

Pressure-dependence of arterial stiffness: potential clinical implications

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PRESSURE-DEPENDENCE OF ARTERIAL STIFFNESS: POTENTIAL CLINICAL IMPLICATIONS

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ABSTRACT

Background: Arterial stiffness measures such as pulse wave velocity (PWV) have a known dependence on actual blood pressure, requiring consideration in cardiovascular risk assessment and management. Given the impact of ageing on arterial wall structure, the pressure-dependence of PWV may vary with age.

Methods: Using a non-invasive model-based approach, combining carotid artery echo-tracking and tonometry waveforms, we obtained pressure-area curves in 23 hypertensive patients at baseline and after three months of anti-hypertensive treatment. We predicted the follow-up PWV decrease using modelled baseline curves and follow-up pressures. In addition, based on these curves, we estimated PWV values for two age groups (mean ages 41 and 64 yrs) at predefined hypertensive (160/90 mmHg) and normotensive (120/80 mmHg) pressure ranges.

Results: Follow-up measurements showed a near 1 m/s decrease in carotid PWV when compared to baseline, which fully agreed with our model-prediction given the roughly 10 mmHg decrease in diastolic pressure. The stiffness-blood pressure-age pattern was in close agreement with corresponding data from the "Reference Values for Arterial Stiffness' Collaboration" study, linking the physical and empirical bases of our findings.

Conclusion: Our study demonstrates that the innate pressure-dependence of arterial stiffness may have implications for the clinical use of arterial stiffness measurements, both in risk assessment and in treatment monitoring of individual patients. We propose a number of clinically feasible approaches to account for the blood pressure effect on PWV measurements.

Keywords: carotid artery, pulse wave velocity, hypertension, ultrasonography, remodelling

INTRODUCTION

Beyond blood pressure (BP), arterial wall stiffness measurements have emerged as guidance to target arterial wall structure in anti-hypertensive treatment and vascular risk management [1-3]. Although the field is well aware of the fact that arterial wall stiffness is intrinsically pressure dependent [4, 5], a clinically applicable method to disentangle BP and arterial stiffness is currently lacking. As a consequence, the order of magnitude and relevance of the pressure-dependence of stiffness in the clinical context has not been established.

We previously showed by combining carotid artery ultrasound and tonometry, that arterial stiffness, expressed in terms of pulse wave velocity (PWV), may vary about 0.7 – 4.0 m/s within individuals due to the cyclic diastolic-systolic BP variation [6, 7]. These cyclic stiffness changes clearly do not reflect any change in structural wall properties (Fig. 1; along curve A), but do suggest that the contribution of actual BP to the stiffness measurement in clinical practice may be considerable. In this light, the fixed threshold of 10 m/s for increased arterial stiffness, as advocated in the 2013 ESH/ESC guidelines [8], requires a critical approach in (individual) patient management.

From a treatment perspective, the pharmacological modification of arterial wall structure has gained interest, with a particular focus on pressure-independent changes in PWV [9-11]. An exploratory review of the literature shows that significant differences in PWV between groups or changes with treatment are accompanied by significant BP changes [2, 7, 12]. Thus, the extent to which observed changes in stiffness concurrent with BP changes reflect structural alterations in the arterial wall remains to be established [9, 10, 13].

Next to BP, age is the other major factor influencing arterial stiffness, as established by robust meta-analyses [14, 15]. The structural alterations in the arterial wall related to ageing are well-known and clearly reflected by increased stiffness values found in older subjects [11, 16, 17]. We previously observed that the pressure-dependence itself may vary with age [7], which raises the question whether the BP effect on arterial stiffness measurements is as large in young subjects as in elderly (Fig. 1; compare curvature of curves A and B).

In the present study, we obtained more quantitative insight into the abovementioned aspects of the pressure-dependence of arterial stiffness. To this end, we conducted an observational study in a sample of hypertensive subjects consecutively attending our outpatient hypertension clinic.

We obtained non-invasive data on the carotid artery pressure-area relationship at baseline and at 3-month follow-up (Fig. 2A). At baseline, anti-hypertensive medication was discontinued. Shortly after the baseline measurement, anti-hypertensive medication was increased. At both visits, we calculated carotid pulse wave velocity (cPWV, Fig. 2A) using the Bramwell-Hill equation [18]. In addition, baseline measurements were also used to obtain a pressure-area (P-A) curve model. If it is assumed that the P-A curve does not change, follow-up cPWV can be predicted (cPWV_{pred}) using the baseline P-A curve and follow-up blood pressures (Fig. 2A). The feasibility of this assumption was verified by comparing the measured change in cPWV (Δ cPWV) with the predicted change (Δ cPWV_{pred}).

In order to disentangle pressure and age effects on cPWV, we additionally calculated arterial stiffness at *defined* pressure levels for a young as well as an old subgroup of our population. We discuss our quantitative findings from a clinical perspective, focusing on their relevance in the cardiovascular risk management of individual patients.

METHODS

Study population

The study was approved by the ethical committee of Maastricht University and conducted in accordance with the Declaration of Helsinki (Seoul 2008). All subjects provided written informed consent prior to participation. Thirty consecutive subjects were recruited from patients referred to our outpatient hypertension clinic for a two-day clinical assessment. Participants underwent extensive arterial function and hemodynamic measurements (detailed below) at inclusion and at three-months (3.0 ± 0.6 months) follow-up (Fig. 2A). Baseline characteristics and medication profile in units of daily defined dose (DDD, [22]) are shown in Table 1. After baseline measurements, blood pressure was managed according to European Society of Hypertension (ESH) guidelines [8], while treating physicians were blinded for (intermediate) study results. Seven subjects were excluded due to incomplete follow-up data ($n = 3$ no show; $n = 2$ missing carotid ultrasound) or inconsistent data quality ($n = 2$, see Discussion). Baseline and follow-up measurements obtained in 23 patients are used in the present analyses (Fig. B).

Measurements

Arterial function measurements (total duration 30 – 45 min) were performed in a quiet, temperature-controlled room (22 °C) after a resting period of 15 min with subjects in supine position. Throughout the session four to eight repeated oscillometric BP readings were obtained at the left upper arm (Omron 705IT, Omron Healthcare Europe B.V., Hoofddorp, The Netherlands). Additionally, continuous pulsatile finger BP, heart rate (HR) and an estimated cardiac output (CO), were obtained from the right middle finger by the Peñáz method (Nexfin, BMEYE B.V., Amsterdam, The Netherlands) [19].

Left common carotid artery diameter waveforms were obtained using a 7.5 MHz vascular ultrasound scanner (MyLab70, Esaote Europe, Maastricht, the Netherlands) operated at high frame rate as previously described [20]. Diastolic diameter and distension values over 6 consecutive heartbeats and a real-time distension waveform display were used to judge quality of the recordings (^{RF}QAS utility, Esaote Europe). Subsequently, left common carotid artery tonometric pressure waveforms were

obtained (Sphygmocor, AtCor Medical, Sydney, Australia). Raw carotid artery tonometry waveforms were used to obtain calibrated local left common carotid artery BP waveforms [21]. Signal processing was performed using proprietary MATLAB code (MATLAB R2013b, The MathWorks Inc, Natick, Massachusetts, USA). Carotid ultrasound and arterial tonometry measurements were obtained in triplet by a single experienced operator (JOR). Ambulatory (i.e. 24 h) BP was assessed from clinic assessment day one onto day two (Mobil-o-Graph, IEM, Stolberg, Germany).

Data processing

Waveform analysis and data processing

To enable quantitative assessment of the curvilinearity of the carotid artery pressure-area (P-A) relation at individual subject level, we followed procedures similar to those described previously [20]. Briefly, systolic (peak), diastolic (minimum) points were identified in the diameter (by manual cursor reading, using ^{RF}QAS) and pressure (automatic) waveforms. For diameter typically 9 – 12 and for pressure 18 – 30 heartbeats were included for each subject in each session.

To suppress variability related to echo and tonometry tracking artefacts, we applied the following averaging schemes for processing the acquired diameters (D). Diastolic diameter was averaged over acquired beats to obtain a recording average and subsequently over recordings to obtain a session average. Relative distensions (i.e. $[D_{\text{systolic}} - D_{\text{diastolic}}]/D_{\text{diastolic}}$) were averaged over beats and recordings, yielding a session average of relative distension. The session average of systolic diameter was then obtained by multiplying relative distension by the corresponding diastolic diameter and adding the diastolic diameter. Similarly, the relative distensions of the diastolic notch point (i.e. $[D_{\text{notch}} - D_{\text{diastolic}}]/[D_{\text{systolic}} - D_{\text{diastolic}}]$) were averaged for further analysis, rather than absolute diastolic notch values. Exactly the same scheme was applied for carotid systolic, notch and diastolic blood pressures. Median averaging was used throughout.

Reproducibility

Intra-session measurement variability was quantified as follows. Differences of the three ($m = 3$) recording averages with the session mean were calculated for the

entire study group ($n = 23$). The SD of these values from all subjects ($m \cdot n = 3 \cdot 23 = 69$) is a measure of intra-session variability.

Carotid stiffness calculation

Carotid artery cross-sectional areas were calculated at diastole (A_d), dicrotic notch (A_n) and systole (A_s) using $A = \pi \cdot (D/2)^2$. Local carotid PWVs (cPWV) were calculated using the Bramwell-Hill relationship [23]:

$$\text{cPWV} = \sqrt{\frac{1}{\rho} \cdot \frac{\text{SBP} - \text{DBP}}{A_s - A_d} \cdot A_d} \quad (1)$$

with $\rho = 1.050 \text{ kg/L}$ the blood mass density, and SBP and DBP the calibrated local systolic and diastolic carotid blood pressures, respectively.

Pressure-area curve description

In each individual and session, the three (diastolic, notch and systolic) P-A points obtained were used to fit an established mathematical description of the P-A relation, i.e. a single-exponential model [24]:

$$P(A) = \text{DBP} \cdot e^{\gamma \cdot \left(\frac{A}{A_d} - 1\right)} \quad (2)$$

γ is obtained by minimizing the sum-of-squares of differences between measured and modelled notch and systolic pressures. The line is forced through the diastolic point. As a line with one free parameter (γ) is fitted through two points, the line will, in general, not pass *exactly* through the notch and systolic points.

Model prediction of stiffness at follow-up

Based on the above descriptive model (Equation 2) and baseline P-A data, we predicted cPWV at follow-up (cPWV_{pred}), using BP at follow-up as input. This was done under the explicit assumption that between baseline and follow-up the P-A relationship had remained unaltered. To verify whether this assumption was valid, we calculated stiffness for a prescribed, normotensive BP level of 120/80 mmHg by using the modelled P-A curves from baseline and follow-up (cPWV_{mod_{120/80}}).

Stratification according to BP-lowering at follow-up

To investigate whether measured changes in arterial stiffness were related to changes in BP observed in our study population, we stratified patients to a BP-lowered group ($n = 13$) if the reduction in DBP at three-month follow-up was more than twice the intra-session SD (i.e. 7 mmHg) and to a BP-constant control group ($n = 10$) if the reduction was less than 7 mmHg (Fig. 2b).

Stratification of BP-lowering group to age

To identify age-related differences in hemodynamic and stiffness changes, we divided the BP-lowered group into a young group (< 50 yrs, $n = 6$) and an old group (> 50 yrs, $n = 7$) (Fig. 2b).

Age group data averaging and stiffness calculations for comparison with the "Reference Values for Arterial Stiffness' Collaboration"

For both the young BP-lowered group and the old BP-lowered group, we calculated an average P-A relationship by averaging the individual baseline P-A curves in *A*-direction. To enable comparison with reference values from the "Reference Values for Arterial Stiffness' Collaboration" [15], we estimated cPWV values on these average *baseline* P-A curves, similar to described above. We applied pre-defined normotensive (120/80 mmHg; cPWV_{mod}_{120/80} as mentioned above) and hypertensive (160/90 mmHg; cPWV_{mod}_{160/90}) blood pressure profiles for this analysis.

Statistical analysis

Statistical analyses were performed using MATLAB (MATLAB R2013b, The MathWorks Inc, Natick, Massachusetts, USA). Unless otherwise indicated, non-parametric Wilcoxon signed-rank or rank-sum tests were performed to evaluate statistical differences within patients and between groups, respectively. p -values ≤ 0.05 were considered statistically significant. Unless otherwise indicated, values are given as mean \pm SD.

Agreement (bias and limits of agreement) between cPWV and cPWV_{pred} changes at follow-up was assessed by Bland-Altman analysis.

RESULTS

Reproducibility

Intra-session SDs were 2 % for diastolic diameter, 13 % for relative distension, and 7 % for relative notch amplitude. Intra-session SDs (post calibration) were 4 % for local carotid diastolic pressure, 10 % for pulse pressure and 5 % for relative notch amplitude. The absolute intra-session SD for diastolic blood pressure (DBP) was 3.5 mmHg.

Effect of BP-lowering

At baseline, there were no significant differences in patient characteristics, BP, and arterial properties between the BP-lowered and BP-constant groups (Table 2).

Compared to the control group, the BP-lowered group tended to have less anti-hypertensive medication at baseline (0.8 ± 1.2 vs. 1.2 ± 1.9 DDD; Table 2) and had a more intensified regime at three-month follow-up (2.4 ± 1.4 vs. 1.5 ± 1.9 DDD, of which mainly renin-angiotensin-aldosterone system inhibitors: 1.4 ± 1.0 vs. 0.6 ± 0.9 DDD; not shown in table).

The anti-hypertensive treatment particularly decreased SBP, showing a decrease twice that of DBP (Table 2), whilst HR, CO and SV did not change significantly (data not shown).

Carotid stiffness as expressed by pulse wave velocity (cPWV) significantly decreased in the BP-lowered group (Table 2). The change in cPWV, however, was not significantly different between the BP-lowered and BP-constant groups. Model predictions of the change in cPWV at follow-up (cPWV_{pred}) were on the same order of magnitude (-0.9 ± 0.4 m/s) as the measured change (-0.9 ± 1.1 m/s; $p = 0.95$; Fig. 3). Bias and limits of agreement (Bland-Altman) between measured and predicted changes in cPWV were 0.0 ± 2.0 m/s.

Age-associated differences with BP-lowering

Table 3 discriminates baseline BP and arterial properties as well as their changes at follow-up for the young and old subjects with BP-lowering. There were no differences in sex, height, weight or BMI between age-groups. Differences in BP profiles and

carotid cross-sectional area were noted at baseline but these did not reach statistical significance. Baseline values and follow-up changes in DBP and A_d were not significantly different between age groups. The old group tended to have less anti-hypertensive medication at baseline (0.6 ± 1.2 vs. 1.0 ± 1.4 DDD; Table 3) and had a more intensified regime at three-month follow-up (2.6 ± 1.5 vs. 2.2 ± 1.4 DDD, of which mainly renin-angiotensin-aldosterone system inhibitors: 1.7 ± 1.1 vs. 1.0 ± 0.9 DDD; not shown in table).

Both age groups with BP-lowering showed significant reductions in SBP (-21 ± 9 mmHg, $p = 0.03$ and -29 ± 9 mmHg, $p = 0.02$ for < 50 and > 50 yrs, respectively; $p = 0.18$ for inter-group).

Pulse pressure (PP) showed a significant decrease at follow-up in the old group only (-17 ± 7 mmHg, $p = 0.01$; $p = 0.04$ for inter-group difference). Stroke volume (SV) was unchanged (no difference between age groups; data not shown).

Baseline cPWV differed significantly between age groups (Table 3). The measured change in cPWV was significant only in the old, amounting to -1.2 ± 1.0 m/s, and similar to cPWV changes predicted by the patient-specific single-exponential model (cPWV_{pred}; -1.1 ± 0.4 m/s).

Baseline cPWV_{mod_{120/80}} was significantly different between age groups (Table 3). However, changes in cPWV_{mod_{120/80}} at 3-month follow-up were not significant within the age groups and the changes at follow-up were not significantly different between age groups.

Differences in pressure-area relationships between age groups

Figure 4A shows the group-average of the single-exponential P-A curves of the individuals in both the young and old groups. With respect to the young group's curve, the old group's P-A curve is not only shifted rightward to larger areas but is also steeper, reflecting greater stiffness at corresponding to blood pressure levels.

Figure 4A also indicates the normotensive and hypertensive pressure ranges we defined to assess more generically age-related differences in the P-A relationships (shaded areas). We calculated PWVs for these ranges (PWVs indicated in the figure and in Fig. 5A). These group-averaged PWVs suggest that for a given acute

decrease in SBP and DBP of 40 and 10 mmHg respectively, measured arterial stiffness may decrease more in older hypertensive patients (-1.3 m/s; mean age 64 yrs) than in the younger (-0.9 m/s; mean age 41 yrs). These changes are clearly visible in Fig. 4B, where PWV is plotted as a function of DBP.

Comparison with the "Reference Values for Arterial Stiffness' Collaboration"

Figure 5 compares the stiffness-BP-age pattern found in our mechanistic study (a) with those found on statistical grounds in the reference population (b) [15]. Overall, the arterial stiffness patterns are very similar but their pressure-dependence *at a given age* appears greater in the reference population (*between groups*) than *within* our patients. Interestingly, the difference in pressure-dependence, i.e. the influence of the assumed BP change on measured stiffness, is the same for both: $(1.3 - 0.9) = (1.6 - 1.2) = 0.4$ m/s.

DISCUSSION

The present study shows that clinically observable changes in arterial stiffness and BP are linked through the non-linear arterial P-A relationship, the effect of which appears modified with age. Our findings show that a short-term decrease in DBP of about 10 mmHg leads to a decrease in measured PWV of about 1 m/s. This decrease is not caused by a change in the P-A relationship, since we were able to predict this decrease by imputing BP values at follow-up onto the (modelled) P-A curve at baseline. We did observe a difference in the carotid artery P-A relationship between young (41 yrs) and old (64 yrs) subgroups, the old group having greater cross-sectional area and increased stiffness at comparable DBP. Based on these age-stratified P-A data, we estimated generalized PWV values for predefined normotensive (120/80 mmHg) and hypertensive (160/90 mmHg) BP ranges. Our clinical measurements and the generalized data indicate that, for comparable changes in BP, PWV changes more in older subjects due to a higher degree of nonlinearity of the P-A relationship. The resultant stiffness-BP-age pattern proved strikingly similar to the pattern we read from the "Reference Values for Arterial Stiffness' Collaboration" study [15]. These findings indicate that the innate pressure-dependence of arterial stiffness could have implications regarding patient vascular risk stratification and treatment monitoring.

Influence of blood pressure on arterial stiffness measurements

To quantitatively assess the impact of BP level on PWV measurements and corresponding risk scoring, we approached the BP-dependence of stiffness at the individual/small group level, using an established descriptive model [24]. This model was used to derive PWV at well-defined and comparable BP levels, as opposed to a statistical approach. Adjustment for mean arterial pressure in multiple linear regression models is only possible in moderate to large populations [25], whereas our approach allows individual quantification of the BP effect on stiffness.

With our individualized 3-point P-A measurements and model fitting approach, we *predicted* cPWV changes following three months of anti-hypertensive treatment, under the assumption that no real change occurs in the P-A relationship (cPWV_{pred}). The observation that the changes in cPWV and cPWV_{pred} with BP-lowering were of similar magnitude suggests that short-term anti-hypertensive treatment has no effect

on intrinsic arterial wall stiffness, but reduces measured stiffness mainly via the nonlinear P-A relationship (exemplified with curve A; Fig. 1). The hypothesis of no real change in the P-A relationship could not be rejected, as the measured P-A curves at follow-up and their standardized stiffness values ($cPWV_{mod_{120/80}}$) were not significantly different.

The measured 1 m/s PWV decrease exceeds measurement variability, which is typically on the order of 0.5 m/s. Therefore, the pressure-dependence appears relevant when considering fixed cut-off values to triage individual patients based on PWV measurements. As such, our study specifically links part of the uncertainty in PWV determinations to actual BP levels, which is an issue both in initial risk stratification and in monitoring treatment effects.

It is well known that the white-coat effect can cause office BPs to show higher values than a patient's actual BP as measured using ambulatory BP measurement. We assessed the effect of this artificially elevated measured BP on the measured arterial stiffness in the office (Supplemental Digital Content 1). Our analysis of the white-coat effect on arterial stiffness measurements showed a similar 1 m/s difference in stiffness linked to a 10 mmHg difference between mean ambulatory and study DBP.

Taken together, our quantitative findings indicate that the (physically well-established) pressure-dependence is relevant to consider in initial risk assessment and in monitoring treatment in individual patients.

Influence of ageing on arterial stiffness and its pressure dependence

Based on the stratification to age and on modelled P-A data, we consistently found a larger dependence of PWV on BP in older subjects than in younger. This difference with age is directly related to the steeper slope of the P-A relation, as notable from the modelled curves in Fig. 4. Our analysis based on predefined BP ranges (Fig. 5) further supports the notion of an age-related difference in pressure-dependence and that this observation is not a by-effect of the differing BP (ranges) between age groups. Rather, the intrinsically different P-A relationship explains the age-related difference in elastic behaviour. In addition to the increased slope, a greater average cross-sectional area with age is evident from our data (Fig. 4), which is in line with ex-vivo data [26]. It should however be noted, given discrepant observations in cross-

sectional cohorts [26, 27], that longitudinal data on changes in arterial structure with ageing are much needed. Both the stiffening (increase in slope) and dilatory (increase in mean area) aspects are biomechanically consistent with the established concept of age-related degradation of the elastin structure in the wall and the resulting transfer of mechanical stress to the stiffer collagen network [11, 17, 28].

Stiffness, blood pressure and age as a pattern

We found that the (modelled) within-age-group changes in stiffness with BP-lowering match well with the stiffness-BP-age pattern observed in the reference values population (Fig. 5). This match existed despite the obvious methodological differences, such as physical/statistical approach, number of subjects, intra-/inter-subject comparison, carotid/aortic measurements and stiffness calculations, and outpatients/population characteristics. This prompts critical consideration of the pressure-dependence of stiffness measurements as advocated in clinical-epidemiological research [15, 29, 30] and practice guidelines [8, 31].

Our study provides a physical underpinning of the epidemiological stiffness-BP-age data pattern, implying that at given age a considerable part of the arterial stiffness spread in the population may be simply explained by the non-linear elastic behaviour of arteries, having not so much to do with adaptive hypertrophy or hypertensive remodelling [32, 33]. The structural remodelling that does occur with ageing (Fig. 4) appears to accentuate the BP-related arterial stiffness spread in the older population [15].

In current clinical practice, treatment of hypertension is predominantly focussed on lowering blood pressure and much less on arterial wall stiffening as a potential cause for hypertension. However, current (2013) ESH guidelines [8] do state a PWV above 10 m/s as an additional risk factor. Our study shows that, if the BP effect is not accounted for, consideration of arterial stiffness (as quantified by PWV) in risk scoring may introduce a spurious double scoring of high BP [8]. In this regard, our findings suggest that the arterial stiffness of patient A with a PWV of 9 m/s and diastolic BP of 70 mmHg may be considered equivalent to that of patient B with respective readings of 11 m/s and 90 mmHg. Hence, it may not be justified physically to score patient B +1 for increased arterial stiffness (cf. Table 4 in [8]).

The agreement between reference values data and our findings in clinical patients suggests that risk stratification on the basis of combined BP-age cut-off values would do more justice to the physical and practical aspects of arterial stiffness measurements. Alternative approaches to improve risk stratification would be (1) to use the individual patient's P-A data and calculate from a modelled curve the stiffness value at a fixed or normative (e.g. age-specific) BP level or, as a thumb-rule, or (2) to adjust PWV values for concurrently measured DBP at a rate of 1 m/s per 10 mmHg.

Limitations

Our study did not include a long-term follow-up. Therefore, we could not evaluate whether on the long-term the P-A relationship was modified by the anti-hypertensive treatment, as a sign of structural (re-)remodelling. Moreover, our observational study design and number of subjects do not allow a well-powered drug-specific analysis. In future studies, both short- and long-term follow-up measurements should be performed to be able to fully discriminate and quantify the pressure-dependent and -independent effects of (anti-hypertensive) drugs on arterial wall structure [2, 9, 10, 13].

We found zero bias between measured and predicted changes in cPWV. The limits of agreement, however, were substantial. With our sample size we could have detected a significant difference of > 0.8 m/s at a power of 80%. A large part of the variability is explained by the fact that the measured changes in cPWV were subject to variability in both pressure and area measurements, whereas the model-predicted changes were only subject to variability in pressure.

Our study was set up as an observational study in consecutive patients, which, given non-compliance with the protocol ($n = 3$) and missing data ($n = 2$), led to basic exclusion of subjects (see Study population). Additionally, two subjects were excluded. One subject showed a convex P-A relationship at one visit, which is physically not plausible and very likely a measurement error. In the other subject, we did not obtain sufficiently stable pressure and area waveforms due to vessel movement.

We calculated PWV values not from transit time based measurements but from distensibility based on P-A data (Fig. 1). Cross-sectional arterial distensibility is physically related to PWV via the Bramwell-Hill relationship [23]. This approach is required, because transit time PWV measurement does not allow discrimination of stiffness within the diastolic-systolic range, to which the non-invasive assessment of large artery stiffness is practically limited to. Moreover, our aim was to get a feeling of the order of magnitude of the pressure dependence, not to establish absolute agreement between the two approaches.

It should be stressed that our 3-point P-A approach is not affected by apparent hysteresis caused by phase errors or time-delays between pressure and area waveform signals [6], given that we only consider corresponding P and A amplitudes. Hysteresis due to viscous behaviour of the arterial wall in-vivo using a well-characterized measurement set-up is negligible [7, 34].

Our measurements included carotid artery applanation tonometry, which requires substantial applied pressure to appanate the vessel. Consequently, baroreflex modulation may have potentially affected hemodynamic conditions. Using the continuous finger blood pressure and HR data acquired (Nexfin device), we tested whether HR and relative dicrotic notch height (in the finger pressure waveform) were different between carotid (potential baroreflex effect) and femoral (no baroreflex effect) tonometry recordings. Three repeated and alternating carotid and femoral tonometry acquisitions were performed in all subjects ($n = 23$). We found no difference in HR (62.5 bpm carotid vs. 63.1 bpm femoral, $p = 0.24$) and no difference in relative dicrotic notch height (0.39 carotid vs. 0.38 femoral, $p = 0.24$). Moreover, the tonometric pressure waveform was calibrated to absolute values using session-averaged brachial blood pressures, hence potential baroreflex-mediated noise or bias in mean or pulse pressure during tonometry will not have propagated into our P-A data. Taken together, it appears unlikely that the tonometry measurements in our study affected proper correspondence between P and A datapoints.

We approached ageing by cross-sectional data. Ideally, ageing effects should be assessed longitudinally, following patients over time, as for example in the recently published study by AlGhatrif et al [35]. Unfortunately, AlGhatrif et al. did not include information on the BP change between baseline and follow-up, i.e. only BP category

at baseline was used as a statistical model determinant. Additionally, the question can be asked whether our small study in hypertensives is sufficiently powered and representative. While our stiffness-BP-age pattern agrees well with the reference values data as well as with current mechanistic concepts of arterial wall elastic behaviour and remodelling, we conclude that there is strong mechanistic and epidemiological evidence corroborating our present findings [5, 11, 15-17, 26].

Perspectives

We conclude that short-term changes in arterial stiffness (in PWV terms) concurrent with BP-lowering can be deemed BP-dependent, at a rate of about 1 m/s per 10 mmHg DBP. We also found that this pressure-dependence appears greater in older subjects, which is consistent with changes in the arterial pressure-area relationship due to age-related structural remodelling. Both these BP and age influences are responsible for the clinical and epidemiological patterns observed between stiffness (PWV), BP and age. While current treatment of hypertension is focussed on lowering BP, ESH guidelines (2013) include the option to score a PWV above 10 m/s as an additional risk factor. Based on the physically underpinned insights that our study yields, combined BP-age specific PWV thresholds seem more justified for use in vascular risk management than the current absolute threshold of 10 m/s. Our non-invasive model-based methodology is feasible in a vascular clinic setting and could improve identification of treatment effects on arterial wall structure, by discriminating BP-dependent and -independent changes in arterial wall elastic properties.

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FIGURE LEGENDS

Figure 1. Study scope: quantitative influences of blood pressure and age on measured stiffness. Given a curvilinear pressure-area (P-A) relationship, short term changes in pressure will directly lead to changes in cross-sectional area and incremental slope (as indicated for curve A). The related changes in pulse wave velocity (PWV) in this case are *not* due to a change in the P-A relationship (cf. point 1 vs. 2). The stiffness assessed at the same pressure level in a remodelled vessel, illustrated by curve B, will be different due to a real change in the P-A relationship, as is known to occur with e.g. ageing (cf. point 1 vs. 3). Then ageing is expected to also modulate the pressure-related change in measured stiffness (consider the difference between 1 vs. 2 and 3 vs. 4). ρ , blood mass density.

Figure 2. *A:* Study set-up. At baseline, subjects had discontinued anti-hypertensive (anti-HT) medication, which was increased directly after the baseline visit. During both baseline and follow-up visits, carotid artery tonometry and ultrasound (US) wall tracking were used to obtain a local pressure-area (P-A) relationship of the carotid artery wall. From the P-A relationship, carotid pulse wave velocity (cPWV) was calculated using the Bramwell-Hill relationship. The change in measured cPWV from baseline to follow-up is termed $\Delta cPWV$. The baseline P-A curve of each subject was modelled by an exponential function. Using this baseline model and follow-up blood pressures, the change in cPWV with respect to baseline could be predicted ($\Delta cPWV_{pred}$), assuming that the P-A relationship did not change between baseline and follow-up. *B:* Subject stratification for analyses of blood pressure (BP) and age effects on measured stiffness. BP-constant, subjects which did not show a decreased diastolic blood pressure at follow-up. BP-lowered, subjects that did show a decrease in diastolic blood pressure of at least 7 mmHg. Young, subjects < 50 yrs; Old, subjects > 50 yrs.

Figure 3. Measured (meas) carotid artery stiffness (carotid pulse wave velocity, cPWV; Bramwell-Hill) in the blood pressure-lowered group ($n = 13$) at baseline and at follow-up, in comparison with predicted (pred) changes based on follow-up blood pressures and using the single exponential model fitted to individual pressure-area data obtained at baseline.

Figure 4. *A:* Comparison of the young and old groups' pressure-area relationships. Note that the old group operates at a greater average cross-sectional area than the young group. To study the stiffness-pressure- age relationship more generically, we pre-defined normotensive and hypertensive blood pressure ranges, as indicated by the shaded areas. Pulse wave velocities for these ranges are indicated in the figure, and replicated in Fig. 5A. *B:* Pressure-dependence of pulse wave velocity. Pulse wave velocities for normotensive and hypertensive groups in *A* as a function of diastolic blood pressure. Systolic and diastolic pressures are indicated in the figure as systolic/diastolic blood pressure. Note that in the old group, the pulse wave velocity increase with diastolic blood pressure is larger than in the young group (steeper slope of the lines).

Figure 5. Arterial stiffness, blood pressure and age patterns of the present study and the "Reference Values for Arterial Stiffness' Collaboration" are strikingly similar. Stiffness, as indicated by pulse wave velocity (PWV) is shown for the mean ages of the two age groups in the present study (baseline visit) and pre-defined normotensive (120/80 mmHg) and hypertensive (160/90 mmHg) pressure ranges. Δ : difference in PWV between hypertensive and normotensive conditions. *A:* Carotid artery PWV values derived from the modelled pressure-area curves ($cPWV_{mod_{120/80}}$ and $cPWV_{mod_{160/90}}$) via Bramwell-Hill for young and old groups. *B:* Carotid-femoral PWVs derived from published data from the "Reference Values for Arterial Stiffness' Collaboration" ([15]: Fig. 4, bottom and Table 6, bottom; PWVs linearly interpolated between age categories and at corresponding mean arterial pressures ($MAP = 0.4 \cdot SBP + 0.6 \cdot DBP$), i.e. hypertensive 118 and normotensive 96 mmHg). DBP, diastolic blood pressure; SBP, systolic blood pressure.

TABLES

Table 1. Baseline characteristics of study population

	<i>n</i>	23	
age yrs	56	±	15
sex	11m	/	12f
height cm	172	±	8
BMI kg/m ²	27	±	4
aSBP mmHg	140	±	15 ⁺
aDBP mmHg	91	±	11 ⁺
aHR 1/min	73	±	9 ⁺
dipper	8y	/	14n ⁺

	<i>n</i> [*]	DDD [*]	
anti-HT meds	9	2.6	± 1.6
ACEi/ARB	7	2.0	± 0.5
BB	7	0.6	± 0.3
CCB	1	2.0	
diuretics	5	0.7	± 0.3

Mean ± SD. aSBP and aDBP, 24h-average systolic and diastolic blood pressure; aHR, 24h-average heart rate. dipper defined as night SBP < 85 % of day SBP. ⁺*n* = 22.

*Numbers (*n*) and daily defined doses (DDD) pertain to only those receiving medication at baseline. Most of those not taking anti-hypertensive (anti-HT) drugs at baseline had discontinued medication prior to clinical blood pressure profiling. ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta blockers; CCB, calcium channel blockers.

Table 2. Changes in blood pressure and arterial properties without and with blood pressure-lowering

	all subjects			
	baseline		change at three-month follow-up	
	BP-constant	BP-lowered	BP-constant	BP-lowered
<i>n</i>	10	13	10	13
age yrs	59 ± 17	53 ± 14		
meds DDD	1.2 ± 1.9	0.8 ± 1.2	0.3 ± 0.6	1.6 ± 0.8 ^{*,‡}
SBP mmHg	154 ± 24	163 ± 29	1 ± 14	-25 ± 10 ^{*,‡}
DBP mmHg	87 ± 10	94 ± 9	1 ± 5	-12 ± 6 ^{*,‡}
PP mmHg	67 ± 22	69 ± 29	-0 ± 13	-13 ± 9 ^{*,‡}
cPWV m/s	10.8 ± 2.3	10.7 ± 3.1	0.1 ± 1.5	-0.9 ± 1.1 [*]
cPWVpred m/s			0.1 ± 0.4	-0.9 ± 0.4 ^{*,‡}

Mean ± SD. meds denotes antihypertensive medication in daily defined dose (DDD);

^{*}denotes $p < 0.05$ for change at follow-up compared to baseline (Wilcoxon signed-

rank test); [‡]denotes $p < 0.05$ for difference between BP-constant and BP-lowered

groups (Wilcoxon rank-sum test). Sex differences were not statistically significant

($p = 0.21$, Fisher's exact test). BP, blood pressure; meds, anti-hypertensive

medication; SBP and DBP, systolic and diastolic blood pressures; PP, pulse pressure;

cPWV, carotid pulse wave velocity; cPWVpred, cPWV predicted from the baseline

pressure-area model curve and follow-up BP.

Table 3. Blood pressure lowering-related changes in arterial properties in younger and older patients

	BP-lowered patients			
	baseline		change at three-month follow-up	
	age <50 yrs	age >50 yrs	age <50 yrs	age >50 yrs
<i>n</i>	6	7	6	7
age yrs	41 ± 6	64 ± 9 [‡]		
meds DDD	1.0 ± 1.4	0.6 ± 1.1	1.2 ± 0.8	2.0 ± 0.7*
SBP mmHg	149 ± 17	174 ± 34	-21 ± 9*	-29 ± 9*
DBP mmHg	95 ± 12	92 ± 4	-13 ± 4*	-12 ± 8*
PP mmHg	54 ± 14	82 ± 33	-8 ± 9	-17 ± 7* [‡]
<i>A_d</i> mm ²	46.3 ± 9.0	58.5 ± 16.7	-1.5 ± 0.9	-2.9 ± 5.5
cPWV m/s	8.4 ± 1.2	12.7 ± 2.9 [‡]	-0.5 ± 1.1	-1.2 ± 1.0*
cPWVpred m/s			-0.7 ± 0.3*	-1.1 ± 0.4*
cPWVmod _{120/80} m/s	7.4 ± 1.0	11.0 ± 2.1 [‡]	0.2 ± 0.9	-0.2 ± 1.0

Mean ± SD. meds denotes antihypertensive medication in daily defined dose (DDD);

*denotes $p < 0.05$ for change (Wilcoxon signed-rank test); [‡]denotes $p < 0.05$ for difference between age groups (Wilcoxon rank-sum test). Sex differences were not statistically significant ($p = 0.59$, Fisher's exact test). BP, blood pressure; BMI, body mass index; meds, anti-hypertensive medication; SBP and DBP, systolic and diastolic blood pressures; PP, pulse pressure; *A_d*, diastolic cross-sectional area; cPWV, carotid pulse wave velocity; cPWVpred, cPWV predicted from baseline *P-A* relationship and follow-up blood pressures; cPWVmod_{120/80}, cPWV calculated for standardized BP of 120/80 mmHg.

FIGURES

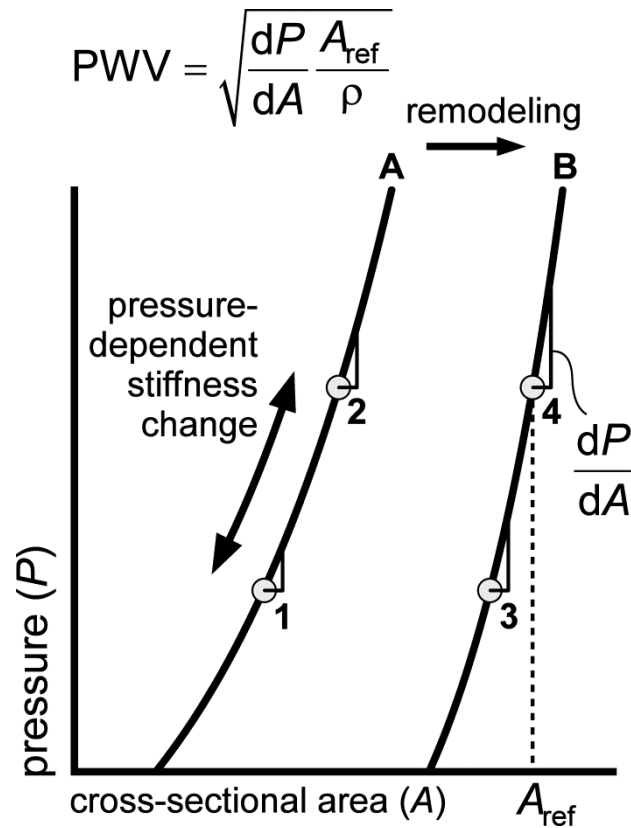


Figure 1. Study scope: quantitative influences of blood pressure and age on measured stiffness. Given a curvilinear pressure-area (P-A) relationship, short term changes in pressure will directly lead to changes in cross-sectional area and incremental slope (as indicated for curve A). The related changes in pulse wave velocity (PWV) in this case are *not* due to a change in the P-A relationship (cf. point 1 vs. 2). The stiffness assessed at the same pressure level in a remodelled vessel, illustrated by curve B, will be different due to a real change in the P-A relationship, as is known to occur with e.g. ageing (cf. point 1 vs. 3). Then ageing is expected to also modulate the pressure-related change in measured stiffness (consider the difference between 1 vs. 2 and 3 vs. 4). ρ , blood mass density.

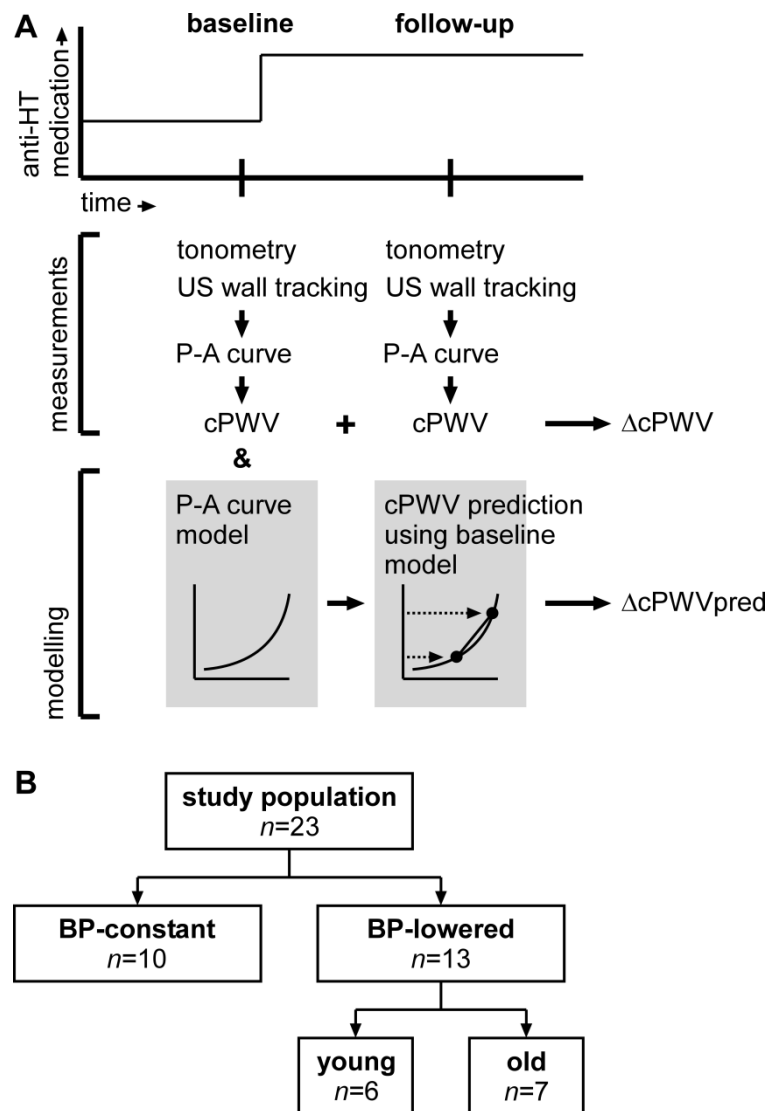


Figure 2. Study set-up and derivation of measured and predicted changes in carotid stiffness. *A:* The change in measured carotid pulse wave velocity (cPWV) from baseline to follow-up is termed ΔcPWV . The baseline pressure-area (P-A) curve of each subject was modelled by an exponential function. Using this baseline model and follow-up blood pressures, the change in cPWV with respect to baseline could be predicted ($\Delta\text{cPWV}_{\text{pred}}$), assuming that the P-A relationship did not change between baseline and follow-up. *B:* Stratification for analyses of blood pressure (BP) and age effects on measured stiffness. Young, subjects < 50 yrs; Old, subjects > 50 yrs; US, ultrasound.

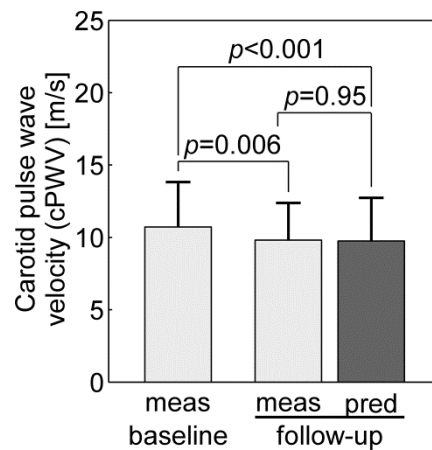


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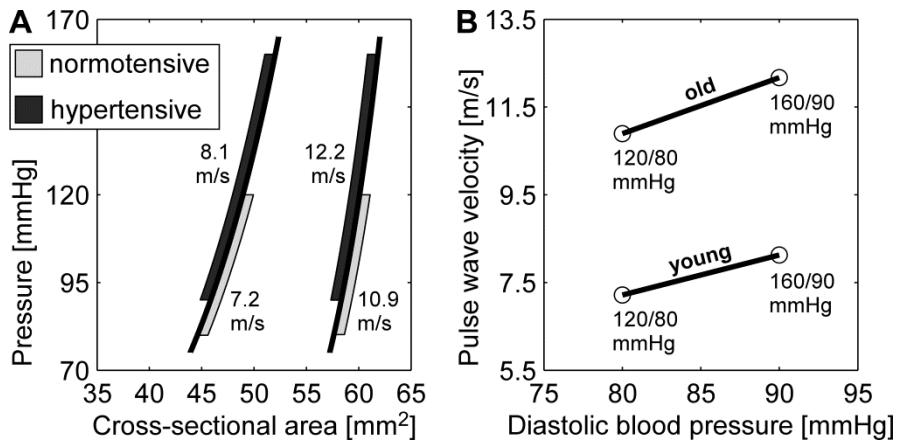


Figure 4. Relationship between age, blood pressure, and pulse wave velocity. *A*: Comparison of the young and old groups' pressure-area relationships. Note that the old group operates at a greater average cross-sectional area than the young group. To study the stiffness-pressure- age relationship more generically, we pre-defined normotensive and hypertensive blood pressure ranges, as indicated by the shaded areas. Pulse wave velocities for these ranges are indicated in the figure, and replicated in Fig. 5A. *B*: Pressure-dependence of pulse wave velocity. Pulse wave velocities for normotensive and hypertensive groups in *A* as a function of diastolic blood pressure. Systolic and diastolic pressures are indicated in the figure as systolic/diastolic blood pressure. Note that in the old group, the pulse wave velocity increase with diastolic blood pressure is larger than in the young group (steeper slope of the lines).

A This study				B The "Reference Values for Arterial Stiffness' Collaboration"					
Estimated pulse wave velocities for predefined pressure ranges [m/s]				Pulse wave velocity [m/s]					
		Age [yrs]				Age [yrs]			
		41	64			41	64		
SBP/DBP [mmHg]	120/80	7.2	10.9	SBP/DBP [mmHg]	120/80	7.1	10.0		
	160/90	8.1	12.2		160/90	8.4	11.5		
		Δ	0.9	1.3			Δ	1.2	1.6

- Intra-subject
- Physical relationship
- 13 subjects

- Inter-subject
- Statistical association
- 11 092 subjects

Figure 5. Arterial stiffness, blood pressure and age patterns of the present study and the "Reference Values for Arterial Stiffness' Collaboration" are strikingly similar. Stiffness, as indicated by pulse wave velocity (PWV) is shown for the mean ages of the two age groups in the present study (baseline visit) and pre-defined normotensive (120/80 mmHg) and hypertensive (160/90 mmHg) pressure ranges. Δ : difference in PWV between hypertensive and normotensive conditions. *A*: Carotid artery PWV values derived from the modelled pressure-area curves ($cPWV_{mod_{120/80}}$ and $cPWV_{mod_{160/90}}$) via Bramwell-Hill for young and old groups. *B*: Carotid-femoral PWVs derived from published data from the "Reference Values for Arterial Stiffness' Collaboration" ([15]: Fig. 4, bottom and Table 6, bottom; PWVs linearly interpolated between age categories and at corresponding mean arterial pressures ($MAP = 0.4 \cdot SBP + 0.6 \cdot DBP$), i.e. hypertensive 118 and normotensive 96 mmHg). DBP, diastolic blood pressure; SBP, systolic blood pressure.

LIST OF SUPPLEMENTAL DIGITAL CONTENT

Supplemental Digital Content 1. Potential white-coat effect on arterial stiffness measurements. pdf