Associations and clinical relevance of aortic-brachial artery stiffness mismatch, aortic reservoir function, and central pressure augmentation

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Abstract

Central augmentation pressure (AP) and index (AIx) predict cardiovascular events and mortality, but underlying physiological mechanisms remain disputed. While traditionally believed to relate to wave reflections arising from proximal arterial impedance (and stiffness) mismatching, recent evidence suggests aortic reservoir function may be a more dominant contributor to AP and AIx. Our aim was therefore to determine relationships among aortic-brachial stiffness mismatching, AP, AIx, aortic reservoir function, and end-organ disease. Aortic (aPWV) and brachial (bPWV) pulse wave velocity were measured in 359 individuals (aged 61 ± 9, 49% male). Central AP, AIx, and aortic reservoir indexes were derived from radial tonometry. Participants were stratified by positive (bPWV > aPWV), negligible (bPWV $\approx$ aPWV), or negative stiffness mismatch (bPWV < aPWV). Left-ventricular mass index (LVMI) was measured by two-dimensional-echocardiography. Central AP and AIx were higher with negative stiffness mismatch vs. negligible or positive stiffness mismatch (11 ± 6 vs. 10 ± 6 vs. 8 ± 6 mmHg, $P < 0.001$ and 24 ± 10 vs. 24 ± 11 vs. $21 \pm 13\%$, $P = 0.042$). Stiffness mismatch (bPWV -aPWV) was negatively associated with AP ($r = -0.18$, $P = 0.001$) but not AIx ($r = -0.06$, $P = 0.27$). Aortic reservoir pressure strongly correlated to AP ($r = 0.81$, $P < 0.001$) and AIx ($r = 0.62$, $P < 0.001$) independent of age, sex, heart rate, mean arterial pressure, and height (standardized $\beta = 0.61$ and 0.12, P 0.001). Aortic reservoir pressure independently predicted abnormal LVMI ($\beta = 0.13$, $P = 0.024$). Positive aortic-brachial stiffness mismatch does not result in higher AP or AIx. Aortic reservoir function, rather than discrete wave reflection from proximal arterial stiffness mismatching, provides a better model description of AP and AIx and also has clinical relevance as evidenced by an independent association of aortic reservoir pressure with LVMI.

Blood pressure (BP) waveform indexes including augmentation pressure (AP) and augmentation index (AIx) are independently associated with premature coronary artery disease, cardiovascular events, and all-cause mortality (39, 41). It is of clinical importance to understand the physiological mechanisms underpinning elevations in AP and AIx so that appropriate therapeutic strategies may be developed. A widely held viewpoint is that aortic (central) AP and AIx can be explained by the magnitude and timing of reflected waves that arise from central-to-peripheral arterial impedance mismatching in elastic arteries (27). In accordance with this idea, comparatively stiffer peripheral arterial segments in relation to central arterial segments should equate to a high-positive stiffness mismatch, large positive wave reflection from the periphery (i.e., reflection that increases pressure and decreases flow), and an elevation in central AP and AIx (27). However, a recent study has found that a negative stiffness gradient (i.e., an increased ratio of aortic-brachial arterial stiffness) independently predicts poor cardiovascular outcomes in high risk patients undergoing dialysis (13). Given the potential importance of arterial stiffness mismatch to clinical outcomes (13) and to changes in AP and AIx (27), further investigation of the complex underlying physiology is needed.

Many wave-related interpretations of the circulation are based on a single elastic tube or asymmetric T -tube model (28, 44). However, this is an oversimplification, and Tyberg et al. (37) have recently advocated that envisaging the aorta and large elastic arteries as a "reservoir" through which waves travel may be a better (simple) model. Parameters derived from this model have been demonstrated to predict adverse cardiovascular outcomes (10), and recent data show that when the reservoir function of the human aorta is considered, the contribution of discrete wave reflection to central BP augmentation is substantially reduced (8). Indeed, growing evidence suggests major determinants of central BP waveform morphology may be proximal aortic compliance and forward compression waves arising from left ventricular (LV) ejection (5, 8, 9, 12, 30, 31, 33, 34, 36, 40).

The aim of this study was to determine the relationship of aortic-brachial stiffness mismatch (representing an impedance mismatch) with AP, AIx, and aortic reservoir pressure. We proposed two alternative hypotheses: 1) the magnitude of central AP and AIx would correlate with degree of positive stiffness mismatching between the aorta and brachial artery or 2) that central AP and AIx would better correlate with aortic reservoir pressure. We also sought to determine the clinical relevance of stiffness mismatch, AP, AIx, and aortic reservoir pressure by association with end organ disease assessed by LV mass index (LVMI) and estimated glomerular filtration rate (eGFR).

MATERIALS AND METHODS

Participants

This study consisted of 359 participants with or without hypertension who were otherwise healthy and at low to moderate cardiovascular risk. Data were analyzed from the baseline examination of participants from two clinical trials in which hemodynamics were recorded using the same methods (www.anzctr.org.au; identifiers: ACTRN12609000835246 and ACTRN12608000041358). The principal results and study inclusion criteria have been reported previously (15, 35). Briefly, participants were included if aged 18 to 75 yr; were

either receiving antihypertensive therapy (1 but 3 medications) for uncomplicated hypertension; or were not taking medication but had a hypertensive response to exercise (defined as an exercise systolic BP 210 mmHg for males, 190 mmHg for females, or a diastolic BP 110 mmHg for both males and females). Exclusion criteria were uncontrolled hypertension, clinical history of coronary artery or renal disease, pregnancy, and aortic valve stenosis. The studies were approved by local research ethics committees, each participant signed written informed consent, and study procedures were carried out in accordance with the Declaration of Helsinki. For this current analysis, only data from participants with measures of both aortic pulse wave velocity (aPWV) and brachial pulse wave velocity (bPWV) at baseline were included as these data were required to estimate stiffness mismatch.

Protocol

All participants attended clinics in the morning for hemodynamic assessments using the same protocol. The clinic rooms were temperature controlled, and each participant was in a postabsorptive state, at least 3 h clear of food and caffeine, and was asked not to complete heavy exercise in the preceding 24 h. Sequential measurements of brachial BP and central BP (via radial tonometry) were taken in the seated posture followed by sequential measurements of supine aPWV and bPWV and finally echocardiography. Medical history was recorded via questionnaires, and blood and urine specimens were collected for biochemical analysis. Data were analyzed post hoc to derive aortic-brachial stiffness mismatch and reservoir characteristics.

Aortic and brachial artery stiffness

Regional artery stiffness was assessed via sequential electrocardiogram gated carotid-to-femoral aPWV and carotid-to-radial bPWV (SphygmoCor 8.1; AtCor Medical, Sydney, Australia). Participants were instrumented in the supine posture and then observed following a further minimum 5 min of supine rest. Adhering to consensus guidelines (21), duplicate measurements of aortic and brachial PWV were then made sequentially, with the final measures completed after at least 8–10 min of rest. These PWV values were averaged for use in analysis.

Aortic-brachial stiffness mismatch

Representing a model of impedance mismatch we considered the stiffness of the aortic arterial segment relative to the stiffness of the brachial arterial segment. To create the stiffness mismatch variable, aPWV was subtracted from bPWV. A comparatively stiffer brachial artery in relation to the aorta constituted a positive stiffness mismatch (i.e., positive impedance mismatch), a comparatively stiffer aorta in relation to the brachial artery constituted a negative stiffness mismatch (i.e., negative impedance mismatch), and if the stiffness of the aorta and brachial arteries was similar, this constituted a negligible stiffness mismatch (i.e., matched impedance). To reflect this, the continuous stiffness mismatch variable was dichotomized into three groups (evenly distributed tertiles); a positive stiffness mismatch group (where bPWV > aPWV), a negligible stiffness mismatch group (where bPWV $\approx$ aPWV), and a negative stiffness mismatch group (where bPWV < aPWV).

Blood pressure

Brachial BP was measured according to clinical recommendations (22) using standard sphygmomanometer or validated automated oscillometric device (Omron HEM-907, Hoofddorp, The Netherlands) (11). Participants were instrumented in the seated posture before observing a minimum of five min of seated rest. Duplicate measurements were then made and repeated between 8 and 10 min following undisturbed rest. The average of these final two readings was used as the systolic and diastolic BP for analysis.

Central hemodynamics

Radial applanation tonometry was performed on all participants and a validated (4) generalized transfer function was applied to generate central pressure waveforms, calibrated with brachial systolic and diastolic BP (SphygmoCor 8.1; AtCor Medical). There is a strong relationship between directly recorded radial AIx and transfer function-derived central AIx (i.e., r = 0.96) (25). All measurements were performed in the seated position following a minimum of 5-min rest. Central systolic and diastolic BPs were taken as the maximum (peak) and minimum (foot) of the central pressure waveform, respectively. Mean arterial pressure (MAP) was calculated via integration of radial pressure waveform by the Sphygmocor software. Central pulse pressure (CPP) was calculated as the difference between central systolic BP and central diastolic BP, with peripheral pulse pressure (PPP) calculated as the difference between brachial systolic BP and diastolic BP. AP was calculated from the central BP waveform as the pressure difference between the first (P1) and second (P2) systolic peaks and expressed as a percentage value of the CPP to define the central AIx. Pulse pressure (PP) amplification was calculated as the difference between CPP and PPP and expressed as a ratio by dividing PPP by CPP. Apparent arrival time of the reflected wave in the aorta [aortic wave timing (Tr)] was calculated as the time from the foot of the waveform to onset of P1. Tension-time index (TTI) was calculated as the integral of the central BP waveform during systole from the foot of the waveform to the incisura at end systole. Diastolic pressure-time integral (DPTI) was calculated as the integral of the central BP waveform during diastole from the incisura to end diastole. The subendocardial viability ratio (SEVR; a correlate of subendocardial perfusion) was calculated as the ratio DPTI/TTI × 100.

Aortic reservoir and excess pressure

Reservoir pressure was calculated as previously described in the online supplement to Davies et al. (10) from radial pressure waveforms acquired at the radial artery by applanation tonometry (without application of a generalized transfer function). Waveforms were calibrated with brachial systolic and diastolic BP before being ensemble averaged and exported to a customized Matlab (Mathworks, Natick, MA) program. Reservoir pressure was derived based on pressure alone (1), using Eq. 1, where a and b are the rate constants of the system (where $a = \gamma$ and $b = 1$), P is measured total pressure, P is reservoir pressure, and $P\infty$ is the pressure at which outflow from the reservoir ceases. Excess pressure was defined as the difference between total (measured) pressure and the reservoir pressure. All values of reservoir and excess pressure are represented as integrals (area under the pressure waveforms) in mmHg·s with diastolic BP subtracted.

$$\frac{\mathrm{d}\overline{P}}{\mathrm{d}t} = a\left(P - \overline{P}\right) - b\left(\overline{P} - P_{\infty}\right)$$

LVMI and systemic hemodynamics

Two-dimensional echocardiography using an iE33 ultrasound system (Philips Electronics, Amsterdam, The Netherlands) was used to measure LVMI as per the Devereux method (indexed to body surface area; g/m^2) according to the American Society of Echocardiography guidelines (20). Participants were stratified according to normal or mildly abnormal LVMI as per guidelines (20), with the cut points of 96 g m^2 for females and 116 g m^2 for males considered to be abnormal. Cardiac output (l/min) was derived by the product of stroke volume and heart rate. Both stroke volume (SVi; ml/m2) and cardiac output (COi; l·min^{-1}·m^{-2}) were indexed to body surface area. Systemic vascular resistance (SVR; mmHg·min·l–1) was calculated as MAP cardiac output.

Blood biochemistry and eGFR

Fasting blood samples were taken for analysis of standard blood biochemistry following accredited laboratory techniques at local hospital pathology services. Serum creatinine (μmol/l) was measured and eGFR (ml·min^{-1}·1.73 m^{-2}) was subsequently calculated using the Modification of Diet in Renal Disease formula.

Statistical analysis

All statistical analysis was performed using IBM SPSS Statistics for Windows (version 20.0; SPSS, Chicago, IL). Continuous variables were compared between stiffness mismatch groups via one-way ANOVA (with Bonferroni post hoc correction for multiple comparisons), and categorical variables were compared by χ^2-tests. Analysis of covariance was also performed to adjust for age and sex. Correlates of AP and AIx were assessed by linear regression. Sex interaction terms were also calculated for stiffness mismatch and aortic reservoir pressure to determine if sex modified associations with AP and AIx. Five multiple linear regression models (detailed in the results and see Table 3) to predict AP and AIx were constructed using the enter method, with only significant univariable predictors progressively entered into models. Colinearity was assessed by the tolerance statistic, with only those variables >0.1 included. We chose to present standardized beta coefficients given the significant heterogeneity in units of measure for each variable. The dependant variables of AP and AIx, along with all covariates entered into regression models were considered to be normally distributed (from visual inspection of data distributions and linearity of Q-Q distribution plots) and thus did not require transformation. Multivariable regression models were also constructed to assess hemodynamic predictors of LVMI and eGFR. P< 0.05 was considered statistically significant.

RESULTS

Clinical characteristics

The clinical characteristics of the study population are outlined within Table 1. Those with positive stiffness mismatch were predominantly male, younger, taller, and had a greater body surface area compared with those with negligible or negative stiffness mismatch. Individuals with positive stiffness mismatch also had significantly lower aPWV but higher bPWV and stiffness mismatch compared with those with negligible or negative stiffness mismatch.

Significantly greater proportions of individuals in the negative stiffness mismatch group had hypertension and were receiving antihypertensive treatment than those with negligible or positive stiffness mismatch. There was no significant difference in LVMI between stiffness mismatch groups. Those with a positive stiffness mismatch had improved (higher) eGFR compared with those with negligible or negative stiffness mismatch.

Hemodynamic differences between types of stiffness mismatch

All hemodynamic data are outlined within Table 2. Central AP and AIx were both lower in the positive stiffness mismatch group compared with the negligible and negative stiffness mismatch groups. However, the reservoir pressure integral was significantly higher in the negative stiffness mismatch individuals. Differences in AP, AIx, and reservoir pressure between groups became nonsignificant after adjustment for age and sex. Those with positive stiffness mismatch also had significantly lower brachial and central systolic BP, central PP, and heart rate with or without adjustment for age compared with those with negative or negligible stiffness mismatch. Cardiac output was significantly lower in those with positive stiffness mismatch compared with negative stiffness mismatch group, and this reached statistical significance following adjustment for age and sex. TTI was higher in those with a negative stiffness mismatch, while the SEVR was higher in those with a positive stiffness mismatch with or without adjustment for age and sex.

Correlates of augmentation pressure

Stiffness mismatch was negatively associated with AP (r = −0.18, P = 0.001; Fig. 1A). Conversely, reservoir pressure was a strong positive correlate of AP (r = 0.81, P < 0.001; Fig. 1B). There was no significant sex × stiffness mismatch or sex × aortic reservoir pressure interaction effects on AP (β = 0.12, P = 0.11 and β = −0.06, P = 0.53, respectively). Other correlates of AP included age (r = 0.36, P < 0.001), heart rate (r = −0.45, P < 0.001), SV (r = 0.46, P < 0.001), MAP (r = 0.21, P < 0.001), height (r = −0.47, P < 0.001), and aPWV (r = 0.13, P = 0.012).

All univariable correlates of AP remained independently associated with AP in multivariable linear regression (Table 3, Augmentation Pressure), except for aPWV [which became nonsignificant after inclusion of one (or more) of any of the other univariable correlates of AP in the regression model] and stiffness mismatch (following addition of sex and age in model 3). Aortic reservoir pressure remained the strongest correlate of AP in all regression models, including the full model (Table 3, Augmentation Pressure, model 5), which

contained age, sex, heart rate, MAP, and height as covariates. Further adding the clinical variables of hypertension and antihypertensive medication to model 5 did not change the independent association of aortic reservoir pressure to AP (β = 0.61, P < 0.001).

Correlates of augmentation index

Stiffness mismatch was not significantly associated with AIx (r = −0.06, P = 0.27; Fig. 2A). onversely, reservoir pressure was a strong positive correlate of AIx (r = 0.62, P < 0.001; Fig. 2B). There was no significant sex × stiffness mismatch interaction effects on AIx (β = 0.012, P = 0.87), but the sex × aortic reservoir pressure interaction was significant (β = 0.35, P = 0.003). Other correlates of AIx included age (r = 0.30, P < 0.001), heart rate (r = −0.43, P < 0.001), SV (r = 0.46, P < 0.001), MAP (r = 0.14, P = 0.007), and height (r = −0.52, P < 0.001). aPWV was not associated with AIx (r = 0.003, P = 0.95).

All univariable correlates of AIx remained independently associated with AIx in multivariable linear regression (Table 3, Augmentation Index). Inclusion of stiffness mismatch and aPWV did not improve the model (Table 3, Augmentation Index, models 1 and 2), and although aortic reservoir pressure remained a significant correlate of AIx in the full regression model (Table 3, Augmentation Index, model 5), the variables of age, sex, heart rate, MAP, and height appeared to make larger contributions to explaining the variance in AIx. Further adding the clinical variables of hypertension and use of antihypertensive medication to model 5 did not change the independent association of aortic reservoir pressure to AIx (β = 0.22, P < 0.001).

Associations with left ventricular structure

Stiffness mismatch was not associated with LVMI (r = 0.04, P = 0.448). However, aortic reservoir pressure was positively associated with LVMI (r = 0.14, P = 0.011). Other univariable correlates of LVMI included sex (r = 0.30, P < 0.001), AIx (r = −0.12, P = 0.025), heart rate (r = −0.23, P < 0.001), SV (r = −0.14, P = 0.015), SV (r = 0.29, P < 0.001), and CO (r = 0.15, P = 0.008). Upon construction of separate multivariable regression models including the univariable correlates of LVMI, aortic reservoir pressure (β = 0.22, P < 0.001), heart rate (β = −0.21, P < 0.001), and SV (β = 0.22, P < 0.001) predicted LVMI in separate models that also contained age and sex as covariates. Aortic reservoir pressure was also significantly higher in those with abnormal LVMI (11% of the population) independent of age and sex (aortic reservoir pressure; normal LVMI, 12 ± 4 mmHg·s vs. abnormal LVMI, 13 ± 5 mmHg·s, β = 0.13, P = 0.024). Stiffness mismatch was not significantly different in those with abnormal LVMI compared with those with a normal LVMI with or without adjustment for age and sex (normal LVMI, −0.09 ± 2.00 m s vs. abnormal LVMI, −1.11 ± 2.17 m s, adjusted β = −0.04, P = 0.49).

Data expectations according to wave-reflection theory

The hemodynamic and end organ disease results of this study were compared with theoretical expectations according to a simple elastic tube wave-reflection model of the arterial system, and these data are presented in Table 4. With a positive aortic-brachial stiffness mismatch, all hemodynamic variables (AP, AIx, reservoir pressure, excess pressure, SV, SVR, central systolic BP, central PP, Tr, SEVR, TTI, and DPTI) and markers

of end organ damage (LVMI and eGFR) were conflicting with the expectations of wave-reflection theory.

DISCUSSION

This study revealed several novel findings. 1) A positive stiffness mismatch between central and peripheral arteries was not associated with higher AP or AIx. This is fundamentally the opposite of expectations associated with a wave-reflection model of central BP augmentation, where reflections are proposed to arise from impedance mismatching in elastic arteries. 2) Aortic reservoir pressure was a strong predictor of central AP and AIx independent of stiffness mismatching and large artery stiffness. 3) Aortic reservoir pressure was independently related to end organ damage as determined by increased LVMI. Taken all together, the prevailing conclusion is that aortic reservoir characteristics provide a better simple model description of central pressure waveform morphology than conventional wave theory and that aortic reservoir pressure has clinical relevance to organs affected by hypertension.

Wave reflection and central BP augmentation

The design of the arterial tree dictates that as waves propagate away from the heart towards the periphery they must cross sites of impedance mismatch. These include arterial bifurcations, anatomical arterial tapering, and stiffness alterations. The exact location of impedance mismatch sites is contentious (38, 42), with some data suggesting a proximal location within large elastic arteries that moves distally with age and elevation in aPWV (26), with others suggesting more distal locations (e.g., the peripheral arterioles), whereby impedance sites move proximally with age resulting in reduced wave-reflection timing (27). Nonetheless, simplistic wave-only models contend that part of the incident propagating wave energy crossing these sites will be reflected proximally, ultimately influencing the shape of the pressure waveform in the aorta (i.e., augmentation) (27).

Established ideas suggest wave reflection may result from stiffness mismatching, such that with a positive stiffness mismatch, a reflected wave associated with a rise in pressure and a fall in flow will return to increase aortic BP. However, in the current study we found no physiological evidence to support the view of high intensity wave reflection within the large arteries, because despite a comparatively stiffer brachial artery in relation to the aorta, there was no elevation in AP or AIx. A positive stiffness mismatch did not predict AIx in any univariable or multivariable model (Table 3) and was negatively associated with AP (the opposite of expectation according to wave-reflection theory). While we cannot exclude a role for immeasurable small reflections from more distal sites, these data suggest that it is unlikely that large reflected waves returning from sites in the large elastic arteries substantially contribute to augment central BP. Although we had a predominance of type A and type B (positive AIx), others have also reported significant deficiencies in AIx as a marker of wave reflection in type C waveforms (where AIx is negative) (17). Our findings are further supported by recent in-human wave intensity analysis studies, which indicate that backward compression waves do not increase commensurate with acute elevations in central BP following exercise and pharmacological stress (12, 31). Moreover, it has been

demonstrated by independent research groups (performing experiments decades apart) that despite an absolute peripheral reflection site generated by arterial occlusion, there is no marked increase in aortic reflected wave intensity, magnitude, or central BP augmentation (2, 19, 43). The most probable explanation for this is that reflected waves generated at peripheral sites become dispersed or trapped in peripheral arterial beds and never return with enough power to discernibly augment BP in the proximal aorta (7, 16).

Wave-reflection timing is also said to reduce as the aorta stiffens with age and disease, moving from diastole (where it contributes to bolster coronary perfusion pressure and minimize LV load) into systole, reducing coronary perfusion pressure, increasing LV afterload, and augmenting central systolic BP. Our data again conflict with this notion, since we observed a contradictory rise in Tr (aortic wave timing) and in DPTI (the area under the diastolic pressure curve that corresponds to coronary perfusion pressure/time) among participants with a negative, negligible, and positive stiffness mismatch respectively. On the one hand, this may have been expected since the time of arrival of wave reflection never occurs within diastole (3, 34), and there is little reduction in reflected wave timing as central BP increases (with age) (3). On the other hand, since aortic stiffness was significantly higher in the negative stiffness mismatch group, our results allude to a fundamental dissociation between aortic stiffness, wave-reflection magnitude, timing, and central BP augmentation.

Aortic stiffness, reservoir function, and central BP augmentation

The dependency of BP on arterial stiffness has been well explored in large epidemiological datasets (24, 26, 32). In the young, the peripheral muscular arteries may be stiffer than the elastic aorta. This creates an impedance mismatch that is hypothesized to protect peripheral organs from pulsatile stress (26), with wave reflection dominating any rise in central BP augmentation in youth (24). Although our data support the former statement regarding organ protection (since eGFR was relatively higher in the presence of a positive stiffness mismatch), AP and AIx were not raised despite positive stiffness mismatch. With aging, the central-peripheral artery stiffness gradient changes as aortic stiffness increases at a rate greater than that within the peripheral arteries (24, 26). Thus, in an impedance-matched system (caused primarily by elevations in aortic stiffness), there may be greater forward propagation of pulsatile stress, which could contribute to target organ damage (26), with the increase in central BP augmentation attributed to the greater rise in aortic stiffness. Indeed, a negative stiffness gradient between the aorta and brachial arteries (i.e., stiffer aorta compared with brachial artery) was recently shown to predict mortality in dialysis patients (13). In our study, aortic stiffness (aPWV) was not an independent predictor of AP or AIx. These findings are in keeping with other noninvasive human studies that show large artery stiffness is not closely correlated with AIx (6, 18). Further placed in context with the recent finding that age-related increases in aPWV do not parallel increases in systolic BP and PP in men beyond the age of 40 yr (32), it is unlikely that raised aortic stiffness is the sole contributor to elevations in central BP augmentation either.

An alternative view to describe arterial hemodynamic is the reservoir-excess pressure hypothesis. Derived from this model, the aortic reservoir pressure was strongly and independently associated with AP, AIx, and LVMI in our study and may make a large

contribution to the shape of the central BP waveform beyond wave reflection and local stiffness properties of the aorta. Indeed, aortic reservoir pressure probably equates to the instantaneous volume of blood stored within the proximal aorta (30, 40) and encompasses several important physiological components. During systole, there is a flow-in or "charging" of the reservoir that is dependent on LV ejection characteristics, on the local compliance properties of the aorta, and on the downstream impedance. During diastole, blood is "discharged" from the reservoir at a rate dependent on the SVR. Therefore, reservoir pressure will rise with increasing aortic stiffness and/or when the resistance to outflow is heightened. Our data support this model description of central BP augmentation, since in the negative stiffness mismatch group when aPWV was high, so too was the reservoir pressure. Moreover, SVR was positively associated with AP and AIx as well as aortic reservoir pressure. Beyond the reservoir pressure, the remaining contributor to the shape of the pressure waveform is the excess pressure. Representing excess LV work (29), the excess pressure envelope is highly correlated with aortic flow-velocity (40) and contributes to aortic pressure in early systole (30). Recent evidence shows that the integral of the excess pressure predicts cardiovascular events and mortality independent of traditional risk factors (10). The independent relationship between LVMI and aortic reservoir pressure, taken together with data showing that aortic reservoir pressure predicts cardiovascular events in high-risk individuals (to the same extent as wave-reflection indexes) (14), suggests that consideration of the reservoir-excess pressure model not only provides a better description of the shape of the central pressure waveform but may also have important clinical ramifications.

Limitations

Our study population were of middle-to-older age and most were undergoing treatment for hypertension. Although this means our results may not be applicable to younger, healthy, or other population groups, our data contained wide ranging stiffness mismatch, waveform type, and augmentation values. Moreover, inclusion of age and hypertension in our regression models did not change the associations among stiffness mismatch, aortic reservoir pressure and central BP augmentation. Furthermore, we did not have simultaneous measures of pressure and flow velocity in the aorta and were therefore unable to perform a separation of waves into their forward and backward components nor directly quantify wave-reflection magnitude. We applied a generalized transfer function to derive central BP parameters and, in the absence of invasively measured aortic pressure, cannot be certain of the accuracy of this method. However, aortic reservoir pressure was derived directly from the radial pressure waveform (without application of a transfer function), and central AIx is a pressure-independent variable that would not be affected by calibration issues associated with noninvasively deriving central BP. Adhering to clinical/consensus guidelines (21, 22), measures of brachial and central BP (and thus AP and AIx) were taken while seated, whereas measures of PWV (and thus stiffness mismatch) were taken while supine. These postural differences may have altered some cardiovascular variables (i.e., AIx) due to autonomic functional changes. However, this is not expected to have significantly influenced the results since the absolute values of AIx differ between seated and supine postures by only ~1% (24).

Conclusions

Although the prognostic value of wave reflection is recognized (23), our study provides persuasive evidence that central AP and AIx should not be regarded as markers of wave reflection. Reservoir pressure indexes intuitively and physiologically provide an explanation for central pressure waveform morphology and are associated to end organ damage. Since recent clinical trial data highlight the strong and independent prognostic value of reservoir pressure indexes in the prediction of cardiovascular events and mortality (10, 14), consideration of this simple model of arterial hemodynamics may provide important new and clinically relevant understanding of BP physiology.

Acknowledgments

REFERENCES

1. Aguado-Sierra J, Hadjilizou N, Davies JE, Francis D, Mayet J, Parker KH. Pressure reservoir-wave separation applied to the coronary arterial data. Conf Proc IEEE Eng Med Biol Soc. 2007; 2007:2693–2696. [PubMed: 18002550]

2. Baksi AJ, Davies JE, Hadjiloizou N, Unsworth B, Baruah R, Foale RA, Parker KH, Francis DP, Mayet J, Hughes AD. Does behaviour of the reflected wave in humans support the prevailing explanation of the arterial pressure waveform? Artery Res. 2009; 2:156.

3. Baksi AJ, Treibel TA, Davies JE, Hadjiloizou N, Foale RA, Parker KH, Francis DP, Mayet J, Hughes AD. A meta-analysis of the mechanism of blood pressure change with aging. J Am Coll Cardiol. 2009; 54:2087–2092. [PubMed: 19926018]

4. Chen CH, Nevo E, Fetics B, Pak PH, Yin FC, Maughan WL, Kass DA. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. Circulation. 1997; 95:1827–1836. [PubMed: 9107170]

5. Cheng K, Cameron JD, Tung M, Mottram PM, Meredith IT, Hope SA. Association of left ventricular motion and central augmentation index in healthy young men. J Hypertens. 2012; 30:2395–2402. [PubMed: 23041752]

6. Climie RE, Nikolic SB, Otahal P, Keith LJ, Sharman JE. Augmentation index and arterial stiffness in patients with type 2 diabetes mellitus. Artery Res. 2013; 7:194–200.

7. Davies JE, Alastruey J, Francis DP, Hadjiloizou N, Whinnett ZI, Manisty CH, Aguado-Sierra J, Willson K, Foale RA, Malik IS, Hughes AD, Parker KH, Mayet J. Attenuation of wave reflection by wave entrapment creates a "horizon effect" in the human aorta. Hypertension. 2012; 60:778–785. [PubMed: 22802223]

8. Davies JE, Baksi J, Francis DP, Hadjiloizou N, Whinnett ZI, Manisty CH, Aguado-Sierra J, Foale RA, Malik IS, Tyberg JV, Parker KH, Mayet J, Hughes AD. The arterial reservoir pressure increases with aging and is the major determinant of the aortic augmentation index. Am J Physiol Heart Circ Physiol. 2010; 298:H580–H586. [PubMed: 20008272]

9. Davies JE, Hadjiloizou N, Leibovich D, Malaweera A, Alastruey-Arimon J, Whinnett ZI, Manisty CH, Francis DP, Aguado-Sierra J, Foale RA, Malik IS, Parker KH, Mayet J, Hughes AD. Importance of the aortic reservoir in determining the shape of the arterial pressure waveform–the forgotten lessons of Frank. Artery Res. 2007; 1:40–45.

10. Davies JE, Lacy P, Tillin T, Collier D, Cruickshank JK, Francis DP, Malaweera A, Mayet J, Stanton A, Williams B, Parker KH, McG Thom SA, Hughes AD. Excess pressure integral predicts cardiovascular events independent of other risk factors in the conduit artery functional evaluation substudy of Anglo-Scandinavian Cardiac Outcomes Trial. Hypertension. 2014; 64:60–68. [PubMed: 24821941]

11. El Assaad MA, Topouchian JA, Darne BM, Asmar RG. Validation of the Omron HEM-907 device for blood pressure measurement. Blood Press Monit. 2002; 7:237–241. [PubMed: 12198340]

12. Fok H, Guilcher A, Li Y, Brett S, Shah A, Clapp B, Chowienczyk P. Augmentation pressure is influenced by ventricular contractility/relaxation dynamics: novel mechanism of reduction of pulse pressure by nitrates. Hypertension. 2014; 63:1050–1055. [PubMed: 24516104]

13. Fortier C, Mac-Way F, Desmeules S, Marquis K, De Serres SA, Lebel M, Boutouyrie P, Agharazii M. Aortic-brachial stiffness mismatch and mortality in dialysis population. Hypertension. 2015; 65:378–384. [PubMed: 25452473]

14. Hametner B, Wassertheurer S, Hughes AD, Parker KH, Weber T, Eber B. Reservoir and excess pressures predict cardiovascular events in high-risk patients. Int J Cardiol. 2014; 171:31–36. [PubMed: 24315153]

15. Hare JL, Sharman JE, Leano R, Jenkins C, Wright L, Marwick TH. Impact of spironolactone on vascular, myocardial, and functional parameters in untreated patients with a hypertensive response to exercise. Am J Hypertens. 2013; 26:691–699. [PubMed: 23412930]

16. Hope SA, Tay DB, Meredith IT, Cameron JD. Waveform dispersion, not reflection, may be the major determinant of aortic pressure wave morphology. Am J Physiol Heart Circ Physiol. 2005; 289:H2497–H2502. [PubMed: 16024572]

17. Hughes AD, Park C, Davies J, Francis D, McG Thom SA, Mayet J, Parker KH. Limitations of augmentation index in the assessment of wave reflection in normotensive healthy individuals. PLoS One. 2013; 8:e59371. [PubMed: 23544061]

18. Kelly RP, Millasseau SC, Ritter JM, Chowienczyk PJ. Vasoactive drugs influence aortic augmentation index independently of pulse-wave velocity in healthy men. Hypertension. 2001; 37:1429–1433. [PubMed: 11408390]

19. Khir AW, Parker KH. Wave intensity in the ascending aorta: effects of arterial occlusion. J Biomech. 2005; 38:647–655. [PubMed: 15713284]

20. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005; 18:1440–1463. [PubMed: 16376782]

21. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006; 27:2588–2605. [PubMed: 17000623]

22. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Burnier M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Tsioufis C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Ferrari R, Hasdai D, Hoes AW, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Gillebert TC, Rosei EA, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Ryden L, Sirenko Y, Stanton A, Struijker-Boudier H, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the

European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013; 34:2159–2219. [PubMed: 23771844]

23. Manisty C, Mayet J, Tapp RJ, Parker KH, Sever P, Poulter NH, Thom SA, Hughes AD. Wave reflection predicts cardiovascular events in hypertensive individuals independent of blood pressure and other cardiovascular risk factors: an ASCOT (Anglo-Scandinavian Cardiac Outcome Trial) substudy. J Am Coll Cardiol. 2010; 56:24–30. [PubMed: 20620713]

24. McEniery CM, Yasmin Hall IR, Qasem A, Wilkinson IB, Cockcroft JR. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). J Am Coll Cardiol. 2005; 46:1753–1760. [PubMed: 16256881]

25. Millasseau SC, Patel SJ, Redwood SR, Ritter JM, Chowienczyk PJ. Pressure wave reflection assessed from the peripheral pulse: is a transfer function necessary? Hypertension. 2003; 41:1016–1020. [PubMed: 12695415]

26. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension. 2004; 43:1239–1245. [PubMed: 15123572]

27. Nichols, WW.; O'Rourke, MF. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. Hodder Arnold; London: 2005.

28. O'Rourke MF. Pressure and flow waves in systemic arteries and the anatomical design of the arterial system. J Appl Physiol. 1967; 23:139–149. [PubMed: 5340142]

29. Parker KH, Alastruey J, Stan GB. Arterial reservoir-excess pressure and ventricular work. Med Biol Eng Comput. 2012; 50:419–424. [PubMed: 22367750]

30. Schultz MG, Davies JE, Hardikar A, Pitt S, Moraldo M, Dhutia N, Hughes AD, Sharman JE. Aortic reservoir pressure corresponds to cyclic changes in aortic volume: physiological validation in humans. Arterioscler Thromb Vasc Biol. 2014; 34:1597–1603. [PubMed: 24812322]

31. Schultz MG, Davies JE, Roberts-Thomson P, Black JA, Hughes AD, Sharman JE. Exercise central (aortic) blood pressure is predominantly driven by forward traveling waves, not wave reflection. Hypertension. 2013; 62:175–182. [PubMed: 23716581]

32. Scuteri A, Morrell CH, Orru M, Strait JB, Tarasov KV, Ferreli LA, Loi F, Pilia MG, Delitala A, Spurgeon H, Najjar SS, AlGhatrif M, Lakatta EG. Longitudinal perspective on the conundrum of central arterial stiffness, blood pressure, and aging. Hypertension. 2014; 64:1219–1227. [PubMed: 25225210]

33. Segers P, Rietzschel ER, De Buyzere ML, Vermeersch SJ, De Bacquer D, Van Bortel LM, De Backer G, Gillebert TC, Verdonck PR. Noninvasive (input) impedance, pulse wave velocity, and wave reflection in healthy middle-aged men and women. Hypertension. 2007; 49:1248–1255. [PubMed: 17404183]

34. Sharman JE, Davies JE, Jenkins C, Marwick TH. Augmentation index, left ventricular contractility, and wave reflection. Hypertension. 2009; 54:1099–1105. [PubMed: 19720955]

35. Sharman JE, Marwick TH, Gilroy D, Otahal P, Abhayaratna WP, Stowasser M. Randomized trial of guiding hypertension management using central aortic blood pressure compared with best-practice care: principal findings of the BP GUIDE Study. Hypertension. 2013; 62:1138–1145. [PubMed: 24060891]

36. Torjesen AA, Wang N, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS, Mitchell GF. Forward and backward wave morphology and central pressure augmentation in men and women in the Framingham Heart Study. Hypertension. 2014; 64:259–265. [PubMed: 24866142]

37. Tyberg JV, Bouwmeester JC, Parker KH, Shrive NG, Wang JJ. The case for the reservoir-wave approach. Int J Cardiol. 2014; 172:299–306. [PubMed: 24485224]

38. Tyberg JV, Bouwmeester JC, Shrive NG, Wang JJ. CrossTalk opposing view: Forward and backward pressure waves in the arterial system do not represent reality. J Physiol. 2013; 591:1171–1173. discussion 1175. [PubMed: 23457374]

39. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta- analysis. Eur Heart J. 2010; 31:1865–1871. [PubMed: 20197424]

40. Wang JJ, O'Brien AB, Shrive NG, Parker KH, Tyberg JV. Time-domain representation of ventricular-arterial coupling as a windkessel and wave system. Am J Physiol Heart Circ Physiol. 2003; 284:H1358–H1368. [PubMed: 12531729]

41. Weber T, Auer J, O'Rourke MF, Kvas E, Lassnig E, Berent R, Eber B. Arterial stiffness, wave reflections, and the risk of coronary artery disease. Circulation. 2004; 109:184–189. [PubMed: 14662706]

42. Westerhof BE, van den Wijngaard JP, Murgo JP, Westerhof N. Location of a reflection site is elusive: consequences for the calculation of aortic pulse wave velocity. Hypertension. 2008; 52:478–483. [PubMed: 18695144]

43. Westerhof N, Sipkema P, van den Bos GC, Elzinga G. Forward and backward waves in the arterial system. Cardiovasc Res. 1972; 6:648–656. [PubMed: 4656472]

44. Westerhof N, Westerhof BE. CrossTalk proposal: Forward and backward pressure waves in the arterial system do represent reality. J Physiol. 2013; 591:1167–1169. discussion 1177. [PubMed: 23457373]

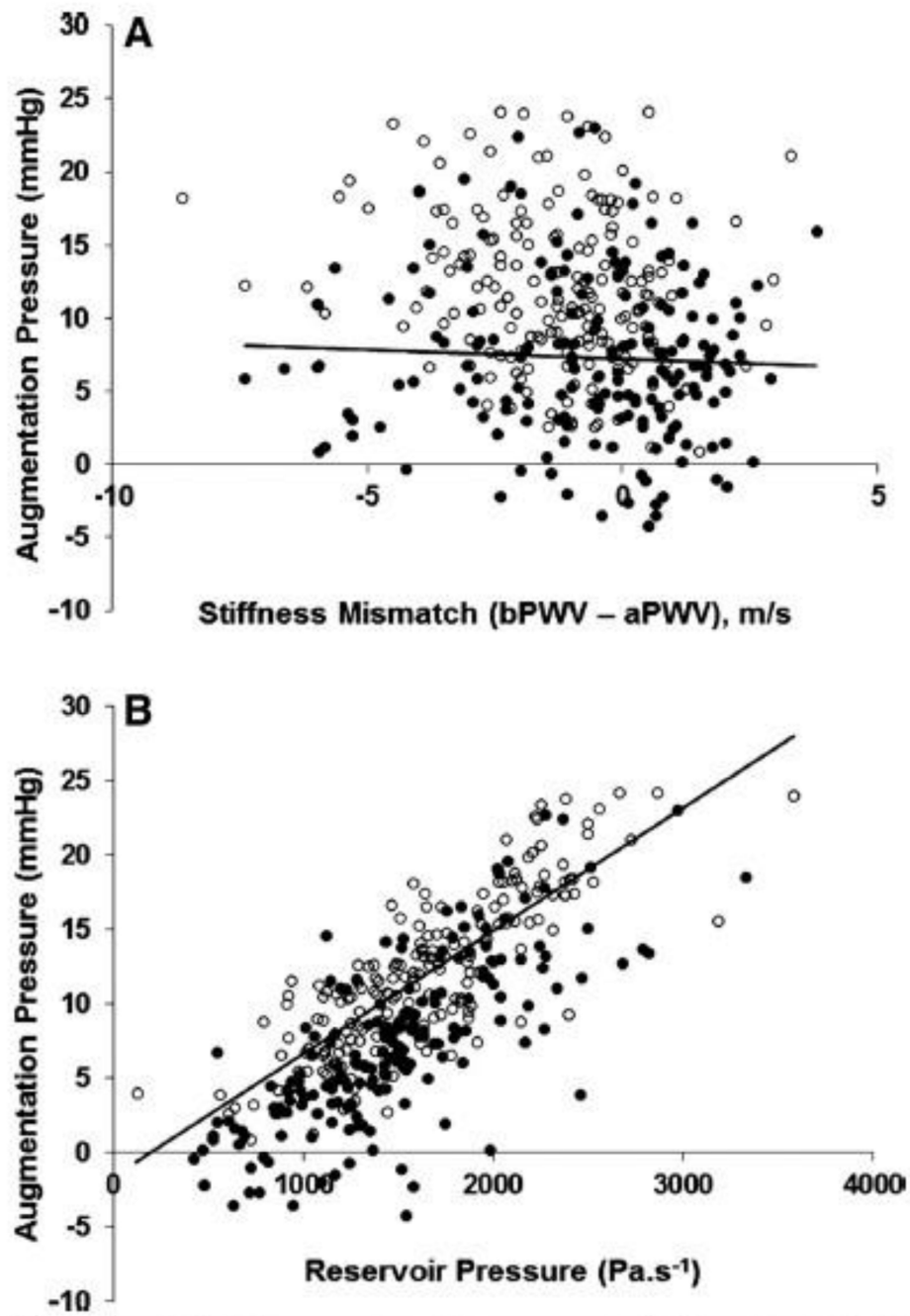**Fig. 1.**
Associations between augmentation pressure and stiffness mismatch (*A*) and reservoir pressure (*B*); ●, males; ○, females. Linear trend lines are pooled sex associations ($n = 359$), where $r = -0.18$, $P = 0.001$ for *A* and $r = 0.81$, $P < 0.001$ for *B*, respectively. aPWV and bPWV, aortic and brachial pulse wave velocity.
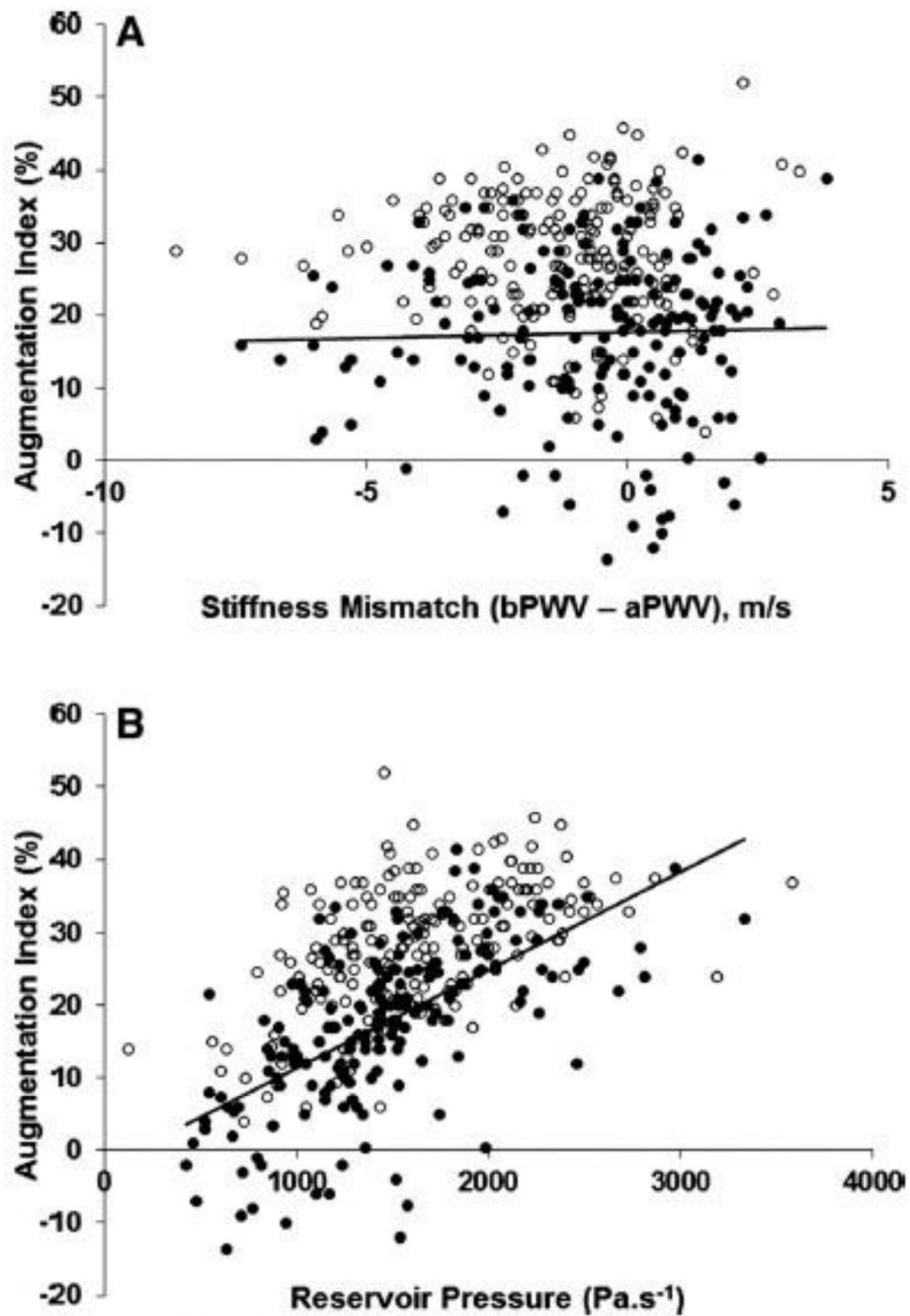
Fig. 2.
Associations between augmentation index and stiffness mismatch (*A*) and reservoir pressure (*B*); ●, males; ○, females. Linear trend lines are pooled sex associations ($n = 359$), where $r = -0.06$, $P = 0.31$ for *A* and $r = 0.62$, $P < 0.001$ for *B*, respectively.

Table 1

Clinical characteristics of the study population stratified by type of stiffness mismatch

	Negative Stiffness Mismatch (bPWV < aPWV) (*n* = 118)	Negligible Stiffness Mismatch (bPWV ≈ aPWV) (*n* = 123)	Positive Stiffness Mismatch (bPWV > aPWV) (*n* = 118)	*P* Value
Age, yr	66 ± 8	61 ± 8[*]	56 ± 10[*†]	<0.001
Male sex, *n* (%)	47 (40)	51 (42)	79 (67)	<0.001
Body mass index, kg/m^2	29.7 ± 5.0	29.2 ± 3.9	28.7 ± 4.6	0.208
Body surface area, m^2	1.9 ± 0.3	1.9 ± 0.3	2.0 ± 0.2[*]	0.016
Height, cm	167 ± 10	168 ± 9	173 ± 9[*†]	<0.001
HDL cholesterol, mmol/l	1.4 ± 0.5	1.4 ± 0.4	1.3 ± 0.4	0.171
LDL cholesterol, mmol/l	2.9 ± 0.9	3.2 ± 1.0[*]	3.2 ± 0.8	0.023
Triglycerides, mmol/l	1.6 ± 0.9	1.8 ± 1.4	1.5 ± 1.0	0.143
Plasma glucose, mmol/l	5.7 ± 1.5	5.8 ± 2.0	5.4 ± 0.8	0.077
LV mass index, g/m^2	85.3 ± 16.0	82.8 ± 14.9	87.3 ± 19.9	0.154
eGFR, ml·min^{-1}·1.73 m^{-2}	65.9 ± 33.4	70.3 ± 34.5	89.0 ± 35.7[*†]	<0.001
Aortic PWV, m/s	11.1 ± 2.0	8.6 ± 1.2[*]	7.4 ± 1.0[*†]	<0.001
Brachial PWV, m/s	7.8 ± 1.2	7.9 ± 1.1	8.5 ± 1.0[*†]	<0.001
Stiffness mismatch, m/s	−3.3 ± 1.4	−0.7 ± 0.5[*]	1.0 ± 0.8[*†]	<0.001
Hypertension, *n* (%)	100 (85)	91 (74)	64 (54)	<0.001
Type 2 diabetes mellitus, *n* (%)	10 (9)	12 (10)	5 (4)	0.225
Antihypertensive agent, *n* (%)	100 (85)	92 (74)	65 (54)	<0.001
Lipid modifying agent, *n* (%)	37 (31)	33 (27)	23 (20)	0.108

Data are means ± SD or *n* (%). BP, blood pressure; aPWV and bPWV, aortic and brachial pulse wave velocity PWV; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; LV, left ventricular. Hypertension was defined as office brachial BP values 140/90 mmHg. *P* value represents significance of overall one-way ANOVA.

[*] *P* < 0.05 vs. negative stiffness mismatch;

[†] *P* < 0.05 vs. negligible stiffness mismatch.

Table 2

Hemodynamic variables compared between types of stiffness mismatch

	Negative Stiffness Mismatch (bPWV < aPWV) (*n* = 118)	Negligible Stiffness Mismatch (bPWV ≈ aPWV) (*n* = 123)	Positive Stiffness Mismatch (bPWV > aPWV) (*n* = 118)	*P* Value	*P* Value Age + Sex Adjusted
Central augmentation pressure, mmHg	11 ± 6	10 ± 6	8 ± 6[*†]	<0.001	0.965
Central augmentation index, %	24 ± 10	24 ± 11	21 ± 13	0.042	0.106
Aortic reservoir pressure, mmHg·s	13 ± 4	12 ± 4	11 ± 3[*]	0.003	0.720
Excess pressure, mmHg·s	4 ± 2	3 ± 1	3± 1	0.103	0.180
Brachial systolic BP, mmHg	129 ± 14	128 ± 13	125 ± 12[*]	0.023	0.013
Brachial diastolic BP, mmHg	74 ± 10	76 ± 9	78 ± 12[*]	0.013	0.320
Central systolic BP, mmHg	117 ± 14	116 ± 13	113 ± 12	0.061	0.245
Mean arterial pressure, mmHg	92 ± 10	94 ± 10	94 ± 9	0.467	0.515
Central pulse pressure, mmHg	43 ± 11	39 ± 10[*]	34 ± 9[*†]	<0.001	0.011
Pulse pressure amplification, mmHg	13 ± 5	12 ± 5	12 ± 5	0.268	0.001
Pulse pressure amplification ratio	1.3 ± 0.2	13 ± 0.2	1.4 ± 0.2	0.037	0.179
Heart rate, beats/min	69 ± 10	67 ± 10	65 ± 10[*]	0.018	0.007
Stroke volume, ml	50 ± 13	54 ± 13	52 ± 16	0.248	0.083
Stroke volume indexed to BSA, ml/m^2	26 ± 6	28 ± 6	27 ± 7	0.085	0.072
Cardiac output, l/m	3.4 ± 0.9	3.6 ± 1.0	3.4 ± 1.0	0.527	0.011
Cardiac output indexed to BSA, l·min^{-1}·m^{-2}	1.8 ± 0.4	1.9 ± 0.5	1.7 ± 0.5	0.155	0.124
Systemic vascular resistance, AU	29 ± 8	28 ± 9	29 ± 9	0.588	0.057
Aortic wave timing (Tr), ms	137 ± 9	141 ± 10[*]	143 ± 12[*†]	<0.001	0.135
Tension-time integral, mmHg·ms	2,181 ± 320	2,132 ± 299	2,040 ± 318[*]	0.002	0.004
Diastolic pressure-time integral, mmHg·ms	3,359 ± 424	3,489 ± 425	3,555 ± 529[*]	0.004	0.100
Subendocardial viability ratio, %	156 ± 25	166 ± 26[*]	179 ± 32[*†]	<0.001	<0.001

Data are mean ± SD. Reservoir pressure is displayed as the integral (area under the curve) with diastolic blood pressure subtracted. Excess pressure is the integral. Systemic vascular resistance is estimated from mean arterial pressure/cardiac output. Differences were adjusted for age and sex using analysis of covariance. BSA, body surface area; AU, arbitrary units. *P* value represents significance of overall one-way ANOVA and adjusted *P* value the overall significance of analysis of covariance.

[*] *P* < 0.05 vs. negative stiffness mismatch (unadjusted);

[†] *P* < 0.05 vs. negligible stiffness mismatch (unadjusted).

Table 3

Multivariable regression models for predictors of augmentation pressure and augmentation index

	Model 1		Model 2		Model 3		Model 4		Model 5	
	β*	P Value	β*	P Value	β*	P Value	β*	P Value	β*	P Value
Augmentation Pressure										
	$R^2 = 0.81$		$R^2 = 0.81$		$R^2 = 0.86$		$R^2 = 0.87$		$R^2 = 0.89$	
Reservoir pressure	0.80	<0.001	0.80	<0.001	0.73	<0.001	0.67	<0.001	0.61	<0.001
Stiffness mismatch	−0.07	0.021	−0.11	0.06	0.03	0.38	—	—	—	—
Aortic pulse wave velocity	—	—	−0.04	0.48	—	—	—	—	—	—
Age	—	—	—	—	0.13	<0.001	0.13	<0.001	0.15	<0.001
Sex (0 = female, 1 = male)	—	—	—	—	−0.27	<0.001	−0.24	<0.001	−0.24	<0.001
Systemic vascular resistance	—	—	—	—	—	—	0.17	<0.001	—	—
Heart rate	—	—	—	—	—	—	—	—	−0.09	0.012
Mean arterial pressure	—	—	—	—	—	—	—	—	0.21	<0.001
Height	—	—	—	—	—	—	—	—	−0.13	0.001
Augmentation Index										
	$R^2 = 0.38$		$R^2 = 0.39$		$R^2 = 0.54$		$R^2 = 0.60$		$R^2 = 0.63$	
Reservoir pressure	0.62	<0.001	0.62	<0.001	0.53	<0.001	0.47	<0.001	0.12	<0.001
Stiffness mismatch	0.02	0.54	−0.10	0.180	—	—	—	—	—	—
Aortic pulse wave velocity			−0.15	0.05	—	—	—	—	—	—
Age	—	—	—	—	0.11	0.006	0.11	0.005	0.16	<0.001
Sex (0 = female, 1 = male)	—	—	—	—	−0.39	<0.001	−0.36	<0.001	−0.34	<0.001
Systemic vascular resistance	—	—	—	—	—	—	0.22	<0.001	—	—
Heart rate	—	—	—	—	—	—	—	—	−0.34	<0.001
Mean arterial pressure	—	—	—	—	—	—	—	—	0.24	<0.001
Height	—	—	—	—	—	—	—	—	−0.22	<0.001

*
Standardized β-coefficient, indicating the number of SD that either augmentation pressure or augmentation index would change if there was a 1 SD unit change in the covariate. If β-coefficients are significant ($P < 0.05$), the covariates are making a significant independent contribution to explaining augmentation pressure or augmentation index while controlling for the variance explained by the other covariates in the model.

Table 4

Comparison of data expectations in the presence of positive stiffness mismatch according to wave-reflection theory and actual results from this study

Hemodynamic Parameter	Theoretical Expectations According to Wave-Reflection Theory	Data from This Current Study
Augmentation pressure	↑	↓
Augmentation index	↑	↓
Reservoir pressure	Not considered	↓
Excess pressure	Not considered	↓
Stroke volume	↓	↔
Systemic vascular resistance	↑	↔
Central systolic pressure	↑	↓
Central pulse pressure	↑	↓
Aortic wave timing (Tr)	↓	↑
Subendocardial viability ratio	↓	↑
Tension-time index	↑	↓
Diastolic pressure time integral	↓	↑
LV mass index	↑	↓
eGFR	↓	↑

Arrows represent the direction of association in the presence of positive stiffness mismatch (bPWV >aPWV), where ↓ is lower compared to a negative stiffness mismatch; ↑ is higher compared to a negative stiffness mismatch; and ⇆ is not different compared with a negative stiffness mismatch.