Journal of the American College of Cardiology
© 2005 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 46, No. 9, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.07.037

Aging and Vascular Function

Normal Vascular Aging: Differential Effects on Wave Reflection and Aortic Pulse Wave Velocity

The Anglo-Cardiff Collaborative Trial (ACCT)

Carmel M. McEniery, PHD,* Yasmin, PHD,* Ian R. Hall, MB, MRCP,† Ahmad Qasem, PHD,‡ Ian B. Wilkinson, MA, DM, MRCP,* John R. Cockcroft, BSC, MB, FRCP†, on behalf of the ACCT Investigators

Cambridge and Cardiff, United Kingdom; and Sydney, Australia

OBJECTIVES The aim of the current investigation was to test the hypothesis that age-related changes in augmentation index (AIx) are more prominent in younger individuals (<50 years), whereas changes in aortic stiffness per se are more marked in older individuals (>50 years).

BACKGROUND Aging exerts a number of deleterious changes in the cardiovascular system, and, in particular, on the large arteries. Previous studies have suggested that AIx and pulse wave velocity (PWV) increase linearly with age, yet epidemiological data concerning pulse pressure suggest that large artery stiffening predominantly occurs later in life.

METHODS Peripheral and central blood pressure, augmentation pressure (AP), and AIx were determined in 4,001 healthy, normotensive individuals, aged 18 to 90 years. Aortic and brachial PWV were also determined in a subset of 998 subjects.

RESULTS Peripheral and central pulse pressure, AP, AIx, and aortic and brachial PWV all increased significantly with age; however, the age-related changes in AIx and aortic PWV were non-linear, with AIx increasing more in younger individuals, whereas the changes in PWV were more prominent in older individuals.

CONCLUSIONS These data suggest that AIx might be a more sensitive marker of arterial stiffening and risk in younger individuals but aortic PWV is likely to be a better measure in older individuals. (J Am Coll Cardiol 2005;46:1753–60) © 2005 by the American College of Cardiology Foundation

Age is one of the most powerful determinants of cardiovascular risk and is associated with a number of deleterious changes in the cardiovascular system (1). Among the more prominent changes are stiffening and dilatation of the large arteries—arteriosclerosis—which has been documented in almost all societies worldwide. Such changes lead to a rise in pulse pressure (PP) and, ultimately, the development of isolated systolic hypertension. This condition affects approximately 50% of individuals over 60 years of age and is associated with considerable excess morbidity and mortality. The importance of large artery stiffening has been further highlighted by the observation that aortic pulse wave velocity (PWV), which is inversely related to distensibility (2), and central augmentation index (AIx), a composite measure that depends on the site and degree of wave reflection (3), are independent predictors of cardiovascular and total mortality in selected patient groups (4–8).

A number of studies have investigated the effects of age on aortic PWV and AIx (9–12). Most suggest a linear, age-related increase in both indexes across a variety of different populations; however, epidemiological data indicate that PP increases significantly only after the fifth decade, suggesting that stiffening of the large arteries occurs predominantly in later life (13). Moreover, data from invasive studies suggest that the intensity of wave reflection becomes less marked in old age as impedance mismatch reduces (14). Such apparent discrepancies might reflect the fact that the majority of hemodynamic studies have been modest in size and encompassed a relatively narrow age range. Moreover, existing studies have not investigated the interaction between age, large artery stiffness, wave reflection, and PP within a single population.

We hypothesized that age-related changes in AIx are more prominent in younger subjects, whereas changes in large artery stiffness per se are more marked in older subjects. The aim of the present study was to test this hypothesis in a large cohort of healthy individuals from the Anglo-Cardiff Collaborative Trial (ACCT) and, in doing so, expand our understanding of the effect of age and gender on these commonly measured parameters of arterial stiffness.

METHODS

Subjects were drawn from the ACCT study population, which consists of 10,096 individuals, selected at random from local General Practice lists and open-access Cardiovascular Risk Assessment Clinics across East Anglia and

From the *Clinical Pharmacology Unit, University of Cambridge, Addenbrooke's Hospital, Cambridge, United Kingdom; †Department of Cardiology, University of Wales, College of Medicine, University Hospital, Cardiff, United Kingdom; and the ‡Graduate School of Biomedical Engineering, University of New South Wales, Sydney, Australia.

Manuscript received March 9, 2005; revised manuscript received July 1, 2005, accepted July 4, 2005.

Abbreviations and Acronyms

ACCT = Anglo-Cardiff Collaborative Trial
AIx = augmentation index
ANOVA = analysis of variance
AP = augmentation pressure
CSBP = central systolic pressure
HR = heart rate
MAP = mean arterial pressure
PP = pulse pressure
PPP = peripheral PP
PWV = pulse wave velocity
Tr = time to return of the reflected pressure wave

Wales. The overall response rate was 83%. Subjects with hypertension (blood pressure ≥140/90 mm Hg), diabetes mellitus, a serum cholesterol ≥6.5 mmol/l, renal disease (defined as a clinical history, creatinine ≥150 μmol/l or an active urinary sediment), or cardiovascular disease (defined as a clinical history or evidence on examination) were excluded from the analysis, as were subjects receiving any medication. This yielded a total of 4,001 individuals who were available for the current analyses, of whom 92% were Caucasian, 4% Asian, 2% Far Eastern, and 2% Afro-Caribbean. Approval for all studies was obtained from the local Research Ethics committees, and written informed consent obtained from each participant.

Hemodynamics. Blood pressure was recorded in the dominant arm with a validated oscillometric technique (HEM-705CP, Omron Corp., Kyoto, Japan) (15). Radial artery waveforms were recorded with a high-fidelity micromanometer (SPC-301, Millar Instruments, Houston, Texas) from the wrist of the dominant arm. Pulse wave analysis (SphygmoCor, AtCor Medical, Sydney, Australia) was then used to generate a corresponding central (ascending aortic) waveform with a generalized transfer function (16), which has been prospectively validated for the assessment of ascending aortic blood pressure (17). With the integral software, augmentation pressure (AP) was calculated as the difference between the second and first systolic peaks, and AIx was calculated as AP expressed as a percentage of the PP. The time to return of the reflected pressure wave (Tr), an estimate of aortic PWV (18), and heart rate (HR) were also determined from the aortic waveform. Mean arterial pressure (MAP) was obtained by integration of the waveform.

The aortic PWV was measured with the same device by sequentially recording electrocardiogram-gated carotid and femoral artery waveforms, as previously described in detail (19). The brachial PWV was determined from carotid and radial waveforms. Carotid waveforms were then re-scaled to the brachial mean and diastolic pressures, and carotid AIx and systolic pressure calculated with the SphygmoCor software (AtCor Medical). This approach provided central hemodynamic data without the use of any transfer function, in a similar manner to that described previously (20,21). All measurements were made in duplicate by trained investigators, and the mean values were used in the subsequent analysis. The within- and between-observer measurement reproducibility values for AIx and PWV were in agreement with our previously published data (19).

Protocol. Height and weight were assessed. After 15 min seated rest, blood pressure and radial artery waveforms were recorded in all subjects. After a further 20 min supine rest, brachial blood pressure and radial artery waveforms were re-measured, and aortic and brachial PWV determined in a subgroup of 998 subjects, with an age range and gender balance that was representative of the group as a whole.

Data analysis. Data were analyzed with SPSS software (version 11.0, SPSS Inc., Chicago, Illinois). To provide an overview of the relationship between age and arterial hemodynamics, data were grouped according to gender and deciles of age. Age-related changes in arterial parameters were compared between genders with two-way analysis of variance (ANOVA) and, where overall differences existed, post-hoc analyses were conducted with the Bonferroni method to compare between genders in each decile of age (i.e., eight comparisons). To further explore any gender differences in the effect of age on arterial hemodynamics, or where such age-related effects were non-linear, regression equations were derived for each gender with first- or second-order polynomial models and the F-test. The slope and curvature (quadratic term) for each parameter were then compared between genders, again on the basis of significance of the F-test.

To determine the factors influencing PP and arterial stiffness, stepwise multiple linear regression analyses were performed. Variables entered into the model were chosen from simple correlation analyses, and, from published observations, those variables known or likely to be associated with arterial stiffness. All values represent means ± SD and a p value of <0.05 was considered significant.

RESULTS

The average values for seated hemodynamic parameters from 4,001 subjects are presented in Table 1, grouped by gender and decade of age. Details of the regression analyses for selected hemodynamic parameters are provided in Table 2. As expected, in men and women, peripheral systolic blood pressure increased progressively with age, whereas diastolic blood pressure increased until approximately 50 years and then declined. This resulted in a widening of peripheral PP (PPP) after the age of 50, which was more prominent in women than men ($p < 0.001$, ANOVA; Fig. 1). Central systolic pressure (CSBP) increased more with age than did peripheral systolic blood pressure ($p < 0.001$, for both genders, ANOVA), and again, the increase in CSBP was more prominent in women than men ($p = 0.01$, ANOVA). The overall result was a decrease in PP amplification (ratio of peripheral to central PP) with age that was non-linear and more marked in subjects under 50 years. Throughout the age range, PP

Table 1. Subject Characteristics and Seated Hemodynamic Parameters According to Age Category for Males (M) and Females (F)

Decile Parameter	M F	<20 yrs n = 172 n = 133	20–29 yrs n = 178 n = 101	30–39 yrs n = 183 n = 165	40–49 yrs n = 258 n = 301	50–59 yrs n = 429 n = 495	60–69 yrs n = 430 n = 509	70–79 yrs n = 280 n = 290	80–90 yrs n = 39 n = 38	ANOVA Age, Gender
PSBP (mm Hg)	M	123 ± 10*	124 ± 10*	123 ± 9*	125 ± 9*	125 ± 9*	126 ± 9	127 ± 9	130 ± 8	<0.001, <0.001
	F	113 ± 10	115 ± 10	115 ± 12	118 ± 11	122 ± 11	126 ± 10	127 ± 10	128 ± 10	
PDBP (mm Hg)	M	73 ± 8	75 ± 8	77 ± 7*	79 ± 6*	79 ± 6*	78 ± 6*	76 ± 6*	75 ± 9*	<0.001, <0.001
	F	72 ± 8	73 ± 8	74 ± 9	75 ± 8	75 ± 7	74 ± 7	72 ± 8	70 ± 9	
PPP (mm Hg)	M	50 ± 9*	49 ± 9*	47 ± 8*	46 ± 7*	46 ± 8	49 ± 8*	51 ± 8*	55 ± 9	<0.001, <0.001
	F	41 ± 8	43 ± 7	41 ± 9	43 ± 9	46 ± 9	51 ± 8	54 ± 9	57 ± 11	
MAP (mm Hg)	M	88 ± 8	89 ± 8	92 ± 8	95 ± 7	95 ± 7	94 ± 7	93 ± 7	92 ± 8	<0.001, NS
	F	86 ± 8	86 ± 8	88 ± 9	90 ± 9	93 ± 8	93 ± 8	92 ± 8	90 ± 8	
CSBP (mm Hg)	M	103 ± 8*	105 ± 8*	109 ± 9*	113 ± 9*	115 ± 9	117 ± 9	118 ± 9	120 ± 8	<0.001, <0.001
	F	98 ± 9	101 ± 9	105 ± 11	109 ± 11	115 ± 11	118 ± 10	119 ± 9	120 ± 11	
CPP (mm Hg)	M	29 ± 5*	30 ± 6*	31 ± 6	34 ± 6	35 ± 7*	39 ± 7*	42 ± 7*	45 ± 9	<0.001, <0.001
	F	25 ± 6	27 ± 7	30 ± 8	33 ± 8	38 ± 8	43 ± 8	56 ± 8	49 ± 12	
PP Amp (ratio)	M	1.72 ± 0.11*	1.7 ± 0.14*	1.50 ± 0.18*	1.39 ± 0.15*	1.33 ± 0.16*	1.26 ± 0.13*	1.24 ± 0.12*	1.25 ± 0.14	<0.001, <0.001
	F	1.67 ± 0.15	1.59 ± 0.2	1.41 ± 0.18	1.29 ± 0.15	1.22 ± 0.11	1.21 ± 0.10	1.19 ± 0.10	1.18 ± 0.11	
AP (mm Hg)	M	−1 ± 3*	1 ± 4*	4 ± 5*	7 ± 4*	9 ± 5*	11 ± 5*	13 ± 5*	14 ± 5*	<0.001, <0.001
	F	1 ± 3	3 ± 4	6 ± 5	10 ± 5	13 ± 5	15 ± 5	16 ± 5	18 ± 7	
AIx (%)	M	−2 ± 8*	2 ± 11*	12 ± 13*	19 ± 10*	24 ± 10*	28 ± 9*	30 ± 9*	30 ± 10*	<0.001, <0.001
	F	5 ± 10	9 ± 14	20 ± 12	28 ± 10	33 ± 9	34 ± 9	35 ± 9	37 ± 10	
Tr (ms)	M	150 ± 17	154 ± 21*	151 ± 21*	148 ± 16*	143 ± 15*	141 ± 12*	136 ± 12*	133 ± 16*	<0.001, <0.001
	F	145 ± 16	143 ± 13	140 ± 16	136 ± 14	133 ± 15	131 ± 14	129 ± 12	125 ± 12	
Tr-Adj (m/s)	M	11.22 ± 1.26	11.69 ± 1.47	11.87 ± 1.77	11.81 ± 1.46	12.24 ± 1.42	12.32 ± 1.16	12.59 ± 1.21	12.96 ± 1.52	<0.001, NS
	F	11.5 ± 1.11	11.56 ± 1.02	11.87 ± 1.19	12.13 ± 1.25	12.37 ± 1.35	12.57 ± 1.26	12.64 ± 1.36	12.64 ± 1.37	
HR (beats/min)	M	73 ± 12	68 ± 12*	65 ± 11*	64 ± 10*	65 ± 11*	63 ± 10*	62 ± 10*	63 ± 11	<0.001, <0.001
	F	76 ± 12	73 ± 13	69 ± 10	69 ± 10	68 ± 10	66 ± 10	66 ± 10	68 ± 9	

Data are mean ± SD. Values in the final column represent results of two-way analysis of variance (ANOVA) for age and gender. Post hoc comparisons were made between genders for each decile with the Bonferroni method, and significant results are represented by *$p < 0.05$.

AIx = augmentation index; AP = augmentation pressure; CPP = central pulse pressure; CSBP = central systolic blood pressure; HR = heart rate; MAP = mean arterial pressure; PDBP = diastolic blood pressure; PP Amp = pulse pressure amplification; PPP = peripheral PP; PSBP = peripheral systolic blood pressure; Tr = time to return of the reflected pressure wave; Tr-Adj = Tr adjusted for height.

Table 2. Associations Between Age and Arterial Parameters for Males and Females

	Males			Females			
Age-Associations	**r^2**	**p**	**Regression Equation**	**r^2**	**p**	**Regression Equation**	**F**	**Overall Significance**
PPP (mm Hg)	0.07	<0.001	$y = -0.577x + 0.007x^2 + 58.569$	0.23	<0.001	$y = -0.218x + 0.005x^2 + 43.188$	45.1	p <0.001, *b*
CPP (mm Hg)	0.29	<0.001	$y = -0.032x + 0.003x^2 + 28.913$	0.41	<0.001	$y = 0.309x + 0.001x^2 + 18.692$	37.9	p = 0.01, *b*
PP Amp (ratio)	0.55	<0.001	$y = -0.02x + 0.0001x^2 + 2.053$	0.55	<0.001	$y = -0.026x + 0.0002x^2 + 2.084$	55.5	p <0.001, *c*
CSBP (mm Hg)	0.24	<0.001	$y = 0.543x - 0.003x^2 + 94.170$	0.28	<0.001	$y = 0.675x - 0.003x^2 + 86.351$	16.0	p <0.001
AIx (%)	0.53	<0.001	$y = 1.30x - 0.008x^2 - 23.744$	0.46	<0.001	$y = 1.586x - 0.011x^2 - 20.510$	93.0	p <0.001, *b*
AP (mm Hg)	0.48	<0.001	$y = 0.241x - 4.434$	0.45	<0.001	$y = 0.272x - 2.626$	130.0	p <0.001
Tr (ms)	0.11	<0.001	$y = -0.296x + 159.505$	0.11	<0.001	$y = -0.292x + 149.502$	95.1	p <0.001
Aortic PWV (m/s)	0.61	<0.001	$y = -0.017x + 0.001x^2 + 5.490$	0.63	<0.001	$y = -0.086x + 0.002x^2 + 6.363$	0.77	p = 0.51

PP Amp refers to PP amplification. Values in the final column represent overall differences between genders, based on F tests; *b* refers to slope, $p < 0.01$, males versus females; *c* refers to curvature, $p < 0.01$, males versus females. Abbreviations as in Table 1.

amplification was significantly higher in males than in females ($p < 0.001$, ANOVA).

Both AP and AIx were significantly and positively correlated with age (Table 2), and values were higher in women than men at each decade of life ($p < 0.001$). Whereas the association between age and AP was linear, changes in AIx were non-linear and more prominent in those under 50 years of age (Fig. 2A). There was an inverse, non-linear correlation between Tr and age, with greater changes later in life. At all ages, Tr was significantly higher in men than in women ($p < 0.001$, ANOVA), but this difference did not persist after correcting Tr for path length (the carotid-femoral distance) or height.

There were no significant differences in aortic or brachial PWV between men and women, and both correlated significantly with age, although this relationship was considerably stronger for aortic PWV (Table 2). Although age-related changes in brachial PWV appeared linear, changes in aortic PWV were not, being much more prominent in subjects over 50 years of age (Fig. 2B).

To demonstrate that aging exerts differential effects on various hemodynamic indexes, the effect of aging by 10 years was compared for younger (age 20 years) versus older (age 70 years) individuals (Table 3). As expected, the increases in PPP, central PP, and aortic PWV were more marked in older subjects compared with younger subjects, whereas the age-related changes in AIx were more prominent in younger subjects. These findings are in keeping with the observations that age-related changes in PPP, central PP, and aortic PWV are non-linear and more marked in subjects over 50 years, whereas age-related changes in AIx are more marked in subjects under 50 years. The age-related changes in AP and brachial PWV, however, were of a similar magnitude in younger and older individuals, reflecting their linear relationship with age.

In separate analyses ($n = 998$), aortic PWV was correlated with supine Tr ($r = 0.34$, $p < 0.001$), AP ($r = 0.64$, $p < 0.001$), and AIx ($r = 0.56$, $p < 0.001$). There was a higher correlation between aortic PWV and Tr, when Tr was adjusted for carotid-femoral path length ($r = 0.49$, $p < 0.001$) rather than for subject height ($r = 0.31$, $p < 0.001$).

Factors determining measures of stiffness. Stepwise multiple regression models were constructed to determine the factors influencing AIx, AP, PP amplification, Tr, and aortic and brachial PWV (Table 4). As expected, age, male gender, and MAP emerged as the major determinants of each of the dependent variables, with the exception of brachial PWV, where gender was not predictive.

Carotid versus derived aortic indexes. There was a high degree of correlation between the derived aortic AP and carotid AP, with a mean difference of 5 ± 3 mm Hg ($r = 0.91$, $p < 0.001$). Similarly, derived aortic and carotid AIx (12 ± 3%, $r = 0.9$, $p < 0.001$) and CSBP and carotid systolic blood pressure (5 ± 6 mm Hg, $r = 0.86$, $p < 0.001$) were highly related and without evidence of systematic bias.

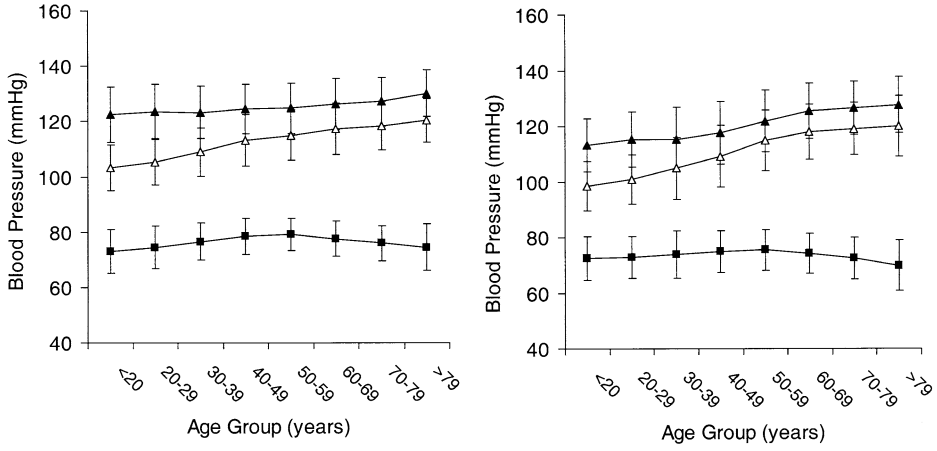

Figure 1. Blood pressure averaged for deciles of age for males **(left)** and females **(right)**. Symbols represent peripheral systolic **(closed triangles)**, central systolic **(open triangles)**, and diastolic **(closed squares)** blood pressures.

Comparison between seated and supine hemodynamics. Values for seated AIx and PP amplification were significantly higher than supine values (AIx, 8 ± 14% vs. 7 ± 16%, $p < 0.001$; PP amplification, 1.59 ± 0.21 vs. 1.55 ± 0.21; $p < 0.001$). These differences disappeared, however, when the data were corrected for the postural-induced changes in MAP and HR ($p = 0.32$, and $p = 0.19$, respectively).

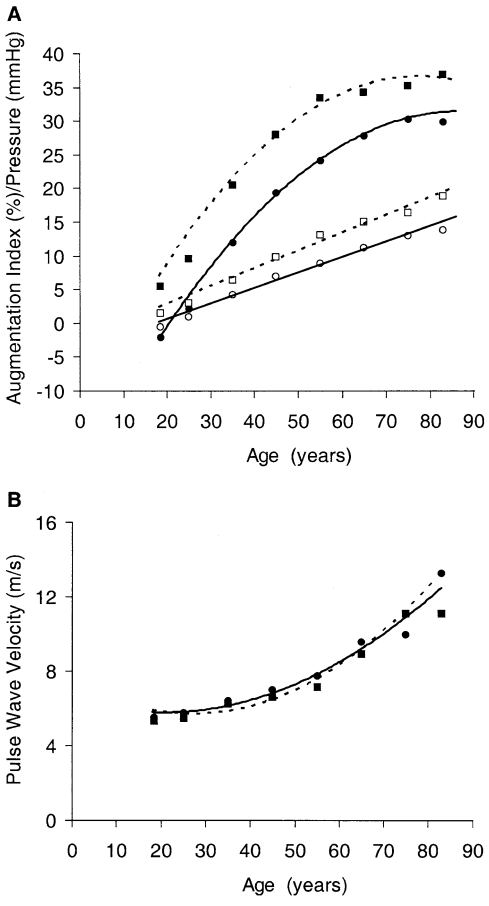

Figure 2. Regression curves representing the effect of age on parameters of arterial stiffness and wave reflection for males **(circles, solid lines)** and females **(squares, dashed lines)**. **Panel A** represents augmentation pressure **(open circles/open squares)** and augmentation index **(closed circles/closed squares)**. **Panel B** represents aortic pulse wave velocity. Data points are the group means for each decile of age. The estimated functions for these relationships appear in Table 2.

DISCUSSION

Although age is one of the most important determinants of cardiovascular risk, large artery stiffness is also a key independent predictor of cardiovascular mortality (4–8). A number of indexes, including aortic PWV and AIx, can now be easily assessed non-invasively and have been included in several outcome studies. The aim of the current study was to determine the effect of aging on these indexes in a large cohort of healthy, normotensive individuals. Our main novel findings were that the age-related changes in central AIx and aortic PWV follow different patterns. Changes in AIx were more prominent in younger individuals (<50 years), whereas the changes in aortic PWV were more marked in older individuals (>50 years). In addition, we confirmed previous observations of a widening of peripheral PP after the age of 50 years, but extended this to show for the first time that central PP rises linearly with age. Overall, these data suggest that central AIx might be a more sensitive marker of arterial aging in younger individuals, and aortic PWV more sensitive in those over 50 years of age.

Several previous studies have highlighted the positive association between age and central AIx, which is often considered to be linear (22). Mitchell et al. (12) recently questioned this view, reporting that AIx changes less with age in older individuals and actually declines after the age of 60 years. In the present study, the relationship between age and AIx was clearly non-linear, with a greater age-related effect in younger individuals, supporting the findings of Mitchell et al. (12) and suggesting that AIx might be a more sensitive marker of arterial aging in younger individuals. Indeed, previous data demonstrate that low birth weight is associated with increased AIx in adolescents (23); however, we found no evidence of a decline after the age of 60, rather,

Table 3. Comparison of the Effect of Aging by 10 Years on Arterial Parameters in Younger (20 to 30 Years) and Older (70 to 80 Years) Subjects

	Males		Females	
	20–30 yrs	70–80 yrs	20–30 yrs	70–80 yrs
PPP (mm Hg)	−3	+4	0	+5
CPP (mm Hg)	+2	+4	+4	+5
AIx (%)	+9	+1	+10	0
AP (mm Hg)	+3	+2	+3	+3
Aortic PWV (m/s)	+0.48	+1.36	+0.35	+2.35
Brachial PWV (m/s)	+0.38	+0.38	+0.19	+0.19

PWV = pulse wave velocity; other abbreviations as in Table 1.

a plateau effect, which might reflect our larger sample size or differences in demographics between the populations studied. We also confirmed that, at all ages, central AIx is higher in female subjects (8). Although the shorter average height of females—and, hence, a closer proximity between the heart and sites of wave reflection—is one obvious explanation, AIx corrected for height remained significantly higher in females, and gender remained an independent predictor of AIx in multiple regression models. Clearly, this requires further investigation.

In contrast to previous studies (11,24,25), our data also suggest that the relationship between age and aortic PWV is non-linear and much better represented with second order polynomial rather than simple linear regression. In contrast to AIx, however, the most marked increase in aortic PWV occurred in older individuals. Interestingly, closer examina-

Table 4. Stepwise Regression Analyses

Model	Regression Coefficient	SE	Beta	p	r^2 Change (%)
Augmentation index, adjusted $r^2 = 0.72$, $p < 0.001$					
Age	0.343	0.009	0.405	<0.001	44
HR	−0.520	0.013	−0.381	<0.001	10
Tr	−0.255	0.009	−0.287	<0.001	8
Female gender	7.117	0.320	0.241	<0.001	5
MAP	0.400	0.017	0.219	<0.001	4
Height	−10.213	1.579	−0.069	<0.001	1
Augmentation pressure, adjusted $r^2 = 0.75$, $p < 0.001$					
Age	0.164	0.004	0.422	<0.001	45
HR	−0.238	0.006	−0.384	<0.001	10
Tr	−0.112	0.004	−0.277	<0.001	8
Female gender	3.204	0.143	0.240	<0.001	4
MAP	0.211	0.008	0.254	<0.001	6
Weight	−0.016	0.005	−0.034	0.002	1
Height	−2.121	0.820	−0.032	0.010	1
Pulse pressure amplification, adjusted $r^2 = 0.73$, $p < 0.001$					
Age	−0.059	0.001	−0.493	<0.001	49
HR	0.839	0.001	−0.433	<0.001	11
Female gender	−0.979	0.004	−0.234	<0.001	7
MAP	−0.553	0.001	−0.213	<0.001	4
Tr	0.133	0.001	0.106	<0.001	1
Height	0.147	0.022	0.070	<0.001	1
Tr, adjusted $r^2 = 0.25$, $p < 0.001$					
Age	−0.312	0.015	−0.328	<0.001	11
Female gender	−7.628	0.578	−0.230	<0.001	9
HR	−0.238	0.023	−0.155	<0.001	2
Weight	0.069	0.020	0.061	0.001	1
MAP	−0.098	0.032	−0.048	0.002	1
Height	8.257	3.384	0.049	0.015	1
Aortic PWV, adjusted $r^2 = 0.65$, $p < 0.001$					
Age	0.078	0.003	0.709	<0.001	60
MAP	0.034	0.004	0.180	<0.001	3
HR	0.016	0.004	0.086	<0.001	1
Female gender	−0.266	0.086	−0.064	0.002	1
Brachial PWV, adjusted $r^2 = 0.28$, $p < 0.001$					
Age	0.021	0.002	0.307	<0.001	20
MAP	0.037	0.004	0.310	<0.001	6
Weight	−0.011	0.003	−0.122	<0.001	2

Abbreviations as in Tables 1 and 3.

tion of previous studies (11,24,25) supports a non-linear relationship, which might have been more apparent in our own study because of the larger sample size and wider age range. We did not observe any age-related change in MAP after the third decade, suggesting a true reduction in isobaric distensibility with age. One possible explanation for this is elastin fatigue fracture and degradation, with a consequent increased loading on stiffer collagen fibers (26). In addition, there is a marked increase in calcification of the aortic media with age, particularly after the fifth decade, that might also to contribute to a loss of arterial distensibility (27).

As compared with the changes in the aorta, brachial PWV increased linearly with age and to a much lesser degree. This difference might reflect the higher proportion of smooth muscle in the brachiocephalic system compared with the aorta or differential remodeling between the two arteries. The lack of any difference between men and women in either aortic or brachial PWV suggests that gender does not directly influence either central or peripheral arterial stiffening, at least in healthy normotensive individuals. It also implies that our observation of a higher AIx observed in females is predominantly due to gender differences in wave reflection rather than an effect on large artery stiffening per se.

The age-related changes in peripheral blood pressure in the present study are similar to those reported previously (13) and in a wealth of literature showing a marked increase in PPP in individuals over the age of 50 years. Peripheral PP is largely determined by stroke volume, which changes little with age (20), and large artery compliance. This explains why the age-related changes in PPP in the current study mirrored those in aortic PWV. In contrast, central PP increased linearly with age, which might have important clinical implications, because recent data suggest that central PP might provide a better marker of cardiovascular risk than peripheral values do (20). Central systolic PP depends on stroke volume and large artery stiffness but also on wave reflection. Augmented pressure, which represents the absolute amount of aortic pressure augmentation resulting from wave reflection, increased linearly with age. This suggests that the linear rise in central PP was largely driven by increased wave reflection. We hypothesize that two separate physiological processes are responsible for the changes in AP. In younger individuals, AIx rises steeply with age, whereas aortic PWV does not, suggesting that rise in AP is due to an increase in the magnitude of wave reflection rather than increased wave velocity. Conversely, in older individuals, AIx changes little, but aortic PWV increases markedly, suggesting that the rise in AP is driven by an earlier return of the reflected wave and a less compliant aorta rather than predominant changes in the magnitude of wave reflection. As we have previously noted (28), HR was also significantly associated with both AIx and AP, however, this accounted for only approximately 10% of the variance in each and, therefore, the age-related decrease in HR observed in the current study is unlikely to explain the majority of the changes in AIx and AP.

One limitation of the current study is its cross-sectional design, and further studies with longitudinal follow-up of healthy individuals are clearly required to confirm these data. Moreover, our data do not provide information on the impact of cardiovascular risk factors, such as hypertension or disease on large artery stiffness. The present study, however, does provide normative data from a large cohort of healthy normotensive individuals that can be used to more fully understand the effect of cardiovascular disease on the arterial hemodynamics. Although the validity of the transfer function has been questioned, we observed tight correlation between derived aortic and measured carotid AIx, and the same age-related patterns were observed when we substituted carotid for aortic indexes.

Clinical implications. Our findings suggest that, although related, AIx and PWV provide different information. Specifically, AIx might provide a more sensitive marker of arterial aging in younger individuals, whereas aortic PWV might be a more sensitive marker in older individuals. Therefore, to fully assess the impact of age and risk factors on large artery hemodynamics, both markers might need to be assessed. In an aging society, where clinical decisions will increasingly be made on the basis of risk prediction and stratification, the current findings might be particularly useful in defining usual patterns of age-related hemodynamic changes. Moreover, the age-related changes in PP amplification and AIx indicate that central and peripheral systolic BP are not the same and change differently with age. Current guidelines on hypertension are on the basis of only peripheral BP and, therefore, we now need to assess the predictive value of central hemodynamic indexes in a large cohort, which might improve risk prediction.

In conclusion, we have demonstrated that, whilst there is a marked increase in PPP in individuals over 50 years of age, central PP increases linearly with age. We have also demonstrated that central AIx and aortic PWV are differentially affected by aging. Age-related changes in AIx are more marked in younger individuals, whereas aortic PWV only increases significantly in individuals over the age of approximately 50 years. Further investigations are now required to determine the extent to which these hemodynamic patterns are altered in individuals with cardiovascular risk factors or disease.

Reprint requests and correspondence: Dr. Carmel M. McEniery, University of Cambridge, Clinical Pharmacology Unit, Addenbrooke's Hospital, Box 110, Cambridge, Cambridgeshire CB2 2QQ, United Kingdom. E-mail: cmm41@cam.ac.uk.

REFERENCES

1. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: part I: aging arteries: a "set up" for vascular disease. Circulation 2003;107:139–46.
2. Bramwell JC, Hill AV. Velocity of transmission of the pulse-wave in man. Proc R Soc London Biol Sci 1922;93:298–306.
3. Safar ME, London GM. Therapeutic studies and arterial stiffness in hypertension: recommendations of the European Society of Hyper-

tension. The Clinical Committee of Arterial Structure and Function. Working Group on Vascular Structure and Function of the European Society of Hypertension. J Hypertens 2000;18:1527–35.
4. Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension 1999;33:1111–7.
5. 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.
6. Meaume S, Benetos A, Henry OF, Rudnichi A, Safar ME. Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. Arterioscler Thromb Vasc Biol 2001;21:2046–50.
7. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation 2002;106:2085–90.
8. London GM, Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME. Arterial wave reflections and survival in end-stage renal failure. Hypertension 2001;38:434–8.
9. Avolio AP, Fa-Quan D, Wei-Qiang L, et al. Effects of ageing on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. Circulation 1985;71:202–10.
10. Hayward CS, Kelly RP. Gender-related differences in the central arterial pressure waveform. J Am Coll Cardiol 1997;30:1863–71.
11. Smulyan H, Asmar RG, Rudnicki A, London GM, Safar ME. Comparative effects of aging in men and women on the properties of the arterial tree. J Am Coll Cardiol 2001;37:1374–80.
12. 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.
13. Franklin SS, Gustin IVW, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure: The Framingham Heart Study. Circulation 1997;96:308–15.
14. MacDonald DA. Blood Flow in Arteries. 2nd edition. London: Edward Arnold, 1974.
15. O'Brien E, Mee F, Atkins N, Thomas M. Evaluation of three devices for self measurement of blood pressure according to the revised British Hypertension Society Protocol: the Omron HEM-705CP, Philips HP5332, and Nissei DS-175. Blood Press Monit 1996;1:55–61.
16. Karamanoglu M, O'Rourke MF, Avolio AP, Kelly RP. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. Eur Heart J 1993;14:160–7.
17. Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. Hypertension 2001;38:932–7.
18. Murgo JP, Westerhof N, Giolma JP, Altobelli SA. Aortic input impedance in normal man: relationship to pressure waveforms. Circulation 1980;62:105–16.
19. Wilkinson IB, Fuchs SA, Jansen IM, Murray GD, Cockcroft JR, Webb DJ. The reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. J Hypertens 1998;16 2079–84.
20. Safar ME, Blacher J, Pannier B, et al. Central pulse pressure and mortality in end-stage renal disease. Hypertension 2002;39:735–8.
21. Chen C-H, Ting C-T, Nussbacher A, et al. Validation of carotid artery tonometry as a means of estimating augmentation index of ascending aortic pressure. Hypertension 1996;27:168–75.
22. Nichols WW, O'Rourke MF. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 4th edition. London: Arnold, 1998.
23. Lurbe E, Torro MI, Carvajal E, Alvarez V, Redon J. Birth weight impacts on wave reflections in children and adolescents. Hypertension 2003;41:646–50.
24. Avolio AP, Chen S-G, Wang R-P, Zahang C-L, Li M-F, O'Rourke MF. Effects of ageing on changing arterial compliance and left ventricular load in a northern Chinese urban community. Circulation 1983;68:50–8.
25. Vaitkevicius PV, Fleg JL, Engel JH, et al. Effects of age and aerobic capacity on arterial stiffness in healthy adults. Circulation 1993;88: 1456–62.
26. O'Rourke MF. Pulsatile arterial hemodynamics in hypertension. Aust N Z J Med 1976;6 Suppl 2:40–8.
27. Yu SY, Blumenthal HT. The calcification of elastic fibers. I. Biochemical studies. J Gerontol 1963;18:119–26.
28. Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. J Physiol 2000;525:263–70.

APPENDIX

The ACCT Investigators: Derin Balogun, Ross Campbell, Zahid Dhakam, Rhiannon Edwards, Patrick Harnett, Isla Mackenzie, Kaisa Maki-Petaja, Barry McDonnell, Maggie Munnery, Pawan Pusalkar, Christopher Retallick, Matthias Schmitt, James Sharman, Rachel Stainsby, Justin Taylor, Edna Thomas, Neil Thomas, Sian Tyrell, Sharon Wallace, Olwyn Westwood, Simon Williams.