ORIGINAL ARTICLE

Age-Specific Acute Changes in Carotid–Femoral Pulse Wave Velocity With Head-up Tilt

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BACKGROUND
Aortic stiffness as measured by carotid–femoral pulse wave velocity (cfPWV) is known to depend on blood pressure (BP), and this dependency may change with age. Therefore, the hydrostatic BP gradient resulting from a change in body posture may elicit a cfPWV change that is age-dependent. We aimed to analyze the relationship between BP gradient—induced by head-up body tilting—and related changes in cfPWV in individuals of varying age.

METHODS
cfPWV and other hemodynamic parameters were measured in 30 healthy individuals at a head-up tilt of 0° (supine), 30°, and 60°. At each angle, the PWV gradient and resulting cfPWV were also estimated (predicted) by assuming a global nonlinear, exponential, pressure–diameter relationship characterized by a constant β_0, and taking into account that (diastolic) foot-to-foot cfPWV acutely depends on diastolic BP.

RESULTS
cfPWV significantly increased upon body tilting (8.0 ± 2.0 m/s supine, 9.1 ± 2.6 m/s at 30°, 9.5 ± 3.2 m/s at 60°, P for trend <0.01); a positive trend was also observed for heart rate (HR; P < 0.01). When the observed, tilt-induced cfPWV change measured by applanation tonometry was compared with that predicted from the estimated BP hydrostatic gradient, the difference in observed-vs.-predicted PWV change increased nonlinearly as a function of age (R^2 for quadratic trend = 0.38, P < 0.01, P vs. linear = 0.04). This result was unaffected by HR tilt-related variations (R^2 for quadratic trend = 0.37, P < 0.01, P vs. linear = 0.04).

CONCLUSIONS
Under a hydrostatic pressure gradient, the pulse wave traveling along the aorta undergoes an age-related, nonlinear PWV increase exceeding the increase predicted from BP dependency.

Keywords: arterial function; arterial stiffness; blood pressure; early vascular aging; hypertension; pressure dependence

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Blood pressure (BP) is a major determinant of the carotid–femoral pulse wave velocity (cfPWV) which is classically assumed to be constant along the carotid-to-femoral segment, as it reasonably occurs when cfPWV is measured with the subject lying supine. On the contrary, when the subject is standing in the upright position, the carotid–femoral segment is exposed to a hydrostatic BP gradient and an associated PWV gradient, resulting in a wave speed increase when the pressure wave travels along the pressure gradient (e.g. from the heart to lower limbs), and speed decrease when it moves contra-gradient (from the heart to the head). The magnitude of cfPWV variations in response to a BP gradient and its main determinants have been, to date, understudied.

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Many studies suggest that, at a physiological BP level, the relation between BP and stiffness is nonlinear, rather than linear, because of the progressive shift of pressure load from elastic structures of the arterial wall to stiffer components.[1,2] Hayashi *et al.* proposed that the relationship between BP and diameter is well captured by an exponential law,[3] characterized by an exponent β_0. An approximated, simplified version of this exponent, β,[4] was used in the derivation of cardioankle vascular index (CAVI),[5] which was later refined into $CAVI_0$, corresponding analytically to β_0.[6] Taking into account that PWV is measured with the foot-to-foot method at the diastolic BP (DBP) level of the pressure waveform, predicted changes in PWV for any DBP gradient could be estimated at the individual level from this formula, by keeping β_0 constant.[7,8]

It has been also observed that the BP point at which the shift of pressure load occurs, named point of maximum compliance, progressively decreases with aging.[9,10] Therefore, for a given hydrostatic pressure gradient, associated acute cfPWV variations may follow a more curved, nonlinear, behavior, and a differential cfPWV scaling with pressure changes at varying ages may be expected. In other terms, independently from supine cfPWV, aging could be associated with a more pronounced cfPWV increase when the subject is standing upright.

The aim of the present study is to test the main hypothesis that aging is associated with more pronounced cfPWV variations in response to gravitational pressure. To this aim, cfPWV was measured in a cohort of healthy individuals with body position progressively shifted from supine to upright during passive tilting at 30° and 60°. Values were compared with the PWV gradient as predicted solely from the gravitational pressure gradient, obtained by assuming a constant value of β_0 (as measured in supine position) along the

arterial tree. Finally, the relationship between the difference in measured-vs.-predicted PWV and age was analyzed.

METHODS

Participants

A cohort of 30 healthy volunteers was enrolled among employees from the Division of Geriatrics at the Erasmus University Medical Center, Rotterdam, The Netherlands. Those with a positive history of cardiovascular disease, history of hypertension, chronic kidney disease, diabetes mellitus, or any relevant disease which could have affected the results were excluded from the study. None of the included participants regularly took cardiovascular or other medications.

All measurements were performed under fasting conditions. Subjects were also asked to refrain from smoking or caffeine use at least 13 hours before the procedure. All details related to measurements, including potential hemodynamic reactions induced by body tilting, were clearly explained to participants before initiating the test. Two medical doctors supervised the entire procedure and performed all the measurements. All participants were informed about the aim and procedures of the study and gave written consent. The protocol was approved by the Institutional Ethics Committee.

Study protocol

The measurement protocol is shown in Figure 1. Participants were asked first to lie down in supine position on a motor-driven tilt table placed horizontally (0°). After at least 10 minutes' resting, BP was measured in triplicate at the nondominant upper arm with a validated brachial-cuff
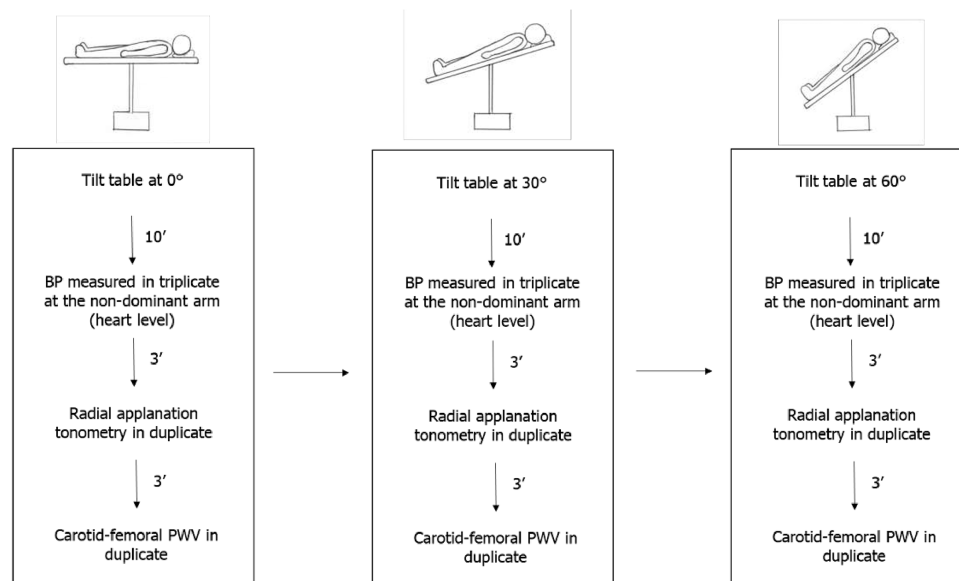

Figure 1. Measurement protocol. Participants were placed supine on a tilt table placed horizontally (0°). After at least 10 minutes' resting, blood pressure (BP) and radial tonometry were measured at the upper arm, always kept at the heart level. Then, carotid–femoral pulse wave velocity (PWV) was performed by applanation tonometry. Afterwards, participants were head-up tilted to 30° and 60° and the same set of measurement was repeated at each position after 10 minutes resting.

oscillometric device (Omron HEM-907, Omron Healthcare, Kyoto, Japan), and average brachial BP was considered for further analysis; the upper arm was gently supported in order to keep it always at the heart level during subsequent measures. Radial tonometry was performed using the SphygmoCor device (AtCor Medical, Sydney, New South Wales, Australia). Two sets of 10 s high-quality waveforms were taken with a high-fidelity applanation tonometer with a 2-minute interval and averaged. Afterwards, cfPWV was measured by applanation tonometry, sequentially taken at the right common carotid and femoral arterial sites. At least 10 seconds of good quality waves were obtained for each side and averaged. The R-wave on the surface electrocardiogram was taken as reference to calculate the (carotid–femoral) transit time interval between R-wave and the foot of each waveform. The effective travel distance (ETD) was measured as 80% of the straight distance between carotid and femoral site using a caliper.[11] cfPWV (in m/s) was calculated as the ratio between ETD and the transit time. Central BP was reconstructed from radial tonometry and the built-in generalized transfer function. Heart rate (HR) was recorded during PWV measurement.

Subjects were slowly head-up tilted, after securing their bodies with belts on a motorized tilt table. Measures were repeated in the same order both at 30° and 60°, after at least 10 minutes' resting in order to avoid acute effects of passive tilting on respiration and brain perfusion, and to minimize the effects of control mechanisms on BP regulation, such as autonomic function and local autoregulation.[12] The measurement protocol for each patient lasted about 1 hour.

Datam processing

The stiffness index β_0 was estimated from measurements in the supine position, using the following equation[11]:

$$\beta_0 = \frac{2\rho \cdot \text{PWV}^2}{P_\text{d}} - \ln \frac{P_\text{d}}{P_\text{ref}}, \quad (1)$$

with ρ the blood mass density, taken to be 1,050 kg/m³, PWV the measured cfPWV, P_d the central DBP, and $P_\text{ref} = 100$ mm Hg a reference pressure.

To estimate the effects of the hydrostatic pressure gradient on changes in PWV, the aorta was assumed to be a straight tube with the brachiocephalic trunk originating from the top of the aortic arch. Based on this, the ETD could be assumed to begin at the level of the descending aorta corresponding to the heart level. This could be extrapolated from magnetic resonance imaging studies, which showed that the path length between the aortic annulus and the femoral site minus the ETD is approximately similar to the distance between the aortic annulus and the carotid site.[13] The DBP hydrostatic gradient was also approximated from the height of the blood column using:

$$\Delta P_\text{d} = \rho \cdot g \cdot \Delta h, \quad (2)$$

with $g = 9.81$ m/s² the gravitational acceleration and Δh the height of the blood column. For ΔP_d in mm Hg and Δh in cm, this reduces to $\Delta P_\text{d} = 0.77 \cdot \Delta h$.[14] In such a way, the height of the blood column generating a hydrostatic pressure at the femoral site is estimated by ETD multiplied by the sine of the corresponding tilt angle. Therefore, DBP at the site of femoral recording site is approximated from DBP_aortic measured at the upper arm at any tilt angle, as

$$\text{DBP}_\text{femoral} = \text{DBP}_\text{aortic} + (0.77 \cdot \text{ETD} \cdot \sin(\alpha)), \quad (3)$$

with pressure in mm Hg and ETD in cm. Furthermore, assuming β_0 as a constant BP-independent stiffness index, for each tilt angle, local PWV at the aortic (PWV_aortic) and femoral level ($\text{PWV}_\text{femoral}$) were predicted by rearranging equation (1):

$$\text{PWV}_\text{aortic or femoral} = \sqrt{\frac{P_\text{d}}{2\rho} \left(\beta_0 + \ln \frac{P_\text{d}}{P_\text{ref}} \right)}, \quad (4)$$

using $P_\text{d} = \text{DBP}_\text{aortic}$ to obtain PWV_aortic and $P_\text{d} = \text{DBP}_\text{femoral}$ to obtain $\text{PWV}_\text{femoral}$.

As PWV (a velocity) can be expressed as dx/dt, one can arrange equation (4) as

$$dt = \frac{1}{\sqrt{\frac{P_\text{d}}{2\rho} \left(\beta_0 + \ln \frac{P_\text{d}}{P_\text{ref}} \right)}} dx, \quad (5)$$

and integrate to obtain the total pulse transit time (PTT):

$$\text{PTT} = \int_0^{\text{ETD}} \frac{1}{\sqrt{\frac{P_\text{d}}{2\rho} \left(\beta_0 + \ln \frac{P_\text{d}}{P_\text{ref}} \right)}} dx, \quad (6)$$

with P_d a function of pressure through equation (2). PWV then follows from

$$\text{PWV}_\text{integral} = \frac{\text{ETD}}{\text{PTT}}. \quad (7)$$

Although the integral in equation (6) can be solved numerically with relative ease, it turns out that $\text{PWV}_\text{integral}$ is very closely approximated by the average of aortic and femoral PWVs:

$$\text{PWV}_\text{averaged} = \frac{\text{PWV}_\text{aortic} + \text{PWV}_\text{femoral}}{2}. \quad (8)$$

Please refer to Supplemental Digital Content 1 online for details. In the present study, we will use equation (8) to predict the influence of hydrostatic pressure on cfPWV.

Statistical analysis

Continuous variables are presented as mean ± SD. The Kolmogorov–Smirnov z test was used to test the assumption of satisfactory normal distribution (this assumption was satisfied for all the variables). Within-subject changes in response to head-up tilting at different angles (30° and 60°) were analyzed using repeated-measures analysis of variance. The association between variables was assessed using as Pearson's correlation coefficients and partial correlation coefficients when associations between 2 variables were to be adjusted for the effect of a third one. The relationship between observed-vs.-predicted cfPWV and age was analyzed by univariable and multivariable regression models, before and after adjustment for associated HR variations (as detailed below). Sex, body mass index, height, brachial SBP, brachial DBP, central SBP, central DBP measured at 0° and related percentage changes induced by body tilting were introduced as independent variables in multivariate models. Variables characterized by high collinearity were introduced, one at a time, in separate multivariate models. The estimation of best-fit model was conducted by comparing linear vs. quadratic equations through the F-test for the difference between linear vs. quadratic regression coefficients.[14] A P value less than 0.05 was considered statistically significant. Statistical analysis was performed with SPSS statistics 21.0 (SPSS, Chicago, IL).

RESULTS

All individuals completed the study maintaining stable clinical conditions during the entire procedure. No fainting, pain, nausea, discomfort, or any other clinically relevant

Table 1. Main characteristics of the study population

	Mean (SD)
N	30
Age, years	45 (18)
Men, %	38
Height, cm	166 (26)
BMI, kg/m^2	23.5 (4)
SBP/DBP, mmHg	130 (12)/74 (8)
Heart rate, bpm	62 (9)
ETD, mm	514 (39)
cfPWV, m/s	8.0 (1.9)
β_0	14.5 (6)

Abbreviations: BMI, body mass index; cfPWV, carotid–femoral pulse wave velocity; DBP, diastolic blood pressure; ETD, effective travel distance; SBP, systolic blood pressure. β_0: stiffness index constant estimated at 0°. All values were reported as mean (SD).

sign or symptom were reported by participants during the tilt test.

The main features of the study population are reported in Table 1. Subjects were well balanced across age ranges (range 21–82 years, skewness 0.4, kurtosis −0.5). Three patients (10%) had BP values consistent with grade 1 hypertension according to the European Society of Cardiology/European Society of Hypertension criteria,[15] the remaining subjects were normotensive. β_0 values showed a direct correlation with age ($R^2 = 0.49$, $P < 0.01$, Figure 2).

The main effects of head-up tilting are described in Table 2. Significant increases of brachial SBP, brachial DBP, central DBP, and HR were recorded upon body tilting (all P for trend ≤0.01), At variance, central pulse pressure showed a decrease (P for trend <0.01), whereas no significant changes were observed for central SBP and brachial pulse pressure.

cfPWV significantly increased upon body tilting (cfPWV = 9.1 ± 2.6 m/s at 30°, +14% vs. supine; 9.5 ± 3.2 m/s at 60°, +19% vs. supine, P for trend <0.01). The same trend was observed for PWV$_{averaged}$ calculated based on equation (8) (8.8 ± 2.1 m/s at 30°, +10% vs. supine; 9.3 ± 2.2 m/s at 60°, +16% vs. supine, P for trend <0.01).

We observed that the difference between cfPWV and PWV$_{averaged}$ (indicated as observed-vs.-predicted PWV) progressively increased at increasing age, displaying a curvilinear, nearly quadratic, behavior (R^2 for quadratic trend = 0.38, $P < 0.01$, P vs. linear = 0.04). When PWV$_{averaged}$ values were adjusted for associated HR changes, based on a previously published equation,[16] overall results did not markedly change (R^2 for quadratic trend = 0.37, $P < 0.01$, P vs. linear = 0.04, Figure 3). The same results were found when cfPWV and PWV$_{averaged}$ values at 30° and 60° were represented as percentage changes from supine PWV (R^2 for quadratic trend = 0.27, $P < 0.01$, P vs. linear < 0.05). Similar trends were also confirmed when the relationship between age
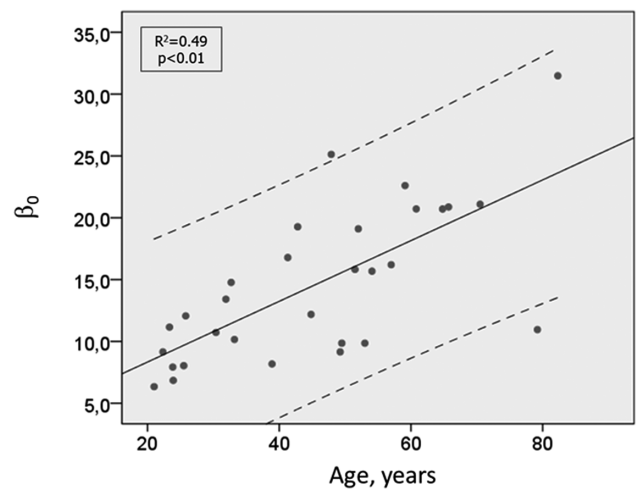

Figure 2. Correlation between β_0 and age. Stiffness index β_0 is the constant (exponent) of the exponential pressure–diameter relationship, named "stiffness index," and was measured in each patient at 0°, using data from measured carotid–femoral pulse wave velocity and central diastolic blood pressure. See equation (1) in the methods session for further details. Solid line: prediction line. Dashed lines: 95% confidence intervals of the prediction line.

Table 2. Changes in carotid–femoral pulse wave velocity (cfPWV) and other hemodynamic parameters induced by head-up body tilting

	Supine	30°	60°	P (trend)
Brachial SBP, mm Hg	130 (12)	133 (17)	134 (18)	0.01
Brachial DBP, mm Hg	74 (8)	77 (9)	80 (10)	<0.01
Brachial PP, mm Hg	56 (11)	54 (13)	54 (14)	0.08
Central SBP, mm Hg	115 (14)	116 (18)	116 (18)	0.63
Central DBP, mm Hg	75 (7)	78 (9)	82 (10)	<0.01
Central PP, mm Hg	40 (12)	38 (13)	34 (12)	<0.01
HR, bpm	62 (9)	65 (7)	73 (7)	<0.01
cfPWV, m/s	8.0 (2.0)	9.1 (2.6)	9.5 (3.2)	<0.01
PWV_{heart}, m/s[a]	8.0 (2.0)	8.2 (2.1)	8.4 (2.1)	<0.01
$PWV_{femoral}$, m/s[a]	8.0 (2.0)	9.3 (2.2)	10.1 (2.4)	<0.01
$PWV_{averaged}$, m/s	8.0 (2.0)	8.8 (2.1)	9.3 (2.2)	<0.01
BP gradient, mm Hg	—	19 (2)	33 (3)	<0.01
ΔcfPWV, m/s	—	1.0 (1.2)	1.5 (1.9)	<0.01
$ΔPWV_{averaged}$, m/s	—	0.7 (0.3)	1.2 (0.4)	<0.01

[a]PWV_{heart} and $PWV_{femoral}$ were calculated based on equation (3), see Methods for further details. Abbreviations: DBP, diastolic blood pressure; HR, heart rate; PP, pulse pressure; SBP, systolic blood pressure. BP gradient: hydrostatic pressure gradient along the effective travel distance pathway, calculated at tilt angles of 30° and 60° from equation (2). ΔcfPWV: changes in cfPWV vs. 0°; $ΔPWV_{averaged}$: changes in $PWV_{averaged}$ vs. 0°. All values were reported as mean (SD).
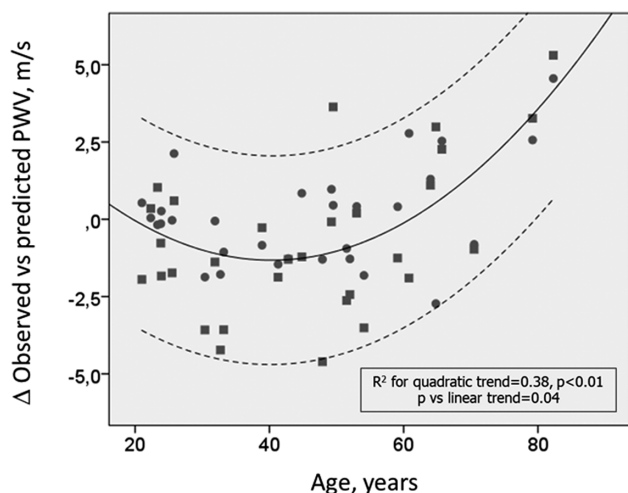

Figure 3. Association between age and the difference of measured (by arterial tonometry) vs. predicted (by equation (7)) pulse wave velocity (PWV) at each tilt angle (30° = circles, 60° = squares), expressed as observed-vs.-predicted PWV and adjusted for tilt-related heart rate changes. Solid line: prediction line. Dashed lines: 95% confidence intervals of the prediction line.

and observed-vs.-predicted PWV was evaluated separately by each tilt angle ($P < 0.01$ at both 30° and 60°). The association between age, observed cfPWV, and predicted PWV ($PWV_{averaged}$) at each tilt angle was reported in Supplementary Figure S1 online.

The age-dependent association of observed-vs.-predicted PWV differences remained significant even after adjustment for sex, body mass index, height, brachial SBP and brachial DBP, or central SBP and central DBP supine values, and related

percentage changes observed with body tilting ($P < 0.05$ in all the models). In a sensitivity analysis, we found similar results after excluding subjects with untreated grade 1 hypertension (R^2 for quadratic trend = 0.22, $P < 0.01$). Casewise diagnostics showed that residuals were normally distributed at every value of the variable predicted from the model.

DISCUSSION

In the present study, we analyzed changes in cfPWV and other hemodynamic parameters induced by variations in body position during passive head-up tilting at 30° and 60° in a cohort of healthy individuals with a broad age range. Head-up tilting represents an ideal setting to gain insight into the relationship between an acute, tilt-related, hydrostatic pressure gradient imposed to the aorta and associated PWV variations, under relatively stable hemodynamic conditions and after minimizing the effect of external factors.

We observed that cfPWV significantly and progressively increases at increasing tilt angles, partly because head-up body tilting influenced HR and DBP, which are known to have significant impact on changes in the viscoelastic properties of the arterial wall.[17] Specifically, DBP changes are linked to PWV variation by an exponential relationship, which does not affect the BP-independent component of arterial stiffness β_0, typically related to structural properties of the arterial wall.[11] Since we could not noninvasively measure DBP at the femoral site, this latter was estimated from the height of the blood column by the sine of the tilt angle and a previously described equation,[14] as reported in equation (2). When cfPWV changes at different tilt angles measured by arterial tonometry were compared with those predicted

based on the exponential pressure–diameter relationship, we found that measured cfPWV was higher than expected particularly in the aging population. Indeed, independently from supine PWV and BP, in young and middle-aged individuals, the predicted PWV change with gravity was very close to the observed PWV change; conversely, in the elderly, the predicted PWV change underestimated the observed PWV change. This original finding was confirmed even after adjusting for tilt-induced HR changes and after accounting for other potential determinants.

Taken together, these results unveil a novel interesting aspect of vascular aging: when exposed to a given pressure gradient, such as it occurs by assuming the upright position, arterial stiffening associated with a given pressure gradient is more pronounced at increasing age. Although speculative, it is plausible that this phenomenon has some relationship with increased pulse pressure, which typically follows the same age-associated distribution. A hydrostatic pressure gradient along the carotid–femoral pathway as it occurs when assuming the upright position, when coupled with stiffer arterial walls, could result in an increase of input impedance which, in turn, increases pressure and flow pulsatility.[18] Therefore, for a given BP gradient, vascular aging resulting in a higher increase in PWV gradient may be associated with an increased risk of organ damage especially for organs located below the heart, such as kidneys and lower limbs.[19]

Previous works evaluated the influence of body posture on aortic stiffness and other hemodynamic parameters. Nürnberger *et al.* found, in a mixed population of healthy individuals and individual with cardiovascular disease, that sitting vs. supine posture induced an increase in DBP and HR, and a nonsignificant trend toward increasing aortic PWV values.[17] Other studies suggested that PWV changes in body position during head-up tilt was associated with hydrostatic BP variations.[20,21] Notwithstanding profound differences in the aim and design of studies, our results are in keeping with these observations. Because neither of these studies reported age-specific results, to the best of our knowledge this is the first demonstration of an age-dependent, nonlinear association between pressure gradient and dynamic stiffness changes. We believe that this finding is of clinical importance, given that it might represent a further mechanism of organ damage related to structural properties of the arterial wall of aorta and large arteries that is not detected when cfPWV measurement is performed with the patient lying supine. Therefore, the clinical role of age-dependent changes in cfPWV in response to a given pressure gradient, as a marker of vascular aging, should receive more attention in future studies.

Other findings should be commented in our study. We provide experimental demonstration of the robust age-dependency of the intrinsic stiffness index β_0. This evidence further reinforces the clinical importance to view to arterial stiffness as the result of a BP-dependent and a BP-independent component, this latter significantly affected by functional and structural properties of the arterial wall. It is noteworthy that, on an individual basis, this parameter allows the evaluation of the BP-dependent component of arterial stiffness when exposed to acute hemodynamic stressors.

We acknowledge that some aspects of our study could limit the validity of our results. First, the sample size is suboptimal to derive definite conclusions. Our population was carefully selected in order to exclude patients with any evidence of disease of potential impact (e.g. autonomic dysfunction). The protocol design was sufficiently rigorous to obtain measures under stable and reproducible conditions, at least at the hypothesis-generating level, suited to be reproduced in larger samples and different clinical contexts. Moreover, no evidence of postural tachycardia or orthostatic hypotension or orthostatic hypertension was noted in our cohort. However, we cannot exclude a priori the possibility of making a type II error, which depends on the sample size. Another limitation is related to the impossibility to rule out the potential interaction effect of venous pooling at different angles during head-up tilting, which could influence the hemodynamic response to orthostatism.[22] We also lacked data about invasive BP as well as other hemodynamic parameters. Finally, when computing (predicting) the expected BP-dependent PWV changes, we assumed an exponential pressure–diameter relationship. Although for physiological pressure ranges this relationship has been shown to be appropriate,[23] in individual cases, this relationship may not exactly capture the pressure–diameter relationship.[10] However, the amount of data available to us precludes the use of more complicated (e.g. Langewouters' or constitutive-based) pressure–diameter relationships to capture PWV's BP dependency.[9,24]

In conclusion, we found that under a hydrostatic pressure gradient, the pulse wave traveling along the aorta undergoes age-related, BP-independent, PWV nonlinear increases. The evaluation of aortic pulse wave acceleration induced by predictable BP gradient may be of clinical relevance as a marker of vascular aging.

SUPPLEMENTARY MATERIAL

FUNDING

DISCLOSURE

The authors declared no conflict of interest.

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