

Increased Wave Reflection Rather Than Central Arterial Stiffness Is the Main Determinant of Raised Pulse Pressure in Women and Relates to Mismatch in Arterial Dimensions

A Twin Study

Marina Cecelja, BSc,* Benyu Jiang, PhD,* Karen McNeill,* Bernet Kato, PhD,† James Ritter, PhD,* Tim Spector, MD,† Phil Chowienczyk, BSc*

London, United Kingdom

- Objectives** Our aim was to examine the relative contributions of the first systolic shoulder (P1) and augmentation pressure (ΔP_{aug}) to central pulse pressure (cPP), their relation to central arterial stiffness (pulse wave velocity [PWV]) and arterial diameters, and their respective heritability estimates.
- Background** cPP is augmented above P1 by ΔP_{aug} due to pressure waves reflected from the periphery of the circulation.
- Methods** Women (n = 496) from the Twins UK adult twin registry (112 monozygotic, 135 dizygotic pairs) age 21 to 81 years were studied. cPP, P1, and ΔP_{aug} were estimated using the SphygmoCor system (Atcor, West Ryde, Australia) from transformed radial waveforms. Carotid-femoral PWV was measured using the same system. Aortic and femoral artery diameters were measured by ultrasonography. Heritability was estimated using structural equation modeling.
- Results** P1 and ΔP_{aug} accounted for 22% and 76%, respectively, of the variance in cPP. After adjustment for mean arterial pressure and heart rate, P1 strongly independently positively correlated with PWV (standardized regression coefficient, $\beta = 0.4$, $p < 0.0001$), whereas ΔP_{aug} did not independently correlate with PWV but independently negatively correlated with the ratio of the diameter of the femoral to that of the abdominal aorta ($\beta = -0.12$, $p < 0.001$). Estimates of heritability (h^2) of cPP, PWV, P1, and ΔP_{aug} were 0.43, 0.34, 0.31, and 0.62, respectively, after adjustment for mean arterial pressure and heart rate.
- Conclusions** These results suggest that, in women, ΔP_{aug} is highly heritable, is associated with the ratio of distal to proximal arterial diameters, and, independent of PWV, is a major determinant of cPP. (J Am Coll Cardiol 2009;54:695–703) © 2009 by the American College of Cardiology Foundation

Pulse pressure (PP) is a major determinant of cardiovascular risk. In older subjects, peripheral pulse pressure (pPP) measured at the brachial artery is more closely associated with future cardiovascular disease (CVD) events than systolic or diastolic pressure (1–4) and, in middle-age to older subjects, is greater in women compared with men (5). Central pulse pressure (cPP) measured at the aortic root

may be a more important determinant of CVD risk than pPP, possibly as a result of the pulsatile stress imposed on the coronary arteries, myocardium, and cerebral vasculature (6). An outcome study in which cPP was measured invasively supports this hypothesis (7) as do most, but not all, studies employing noninvasive estimates of cPP (8–11). In

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From *King's College London, Cardiovascular Division, and the †Department of Twin Research and Genetic Epidemiology, London, United Kingdom. This work was supported by a British Heart Foundation Project Grant PG/06/032. The Department of Twin Research receives funds from the Wellcome Trust. The authors acknowledge financial support from the Department of Health via the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's and St. Thomas' NHS Foundation Trust, in partnership with King's College London and King's College Hospital NHS Foundation Trust.

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younger subjects, amplification of pPP above cPP by effects of reflection in the upper limb (12) may reduce the association of pPP with CVD events (13). cPP is, in part, determined by the stiffness of central arteries but is also thought to be influenced by left ventricular ejection stroke volume (SV), heart rate (HR), and pressure wave reflection (14). cPP can be separated into 2 components: the height,

Abbreviations and Acronyms

- AIx** = augmentation index
- cPP** = central pulse pressure
- CVD** = cardiovascular disease
- DZ** = dizygotic
- HR** = heart rate
- ISH** = isolated systolic hypertension
- MAP** = mean arterial pressure
- MZ** = monozygotic
- PP** = pulse pressure
- pPP** = peripheral pulse pressure
- PWV** = pulse wave velocity
- P1** = height of first systolic shoulder
- SV** = stroke volume
- T1** = time of arrival of the reflected wave
- ΔP_{aug}** = augmentation pressure

above diastolic pressure, of the first systolic shoulder in the arterial pulse waveform (P1), and augmentation pressure (ΔP_{aug}), the height of central systolic pressure above P1 (Fig. 1) (12,15,16):

$$cPP = P1 + \Delta P_{aug}$$

These components of cPP may be differentially related to arterial stiffness and wave reflection, with P1 formed by the outgoing pressure wave and dependent on SV and arterial stiffness via a “Windkessel” effect and ΔP_{aug} determined mainly by pressure wave reflection and, hence, on the serial distribution of arterial dimensions and stiffness. The purpose of the present study was to examine the relationship of PP and its components to SV, arterial stiffness, and large artery dimensions, and second, to determine the heritability of PP, arterial stiffness, and arterial dimensions.

To do this, we studied a sample of women age 21 to 81 years from the Twins UK cohort.

Methods

Subjects comprised 496 unselected female Caucasian twins, 112 pairs of monozygotic (MZ) and 135 pairs of dizygotic (DZ) twins age 21 to 81 years, with a mean age of 58 years. Ninety-one (18.3%) of these were on treatment with anti-hypertensive drugs, and 58 (11.7%) were on lipid-lowering

treatment. Subject characteristics are summarized in Table 1. The study was approved by the St. Thomas’ Hospital Research Ethics Committee, and written informed consent was obtained from all subjects. Measurements were performed during a single visit to a quiet temperature-controlled vascular laboratory (22°C to 24°C).

Hemodynamic measurements. Brachial blood pressure was measured in duplicate, using a validated oscillometric device (Omron 705CP, Omron, Tokyo, Japan), after subjects had been seated in a quiet room for at least 10 min. Radial pulse waveforms and measurements of central arterial stiffness (carotid-femoral pulse wave velocity [PWV]) were obtained with the subject in a supine position using the SphygmoCor system (Atcor, West Ryde, Australia). Applanation tonometry of the radial artery with a high-fidelity transducer (Millar Instruments, Houston, Texas) was used to obtain an ensemble averaged radial pulse. The radial artery pressure waveform was calibrated to supine brachial blood pressure. The inbuilt transfer function in the SphygmoCor system provided a corresponding aortic pulse waveform from which cPP, P1, ΔP_{aug} , and central systolic blood pressure were identified (16). Carotid-femoral PWV was calculated from sequential recordings of electrocardiogram-referenced carotid and femoral pressure waveforms obtained by tonometry using the same device and transducer. The path distance between the carotid and femoral sites was estimated from the distance between the sternal notch and femoral artery at the point of applanation. This reduces errors introduced by multiple measurements and is closer to the true path length than the carotid to femoral distance (17). PWV and cPP measurements were made in triplicate, and mean values were used for analysis. Only waveforms that passed the automatic quality control criteria of the SphygmoCor system were used.

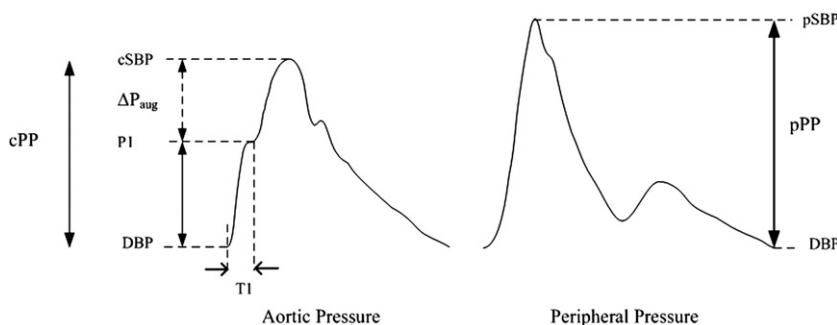


Figure 1. Aortic and Peripheral Pressure Waveforms

Aortic and peripheral pressure waveforms showing central systolic pressure (cSBP), peripheral systolic pressure (pSBP), central pulse pressure (cPP), and peripheral pulse pressure (pPP). cPP can be divided into 2 components: the height of the first systolic shoulder (P1) above diastolic blood pressure (DBP) (equal at central and peripheral sites) and augmentation pressure (ΔP_{aug}), thought to be determined by wave reflection. T1, the time of the first systolic shoulder, is thought to be determined by the time of arrival of the reflected wave.

Table 1 Characteristics of MZ and DZ Twins

Characteristics	Total Cohort	MZ		DZ	
		<60 Years of Age	≥60 Years of Age	<60 Years of Age	≥60 Years of Age
n	496	118	106	138	132
Age (yrs)	58 ± 10	48 ± 9.2	66 ± 5.7	52 ± 7.0*	65 ± 4.6
Height (cm)	162 ± 5.9	162 ± 5.6	160 ± 6.1	162 ± 5.8	162 ± 5.7
Weight (kg)	71 ± 13.3	69 ± 13.9	70 ± 12.1	71 ± 13.4	72 ± 12.6
Peripheral SBP (mm Hg)	123 ± 17.0	116.8 ± 12.9	129.2 ± 20.0	121.2 ± 17.0*	125.5 ± 15.7
Peripheral DBP (mm Hg)	71.8 ± 8.9	71.5 ± 8.4	71.4 ± 9.0	72.4 ± 9.5	71.8 ± 8.8
Heart rate (beats/min)	64.7 ± 9.6	64.1 ± 9.7	65.0 ± 9.7	64.2 ± 9.9	65.0 ± 9.1
Total cholesterol (mmol/l)	5.7 ± 1.1	5.5 ± 1.2	5.9 ± 1.1	5.6 ± 0.9	5.7 ± 1.0
LDL (mmol/l)	3.4 ± 1	3.4 ± 1.0	3.5 ± 1.2	3.3 ± 0.9	3.3 ± 1.1
HDL (mmol/l)	1.8 ± 0.5	1.7 ± 0.5	1.8 ± 0.5	1.7 ± 0.5	1.9 ± 0.5
Triglycerides (mmol/l)	1.0 ± 0.5	0.97 ± 0.6	0.97 ± 0.3	1.1 ± 0.5	1.1 ± 0.5
Antihypertensive treatment	91 (18.3)	11 (9.5)	40 (37.7)	14 (10.3)	26 (19.7)*
Lipid-lowering treatment	58 (11.7)	7 (6)	21 (19.8)	11 (8.1)	19 (14.4)
Diabetes mellitus	6 (1.2)	1 (0.9)	2 (1.9)	0	3 (2.3)
Current smoker	58 (11.7)	14 (12.1)	5 (4.7)	27 (19.9)	12 (9.1)
Abdominal aortic diameter (mm)	19.0 ± 2.2	18.2 ± 2.4	19.9 ± 1.7	18.6 ± 2.1	19.7 ± 1.9
Femoral artery diameter (mm)	8.3 ± 1.0	8.0 ± 1.1	8.8 ± 0.9	8.1 ± 0.9	8.6 ± 1
D _{FA} (mm)	0.44 ± 0.1	0.45 ± 0.1	0.44 ± 0.1	0.44 ± 0.1	0.44 ± 0.1
P1 (mm Hg)	28.1 ± 6.4	25.7 ± 5.5	31.9 ± 7.3	27.0 ± 5.4	29.2 ± 6.3*
T1 (ms)	105 ± 9.9	106 ± 10	105 ± 7.5	106 ± 11.3	104 ± 9.2
ΔP _{aug} (mm Hg)	13.8 ± 7.0	11.3 ± 6.6	17.1 ± 7.5	13.0 ± 6.6*	15.3 ± 6.5

Values are mean ± SD or n (%). *p < 0.05 between monozygotic (MZ) and dizygotic (DZ) twins in the same age category.

DBP = diastolic blood pressure; D_{FA} = ratio of diameter of femoral to abdominal aortic diameter; HDL = high-density lipoprotein; LDL = low-density lipoprotein; P1 = first systolic shoulder of the central arterial pressure waveform; SBP = systolic blood pressure; T1 = time of arrival of reflected pressure wave; ΔP_{aug} = augmentation pressure (Fig. 1).

Ultrasonography of the aortic root, abdominal aorta, and femoral arteries.

The aortic root was visualized using 2-dimensional echocardiography from a long-axis parasternal view using a Siemens CV70 with a 4-MHz cardiac transducer, and its diameter measured 1 cm from the aortic valve between the anterior and posterior aortic root wall at end diastole. SV was measured in a subgroup of 186 subjects. The cross-sectional area of the aortic valve was estimated from diameter measurements and SV determined by multiplying the cross-sectional area by the velocity time integral obtained from Doppler flow velocity at the level of the aortic valve. To visualize the abdominal aorta, the epigastrium was scanned vertically at the xiphoid process using the same probe. The diameter of the abdominal aorta was measured 1 to 2 cm below the diaphragm at end-diastole. Left and right femoral arteries were visualized with a 13-MHz vascular probe 1 cm proximal to the bifurcation. Automated wall tracking software (Medical Imaging Applications, Coralville, Iowa) was used to measure diameter at end-diastole.

Statistical analysis. Data analysis was performed with SPSS version 14.0 (SPSS Inc., Chicago, Illinois). Genetic modeling was performed using Mx software (Mx statistical modeling, Medical College of Virginia, Richmond, Virginia). Subject characteristics are presented as mean ± SD unless otherwise stated. Student unpaired *t* and chi-square tests were used to test for differences in characteristics between MZ and DZ twins. Univariate regression analysis was first used to examine relationships of cPP, pPP, P1, and ΔP_{aug} as dependent

variables to PWV, mean arterial pressure (MAP), HR, arterial diameters, and potential confounding factors: age, height, weight, smoking status, total cholesterol, high-density lipoprotein cholesterol, and the presence of diabetes. Forward stepwise multiple regression analysis was then performed to examine potential independent determinants of cPP, pPP, P1, and ΔP_{aug}. Variables included in each analysis were age, HR, MAP, PWV, arterial dimensions (aortic root diameter, abdominal aortic diameter, the ratio of femoral to abdominal aortic diameter), and any other confounding variables found to significantly correlate with the dependent variable in the initial univariate analysis. The same analysis was also applied to the time of arrival of the reflected wave (T1) (Fig. 1). The analysis was repeated separately in women age <60 and ≥60 years, because the prognostic importance of PP changes at approximately 60 years in women (1), and age category (<60 and ≥60 years) interactions with variables entering the final model were tested. All statistical tests were done at the 5% level of significance.

Heritability analysis was performed using the classical twin model in which a greater similarity in MZ compared with DZ twins suggests a genetic influence, based on the fact that MZ twins are genetically 100% identical and DZ twins share approximately 50% of their segregating genes. This model assumes that MZ and DZ twins share their common environment to the same extent. Twin resemblance for each of the phenotypes was examined using the intraclass correlation coefficient for each zygosity. A higher intraclass correlation

coefficient for MZ twins compared with DZ twins suggests a genetic influence on the phenotype. For further analysis of genetic and environmental contributions, the variance of each phenotype was assumed to derive from an additive genetic component (sum of individual effects of all loci that influence the trait), shared or unique environment components (ACE model). Measurement error is represented under unique environmental influences. Structural equation modeling implemented in Mx was used to estimate the parameters of the ACE model and corresponding confidence intervals.

Results

Characteristics of the MZ and DZ female twins were similar, but there were small but significant differences between MZ and DZ twins in the separate age groups (Table 1). Mean age and peripheral systolic blood pressure were significantly lower in MZ compared with DZ twins age <60 years. More subjects were on antihypertensive treatment in MZ twins age ≥60 years compared with DZ twins in the same age group.

Relationship of pPP and cPP to PWV and arterial dimensions. Mean cPP was less than pPP by 9 and 7 mm Hg in subjects age <60 and ≥60 years, respectively (each $p < 0.001$). Both cPP and pPP correlated with MAP, HR, age, PWV, high-density lipoprotein cholesterol, aortic root diameter, and smoking but not with height or weight by univariate analysis. However, in multiple regression analysis including all variables correlated with PP on univariate analysis, the only significant correlations were with MAP, HR, age, and PWV (each $p < 0.0001$) (Table 2).

Contribution of P1 and ΔP_{aug} to cPP. Mean values of P1 were greater than those of ΔP_{aug} for subjects in each age group and in each tertile of the distribution of cPP (Fig. 2). However, ΔP_{aug} contributed proportionately more to the increase in cPP across the distribution than P1. Thus, in the whole cohort, P1 increased by a mean of 12.0 mm Hg (52% increase) when comparing women in the first and third tertiles of cPP but ΔP_{aug} increased by 14.1 mm Hg (196% increase). In women meeting a definition of isolated systolic hypertension (ISH)

with peripheral systolic blood pressure >140 mm Hg and diastolic blood pressure <90 mm Hg, P1 was 37.5 compared with 26.7 mm Hg in women without ISH. Corresponding values of ΔP_{aug} were 21.6 and 12.7 mm Hg in women with and without ISH, respectively. In regression analysis (including ΔP_{aug} and P1 as predictors of cPP), ΔP_{aug} and P1 explained 76% and 22% of the variance in cPP. In women age <60 years, this was 73% and 24%, respectively, and in women age ≥60 years was 76% and 21%, respectively.

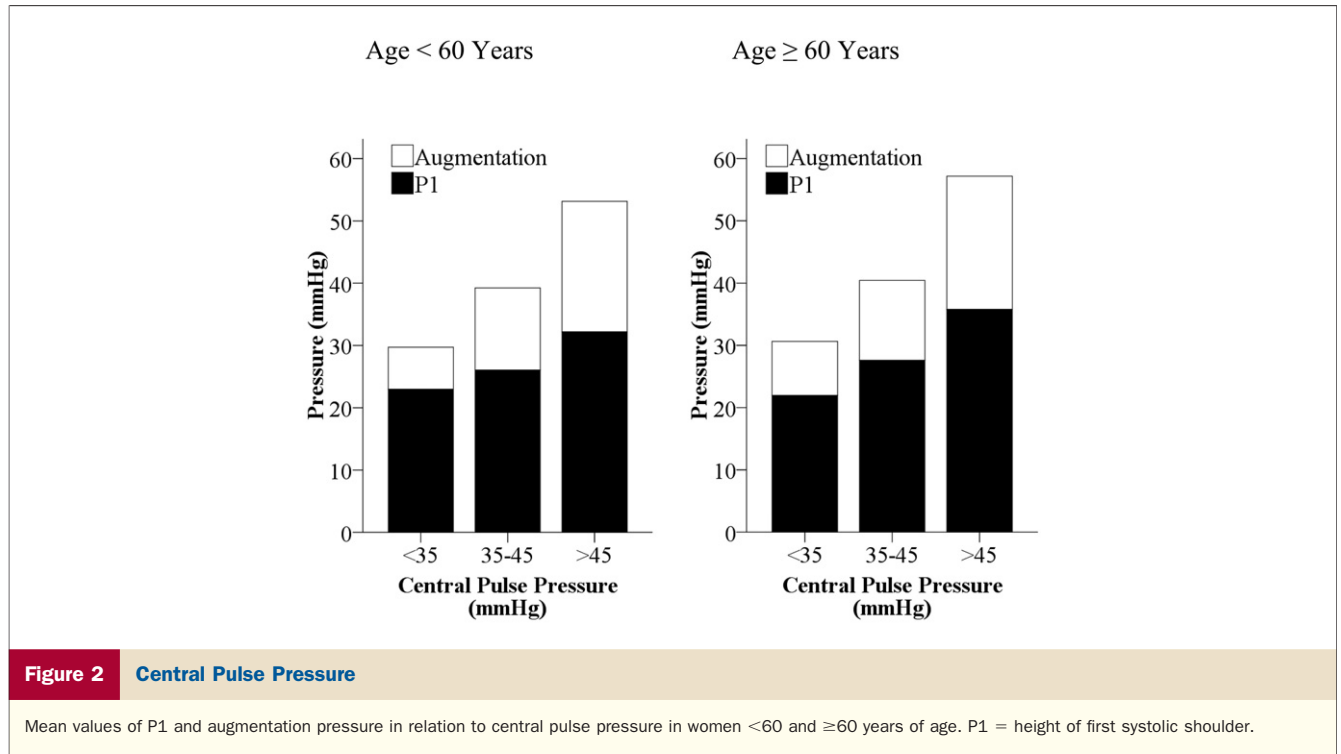
Relationship of P1 and ΔP_{aug} to PWV and arterial dimensions. In multiple regression analysis (incorporating all variables significantly correlated with P1 on univariate analysis), in the whole cohort and in each age group, P1 strongly positively correlated with PWV and MAP but less strongly correlated with HR, arterial diameters, and other variables (Table 3). There were significant interactions between age category and MAP and between age category and HR.

ΔP_{aug} strongly positively correlated with MAP and age and negatively correlated with HR. ΔP_{aug} did not significantly correlate with PWV. T1 did not independently correlate with PWV but independently correlated (standardized regression coefficient, $\beta = 0.23$, $p < 0.001$) with the ratio of femoral to abdominal aortic diameter. T1 also significantly correlated with height and (negatively) with MAP. There were significant interactions between age category and HR and between age category and the ratio of femoral to abdominal aortic diameter. In subjects age <60 years (as in the whole cohort) but not in subjects age ≥60 years, ΔP_{aug} negatively correlated with the ratio of femoral to abdominal aortic diameter. In the subsample of subjects in whom SV was assessed (Table 4), SV was weakly or nonsignificantly related to P1 and ΔP_{aug} , and the main findings with respect to correlations with PWV were unaltered: P1 remained strongly correlated with PWV, whereas ΔP_{aug} did not significantly correlate with PWV. The strength of the correlation between ΔP_{aug} and the ratio of femoral to abdominal aortic diameter in subjects age <60 years was stronger, but that of P1 to the ratio of femoral to abdominal aortic diameter was no longer significant.

Table 2 Determinants of cPP and pPP Other Than Augmentation Pressure by Regression Analysis

Variable	Total Cohort			Age <60 Years			Age ≥60 Years		
	β	R ²	p Value	β	R ²	p Value	β	R ²	p Value
cPP									
MAP	0.50	0.34	<0.0001	0.52	0.33	<0.0001	0.60	0.36	<0.0001
HR	-0.35	0.50	<0.0001	-0.37	0.47	<0.0001	-0.39	0.49	<0.0001
Age	0.30	0.59	<0.0001	0.20	0.52	<0.0001	0.24	0.58	<0.0001
PWV	0.18	0.61	<0.0001	0.12	0.53	<0.05	0.15	0.59	<0.01
pPP									
MAP	0.42	0.28	<0.0001	0.45	0.27	<0.0001	0.53	0.31	<0.0001
PWV	0.27	0.31	<0.0001	0.17	0.28	<0.0001	0.26	0.39	<0.0001
Age	0.20	0.42	<0.0001	—	—	—	0.19	0.42	<0.0001
HR	-0.14	0.45	<0.0001	-0.13	0.29	<0.05	-0.21	0.47	0.001

cPP = central pulse pressure; HR = heart rate; MAP = mean arterial pressure; pPP = peripheral pulse pressure; PWV = pulse wave velocity; R² = coefficient of determination (cumulative); β = standardized regression coefficient; — = variable did not enter model.



Heritability analysis. Intraclass correlations for all measures were greater for MZ compared with DZ twin pairs (Table 5), indicating a genetic influence on all phenotypic traits. Heritability estimates are shown in Table 6. In the full ACE model, heritability of PWV was modest, with an estimated genetic component of 34%. The estimated genetic components of cPP, P1, and ΔP_{aug} were 43%, 31%, and 62%, respectively. Heritability of ΔP_{aug} was reduced to 43% when corrected for height in addition to HR and MAP. PWV was the only measure for which shared environment was significant.

Discussion

PP and PWV. PP is often regarded as a surrogate for PWV, ejection of blood into a stiff aorta resulting in a high systolic and pulse pressure. A correlation between PP (both peripheral and central) and carotid-femoral PWV is a universal finding in large epidemiological studies (18–22), but much of the variation in PP is not explained by PWV or other measures of central artery stiffness (18–22). Other factors invoked to explain PP include left ventricular ejection volume, pressure

Table 3 Determinants of P1 and ΔP_{aug} by Regression Analysis

Variable	Total Cohort			Age <60 Years			Age ≥60 Years		
	β	R ²	p Value	β	R ²	p Value	β	R ²	p Value
P1									
PWV	0.36	0.30	<0.0001	0.19	0.04	<0.01	0.29	0.10	<0.0001
MAP	0.33	0.38	<0.0001	0.28	0.20	<0.001	0.49	0.42	<0.0001
HR	-0.14	0.40	<0.001	—	—	—	-0.18	0.46	<0.001
D _{FA}	0.12	0.41	<0.001	0.24	0.23	<0.001	—	—	—
Age	0.11	0.42	<0.05	—	—	—	0.13	0.48	<0.05
AaD	—	—	—	0.16	0.25	<0.05	-0.18	0.50	<0.001
AoD	—	—	—	—	—	—	0.10	0.51	<0.05
HDL	—	—	—	—	—	—	-0.14	0.52	<0.01
ΔP_{aug}									
MAP	0.59	0.34	<0.0001	0.6	0.35	<0.0001	0.63	0.33	<0.0001
HR	-0.44	0.56	<0.0001	-0.42	0.58	<0.0001	-0.50	0.58	<0.0001
Age	0.35	0.68	<0.0001	0.28	0.67	<0.0001	0.27	0.66	<0.0001
D _{FA}	-0.12	0.70	<0.0001	-0.21	0.71	<0.0001	—	—	—
Weight	-0.11	0.71	0.0001	-0.10	0.72	<0.01	—	—	—

AaD = abdominal aortic diameter; AoD = aortic root diameter; other abbreviations as in Tables 1 and 2.

Table 4 Determinants of P1 and ΔP_{aug} by Regression Analysis in a Subset of 186 Subjects With SV Measurements

Variable	Total Cohort			Age <60 Years			Age \geq 60 Years		
	β	R ²	p Value	β	R ²	p Value	β	R ²	p Value
P1									
PWV	0.46	0.27	<0.0001	—	—	—	0.36	0.21	<0.0001
MAP	0.20	0.30	<0.01	—	—	—	0.47	0.33	<0.0001
HR	-0.18	0.33	<0.01	—	—	—	-0.18	0.39	<0.05
AaD	—	—	—	—	—	—	-0.34	0.44	<0.0001
AoD	—	—	—	—	—	—	0.23	0.49	<0.05
SV	—	—	—	0.25	0.06	<0.05	—	—	—
HDL	—	—	—	—	—	—	-0.14	0.5	<0.01
ΔP_{aug}									
MAP	0.52	0.339	<0.0001	0.49	0.22	<0.0001	0.63	0.379	<0.0001
HR	-0.39	0.54	<0.0001	-0.37	0.34	<0.0001	-0.47	0.58	<0.0001
Age	0.35	0.68	<0.0001	0.25	0.66	<0.0001	0.16	0.61	<0.05
D _{FA}	-0.14	0.70	<0.01	-0.25	0.71	<0.0001	—	—	—
SV	0.11	0.71	<0.05	0.15	0.73	<0.05	—	—	—

SV = stroke volume; other abbreviations as in Tables 1 to 3.

wave reflection, and arterial diameters (23). As in the present study, previous studies have found only a weak relation between left ventricular ejection volume and PP (20,21).

Contribution of P1 and ΔP_{aug} to cPP. To our knowledge, this is the first study to examine separately the contribution of the 2 major components of PP, P1 and ΔP_{aug} , to cPP. Although P1, the component of PP generated by the outgoing pressure wave, was greater than ΔP_{aug} , the variance of ΔP_{aug} was greater than that of P1. Thus, most of the variability in cPP (and in pPP) was accounted for by variation in ΔP_{aug} rather than P1. Partitioning of cPP into ΔP_{aug} and P1 provides physiological insight into the mechanisms governing cPP. P1, the outgoing component of the pressure wave, might be expected to be mainly determined by PWV, which determines the Windkessel function of the central vessels. By contrast, arterial geometry might be expected to influence pressure wave reflection more strongly than arterial stiffness (although stiffness could also influence this through earlier return of reflected waves). In the present study, we found that P1 indeed highly correlated with PWV. However, ΔP_{aug} did not independently correlate with carotid-femoral PWV. This suggests that PWV is not a major determinant of ΔP_{aug} and is consistent with other studies showing dissociation between measures of pres-

sure wave reflection and PWV during interventions that influence vasomotor tone (24,25).

Our findings differ from those of Mitchell et al. (26) in the Framingham offspring cohort of men and women, where although ΔP_{aug} (obtained from carotid tonometry) was seen to account for a considerable proportion of variance in cPP, PWV accounted for a greater proportion of the variance in cPP than ΔP_{aug} . However, subjects with hypertension (47% of the potential study population) were excluded. The present study shows that ΔP_{aug} positively correlated with MAP and so would be expected to provide a greater contribution to cPP in subjects representative of the general population, including those with hypertension. The conclusions of our study also differ from those of Segers et al. (27) who examined wave reflection in middle-age men and women and found wave reflection to explain at most 26% of the variance in carotid PP. Segers et al. (27) used the augmentation index (AIx) (equal to $\Delta P_{aug}/cPP$) as a measure of reflection in their regression models, which also included measures of input impedance. The proportion of variance in cPP explained by AIx compared with ΔP_{aug} will be reduced by cPP being itself a denominator of AIx. Our simple approach, where we have partitioned cPP into the sum of P1 + ΔP_{aug} , provides less insight into impedance but provides an estimation of the relative contributions of P1 and ΔP_{aug} , which is limited only by the accuracy of the measurements.

Physiological and structural determinants of P1 and ΔP_{aug} . Both P1 and ΔP_{aug} could be influenced by arterial geometry. For a given intrinsic elasticity of the aortic wall (to which PWV is related by the Moens-Korteweg equation [28]), the functional compliance of the aorta is directly related to its diameter (29). Although this is offset by the fact that SV and HR are related to body size and aortic root area, P1 might be expected to be inversely related to aortic diameters, particularly those beyond the aortic root. However, one hypothesis of age-related stiffening is that elastin degeneration is associated

Table 5 Intraclass Correlations for MZ and DZ Twin Pairs

Measure	MZ	DZ
cPP	0.78	0.45
P1	0.72	0.37
ΔP_{aug}	0.77	0.38
PWV	0.81	0.59
AoD	0.67	0.53
AaD	0.72	0.34
D _{FA}	0.51	0.40

Abbreviations as in Tables 1 to 3.

Table 6 Heritability Estimates and 95% CIs for Best Fitting Univariate

Measure	A	95% CI	C	95% CI	E	95% CI
cPP	0.43	0.12-0.73	0.24	0.00-0.49	0.33	0.25-0.44
P1	0.31	0.00-0.65	0.31	0.00-0.57	0.38	0.30-0.50
ΔP_{aug}	0.62	0.29-0.75	0.04	0.00-0.32	0.34	0.25-0.45
PWV	0.34	0.11-0.59	0.42	0.19-0.61	0.24	0.18-0.32
D_{FA}^*	0.31	0.00-0.56	0.10	0.00-0.43	0.58	0.44-0.76
AaD*	0.36	0.00-0.66	0.21	0.00-0.51	0.43	0.33-0.56
AoD*	0.34	0.01-0.67	0.30	0.01-0.55	0.36	0.27-0.49

A indicates heritability; C indicates shared environmental variance components; E indicates unique environment. All estimates are adjusted for mean arterial pressure and heart rate. *Adjusted for mean arterial pressure = height and weight.

CI = confidence interval; other abbreviations as in Tables 1 to 3.

with aortic dilation (30), and this might blunt or over-ride the expected inverse relation. In the present study, we found a weakly positive correlation of P1 with abdominal aortic diameter in subjects <60 years of age, a negative correlation in subjects ≥ 60 years of age, and no significant relation in the overall cohort. This result is consistent with recent studies that have found a modest inverse correlation of cPP with aortic root diameter in older women (20,21).

Wave reflections are thought to occur at discontinuities in impedance and thus to depend on the serial distribution of arterial diameter and elasticity, with most reflection arising distal to the aortic bifurcation. In the present study we measured abdominal aortic diameter as a measure of proximal artery dimensions and femoral artery diameter as a measure of distal arterial dimensions. Of all arterial dimensions, ΔP_{aug} was best predicted by the ratio of femoral to abdominal aorta diameter, with an inverse relationship between ΔP_{aug} and femoral/aortic diameter. This is consistent with the amount and/or timing of reflection being determined by the mismatch between femoral and aortic dimensions or between other distal and proximal arterial dimension, with femoral and aortic dimensions acting as a surrogate for these. The highly significant independent association of T1, the time of arrival of the reflected wave, with femoral/aortic diameter suggests that arterial dimensions have a greater influence on the site of reflection than on the amount of reflection. Furthermore, the lack of association of T1 with PWV suggests that it is primarily the site of reflection that determines the time of arrival of reflected waves and over-rides the importance of transit time to and from the site of reflection. The association between ΔP_{aug} and femoral/aortic diameter was driven by subjects <60 years of age. In subjects ≥ 60 years of age, in whom PWV is higher, it may be that serial distribution of elasticity becomes more important than that of diameter. Further studies including prospective studies will be required to explore the complex relation between ΔP_{aug} and arterial diameter.

Heritability of P1 and ΔP_{aug} . To our knowledge, this is the first study to report heritability of the different components of cPP, P1, and ΔP_{aug} in twins. Heritability of P1 (31%) was modest as was that of PWV (34%), consistent with P1 being determined in large part by PWV. The estimate for PWV is consistent with previous estimates of the heritability of PWV

from family and twin studies between 0.26 and 0.40 (31,32). The heritability of ΔP_{aug} (62%) is greater than that observed for most phenotypic traits including systolic blood pressure, and suggests that if other factors such as measurement error are similar, factors additional to PWV that determine reflection have a high genetic component. The findings with respect to ΔP_{aug} are similar to those of AIX, which is known to be highly heritable (33). Although our estimates of the heritability of aortic dimensions were relatively low, these estimates were relatively crude measures of the detailed geometry that determines wave reflection. The high heritability of ΔP_{aug} could be explained by high heritability of detailed arterial geometry, which is, in turn, determined by intrinsic geometry and smooth muscle tone.

Implications for systolic hypertension in women. The finding that ΔP_{aug} accounts for the majority of the variation in cPP and that it is highly heritable and independent of PWV has a number of important implications for systolic hypertension in women. It challenges the view that systolic hypertension arises primarily from irreversible stiffening of the aorta caused, for example, by collagen cross-linking and/or calcification. It raises the potential importance of ΔP_{aug} as a risk factor in addition to the well-established risk associated with elevated PWV in hypertension (6,34). It suggests that drugs with a specific action to dilate muscular arteries (and therefore to increase distal/proximal dimensions and reduce wave reflection) could be effective in reducing PP and systolic pressure. Organic nitrates have such specificity for large muscular arteries (35), but their efficacy may be limited by tolerance, increase in oxidative stress, and possibly other nonhemodynamic adverse effects (36). The high heritability of ΔP_{aug} suggests that ΔP_{aug} is an important trait to examine in relation to potential genes involved in hypertension and CVD.

Study limitations. The study was limited to female twins. The results are likely to be representative of women in the general population, since characteristics and CVD risk profiles of the Twins UK cohort are similar to that of the general population (37), and the mortality of twins is similar to that of the general population (38). The results cannot, however, be generalized to men. We estimated central arterial pressure waveforms from radial waveforms using the SphygmoCor transfer function. Most of the error inherent in this process, at

least when computing cPP, is attributable to the limited accuracy with which peripheral blood pressure can be measured (16). When calibration is performed from brachial blood pressures (as in this study), the approach also ignores amplification from the brachial to the radial artery, which may lead to an overestimation of peripheral amplification (39). Although this affects absolute values of cPP and pPP, it does not affect the relative values of cPP and pPP (40) or those of ΔP_{aug} and P1, and thus is unlikely to affect interpretation of the study. We made limited measurements of arterial diameters and cannot exclude the possibility that other relations between ΔP_{aug} and arterial dimensions would emerge if dimensions of smaller arteries were available.

Conclusions

In a cohort of apparently healthy women age 21 to 81 years, increased wave reflection rather than PWV is the main determinant of raised PP and, especially in younger women age <60 years, may be driven by mismatch in distal-to-proximal arterial dimension. This is likely to be a useful phenotype—both clinically and for gene discovery.

Reprint requests and correspondence: Dr. Phil Chowienzyk, Department of Clinical Pharmacology, St. Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, United Kingdom. E-mail: phil.chowienzyk@kcl.ac.uk.

REFERENCES

1. Franklin SS, Larson MG, Khan SA, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham heart study. *Circulation* 2001;103:1245–9.
2. Glynn RJ, Chae CU, Guralnik JM, Taylor JO, Hennekens CH. Pulse pressure and mortality in older people. *Arch Intern Med* 2000;160:2765–72.
3. Vaccarino V, Holford TR, Krumholz HM. Pulse pressure and risk for myocardial infarction and heart failure in the elderly. *J Am Coll Cardiol* 2000;36:130–8.
4. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham heart study. *Circulation* 1999;100:354–60.
5. Franklin SS, Gustin W, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham heart study. *Circulation* 1997;96:308–15.
6. Laurent S, Boutouyrie P. Recent advances in arterial stiffness and wave reflection in human hypertension. *Hypertension* 2007;49:1202–6.
7. Jankowski P, Kawecka-Jaszcz K, Czarnecka D, et al. Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients. *Hypertension* 2008;51:848–55.
8. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006;113:1213–25.
9. Pini R, Cavallini MC, Palmieri V, et al. Central but not brachial blood pressure predicts cardiovascular events in an unselected geriatric population: the ICARE Dicomano study. *J Am Coll Cardiol* 2008;51:2432–9.
10. Roman MJ, Devereux RB, Kizer JR, et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the strong heart study. *Hypertension* 2007;50:197–203.
11. Dart AM, Gatzka CD, Kingwell BA, et al. Brachial blood pressure but not carotid arterial waveforms predict cardiovascular events in elderly female hypertensives. *Hypertension* 2006;47:785–90.
12. Nichols WW. Clinical measurement of arterial stiffness obtained from noninvasive pressure waveforms. *Am J Hypertens* 2005;18:3S–10S.
13. Wilkinson IB, Franklin SS, Hall IR, Tyrrell S, Cockcroft JR. Pressure amplification explains why pulse pressure is unrelated to risk in young subjects. *Hypertension* 2001;38:1461–6.
14. Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation* 2003;107:2864–9.
15. Murgu JP, Westerhof N, Giolma JP, Altobelli SA. Aortic input impedance in normal man: relationship to pressure waveforms. *Circulation* 1980;62:105–16.
16. O'Rourke MF, Adji A. An updated clinical primer on large artery mechanics: implications of pulse waveform analysis and arterial tonometry. *Curr Opin Cardiol* 2005;20:275–81.
17. Sugawara J, Hayashi K, Yokoi T, Tanaka K. Age-associated elongation of the ascending aorta in adults. *J Am Coll Cardiol Img* 2008;1:739–48.
18. Mitchell GF, Gudnason V, Launer LJ, Aspelund T, Harris TB. Hemodynamics of increased pulse pressure in older women in the community-based Age, Gene/Environment Susceptibility-Reykjavik study. *Hypertension* 2008;51:1123–8.
19. Mitchell GF, Conlin PR, Dunlap ME, et al. Aortic diameter, wall stiffness, and wave reflection in systolic hypertension. *Hypertension* 2008;51:105–11.
20. Mitchell GF, Lacourciere Y, Ouellet JP, et al. Determinants of elevated pulse pressure in middle-aged and older subjects with uncomplicated systolic hypertension: the role of proximal aortic diameter and the aortic pressure-flow relationship. *Circulation* 2003;108:1592–8.
21. Farasat SM, Morrell CH, Scuteri A, et al. Pulse pressure is inversely related to aortic root diameter implications for the pathogenesis of systolic hypertension. *Hypertension* 2008;51:196–202.
22. Dart AM, Kingwell BA, Gatzka CD, et al. Smaller aortic dimensions do not fully account for the greater pulse pressure in elderly female hypertensives. *Hypertension* 2008;51:1129–34.
23. Nichols WW, O'Rourke MF. *McDonald's Blood Flow in Arteries. Theoretical, Experimental and Clinical Principles.* London: Arnold, 1998.
24. Kelly RP, Millasseau SC, Ritter JM, Chowienzyk PJ. Vasoactive drugs influence aortic augmentation index independently of pulse-wave velocity in healthy men. *Hypertension* 2001;37:1429–33.
25. Lemogoum D, Flores G, Van den AW, et al. Validity of pulse pressure and augmentation index as surrogate measures of arterial stiffness during beta-adrenergic stimulation. *J Hypertens* 2004;22:511–7.
26. Mitchell GF, Parise H, Benjamin EJ, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham heart study. *Hypertension* 2004;43:1239–45.
27. Segers P, Rietzschel ER, De Buyzere ML, et al. Noninvasive (input) impedance, pulse wave velocity, and wave reflection in healthy middle-aged men and women. *Hypertension* 2007;49:1248–55.
28. Gosling RG, Budge MM. Terminology for describing the elastic behavior of arteries. *Hypertension* 2003;41:1180–2.
29. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness; definitions and reference values. *Am J Hypertens* 2002;15:426–44.
30. O'Rourke MF, Nichols WW. Aortic diameter, aortic stiffness, and wave reflection increase with age and isolated systolic hypertension. *Hypertension* 2005;45:652–8.
31. Mitchell GF, DeStefano AL, Larson MG, et al. Heritability and a genome-wide linkage scan for arterial stiffness, wave reflection, and mean arterial pressure: the Framingham heart study. *Circulation* 2005;112:194–9.
32. Sayed-Tabatabaei FA, van Rijn MJ, Schut AF, et al. Heritability of the function and structure of the arterial wall: findings of the Erasmus Rucphen Family (ERF) study. *Stroke* 2005;36:2351–6.
33. Snieder H, Hayward CS, Perks U, Kelly RP, Kelly PJ, Spector TD. Heritability of central systolic pressure augmentation: a twin study. *Hypertension* 2000;35:574–9.
34. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001;37:1236–41.
35. Yaginuma T, Avolio A, O'Rourke M, et al. Effect of glyceryl trinitrate on peripheral arteries alters left ventricular hydraulic load in man. *Cardiovasc Res* 1986;20:153–60.
36. Munzel T, Kurz S, Heitzer T, Harrison DG. New insights into mechanisms underlying nitrate tolerance. *Am J Cardiol* 1996;77:24C–30C.

37. Hart DJ, Mootoosamy I, Doyle DV, Spector TD. The relationship between osteoarthritis and osteoporosis in the general population: the Chingford study. *Ann Rheum Dis* 1994;53:158-62.
38. Christensen K, Vaupel JW, Holm NV, Yashin AI. Mortality among twins after age 6: fetal origins hypothesis versus twin method. *BMJ* 1995;310:432-6.
39. Segers P, Mahieu D, Rietzschel ER, De Buyzere ML, Van Bortel LM. Impact of radial artery pressure waveform calibration on estimated central pressure using a transfer function approach. *Hypertension* 2008;52:e24-5.
40. Munir S, Guilcher A, Kamalesh T, et al. Peripheral augmentation index defines the relationship between central and peripheral pulse pressure. *Hypertension* 2008;51:112-8.

Key Words: central pulse pressure ■ arterial stiffness ■ wave reflection ■ augmentation pressure ■ aortic diameter.