Similarly, the minute difference in eGFR in the absence of kidney diseases can be argued to be of little clinical significance.

Aortic BP values were derived from the radial BP signal and required mathematical transformations. The hemodynamic measurements were noninvasive and as such did not represent direct arterial pressures. However, invasive studies are not justified for research purposes in healthy people. The measurement protocols used in this study have been well validated (see Methods), but the reproducibility of the present phenotypes warrants future investigation. Many of the hemodynamic variables are closely correlated, and an explanatory variable in the final model may stand for a group of variables. Due to the multicollinearity problem, the results of the regression analysis should be interpreted with caution.

In conclusion, novel hemodynamic phenotypes undetectable by conventional BP measurements have been found during the recent years. The findings of the present study, constituting a relatively homogenous population without cardiovascular morbidities, showed that differences in the regulation of peripheral arterial resistance can lead to diverse responses of central SBP in the upright posture. Conventional seated brachial BP measurements may miss cardiovascular information that has potentially relevant clinical implications. Routine BP measurements in the upright position should be applied to achieve more personalized diagnostics and treatment of hypertension.

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Data availability: analyses and datasets of the current study are not available publicly as the clinical database contains several indirect identifiers and the informed consent obtained does not allow publication of individual patient data. The datasets are available from the corresponding author on reasonable request.

Conflicts of interest

There are no conflicts of interest.

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